



Control of epileptic seizures by the basal ganglia: clinical and experimental approaches

Feddersen Berend

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UNIVERSITE JOSEPH FOURIER GRENOBLE

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Control of epileptic seizures by the basal ganglia:
clinical and experimental approaches

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ABBREVIATIONS

AN	-	Anterior nucleus (of the thalamus)
CM	-	Centromedian Thalamus
CN	-	Caudate nucleus
DBS	-	Deep brain stimulation
GABA	-	Gamma-Amino-Butyric-Acid
GAERS	-	Genetic Absence Epilepsy Rats from Strasbourg
GP	-	Globus pallidus
GPe	-	Globus pallidus externus
GPI	-	Globus pallidus internus
HFS	-	High-frequency stimulation
ID	-	ictal dystonia
ILAE	-	International League Against Epilepsy
SN	-	Substantia nigra
SNr	-	Substantia nigra pars reticulata
SNC	-	Substantia nigra pars compacta
STN	-	Subthalamic nucleus
MRI	-	Magnet Resonance Imaging
PET	-	Positron emission tomography
SPECT	-	Single photon emission computed tomography
TLE	-	Temporal lobe epilepsy
mTLE	-	mesial temporal lobe epilepsy
nTLE	-	neocortical temporal lobe epilepsy
PLE	-	Parietal lobe epilepsy
OLE	-	Occipital lobe epilepsy
RNS	-	Responsive neuro-stimulation system
SUDEP	-	Sudden Unexpected Death in Epilepsy
VM	-	ventro medial (thalamus)
VNS	-	Vagal nerve stimulation

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RESUME EN FRANÇAIS

Près de 30% des patients qui souffrent d'une épilepsie sont résistants aux traitements pharmacologiques et seuls 30% de ces patients peuvent bénéficier d'une alternative thérapeutique par résection chirurgicale. La recherche de cibles et stratégies thérapeutiques innovantes constitue un enjeu majeur pour la prise en charge de ces patients. De nombreuses études expérimentales chez l'animal indiquent que les ganglions de la base, et en particulier la substance noire, exercent un contrôle sur la survenue des crises d'épilepsie. Des arguments cliniques, obtenus par électrophysiologie ou imagerie médicale, sont également en faveur de la mise en jeu des ganglions de la base dans certains syndromes épileptiques. Chez des patients souffrant d'épilepsie focale, l'influence de la propagation des crises au travers des ganglions de la base a été examinée en rapport avec le taux de généralisation secondaire. Chez ces patients l'activation des ganglions de la base semble associée à une influence inhibitrice sur la propagation des crises lorsque celles-ci envahissent le lobe frontal. L'exploration de ces mécanismes inhibiteurs des crises est susceptible d'ouvrir de nouvelles perspectives thérapeutiques comme celle portant sur la stimulation intracérébrale profonde. Les premières études de cas explorant les effets de la stimulation intracérébrale des ganglions de la base chez quelques patients ont permis d'obtenir des résultats encourageants chez certains d'entre eux. Cependant de nombreuses études précliniques devraient permettre de préciser les paramètres de stimulation à appliquer. Une approche expérimentale chez l'animal nous a permis de déterminer les paramètres optimaux à appliquer pour contrôler la survenue de crises spontanées dans un modèle d'épilepsie-absence chez le rat. Dans ce modèle les paramètres optimaux à appliquer à la substance noire réticulée consistent en des stimulations bilatérales, bipolaires, monophasiques, de 60 Hz en fréquence et de 60 μ s en largeur d'impulsion. Appliqués de façon répétée, ces paramètres ne permettent cependant pas de supprimer durablement la survenue des crises et ont même tendance à augmenter le nombre de crises enregistrées. Un délai d'au moins 60 seconde entre l'application de deux stimulations consécutives est à respecter pour interrompre les crises. Dans nos conditions, bien qu'une stimulation haute-fréquence de la substance noire réticulée appliquée de façon aiguë puisse interrompre une crise en cours, des stimulations répétées semblent inefficaces. Ceci est en faveur du développement en cours, dans de nombreux laboratoires à travers le monde, de procédures de stimulation des crises

asservie à leur détection afin de les supprimer de façon chronique dans le cadre d'applications thérapeutiques. De tels systèmes, dits « adaptatifs », seront particulièrement pertinents s'ils sont couplés à des modifications détectables, signalant l'arrivée d'une crise. Dans le modèle d'épilepsie-absence chez le rat, de telles modifications ont été identifiées au niveau de la cohérence entre signaux électroencéphalographiques issus des deux substances noires réticulées. Ces modifications pourraient être utilisées comme signature spécifique de l'imminence d'une crise dans le couplage de la stimulation à la détection des crises. Toutefois, rien ne permet de dire si ces modifications sont spécifiques du modèle étudié ou encore si de telles modifications existent dans certains syndromes épileptiques en clinique. De nombreux arguments existent pour dire que l'épilepsie n'est pas une pathologie restreinte au seul cortex en tant que circuit générateur de crises, mais implique également des structures sous-corticales susceptibles d'exercer un contrôle à distance sur les circuits générateurs de crises. Cette conception de l'épilepsie permet d'envisager le développement de nouvelles stratégies thérapeutiques pour les patients pharmaco-résistants et qui ne peuvent pas bénéficier d'une intervention chirurgicale.

ENGLISH ABSTRACT

As about one third of epileptic patients are resistant to antiepileptic drugs, and only 30% of them are candidates for resective surgery, it exists a great demand for the development of alternative surgical therapies. It has been shown in animal studies, that the basal ganglia and especially the substantia nigra (SN) are involved in the control of epilepsy. Clinical evidence, using either electrophysiological or imaging approaches, also supports the involvement of the basal ganglia in some epileptic syndromes. The influence of seizure spread into the basal ganglia in patients with focal epilepsies was investigated on the rate of secondary generalization. We showed that activation of the basal ganglia was associated with an inhibitory effect on seizure propagation, when seizures spread into the frontal lobe. The elucidation of inhibitory mechanisms in epilepsy may open a new approach for therapeutic strategies such as electrical deep brain stimulation. First open case series, investigating deep brain stimulation of the basal ganglia to suppress epileptic seizures, showed encouraging results in some patients. However, more preclinical studies are mandatory to investigate the optimal stimulation parameters. The aim of our experimental approach was to determine the optimal stimulation parameters to control spontaneous seizures in a genetic model of absence epilepsy in the rat. In this model, the optimal parameters of single substantia nigra pars reticulata (SNr) stimulation were determined as bilateral, bipolar, monophasic, 60 Hz frequency and 60 μ s pulse width. When these parameters were used for repeated stimulations, no long-term suppression and even increase of the number of seizures was observed. A delay of at least 60 sec was necessary between stimulations to be fully effective. Although single high-frequency stimulation of the SNr can be used to suppress ongoing seizures, repeated stimulation are ineffective and could even aggravate seizures, thus supporting the need of closed-loop stimulation procedures to chronically suppress seizures in therapeutical applications. Such an adaptative device would be effective only when detectable changes heralds the seizure onset. In a genetic model of absence epilepsy such changes in the EEG-coherence between the left and right SNr could be identified. Such changes might be used as an hallmark for adaptative procedures like triggered single stimulation to avoid the occurrence of the presumed seizures. To date it remains unknown, if such changes in coherence between left and right SNr, are specific to the model of GAERS and if such changes occur also in other animal models or humans with different epileptic syndromes.

Accumulating evidences support that epilepsy is not a pathology restricted to the cortex as a seizure generator, but that subcortical structures are also involved, which might open new therapeutic options for patients who are pharmacoresistant and no candidates for a resective surgical treatment.

PROLOGUE

About one third of epileptic patients are resistant to antiepileptic drugs (AED) (Kwan and Brodie, 2000), and only 30% of them are candidates for resective surgery (Hauser et al., 1990; Semah et al., 1998; Wiebe et al., 2001). Such a therapeutic options is only considered in patients who are suffering from focal seizures, and in whom the epileptic zone can be removed safely. Therefore, there is a great need and interest for “alternative” or “novel” therapeutic options for patients who are pharmacoresistant and whose seizures arise from eloquent cortices, from multifocal or bilateral seizure onset zones, or who have generalized seizures (Polkey, 2003).

Since the pioneering work of Iadarola and Gale (1982), suggesting a possible anticonvulsive influence of the SNr (Iadarola and Gale, 1982), the role of structures of the basal ganglia in the pathophysiology of epileptic seizures (Deransart and Depaulis, 2002) has regained increased interest. This interest was amplified by the encouraging results of deep brain stimulation in different forms of movement disorders. For more than twenty years, stimulation of different deep brain targets has been shown to be feasible, safe and effective. This has led to its development and application in an increasing number of different neurological and psychiatric diseases, including epilepsy (Theodore and Fisher, 2004). However, first open case series were only partly effective in some patients (Benabid et al., 2000; Benabid et al., 2002; Chabardes et al., 2002; Fisher et al., 1992; Hodaie et al., 2002; Kerrigan et al., 2004; Loddenkemper et al., 2001; Velasco et al., 2001a; Vesper et al., 2007). This may be due to the often inhomogeneous population investigated with different seizure types and epileptic syndromes, different stimulated targets and different stimulation parameters. Therefore, it appears necessary to address these questions experimentally, before deep brain stimulation may become a real “alternative” or “new” therapy for epileptic patients. The aim should be an appropriate seizure reduction but also an increase in quality of life, which should be superior when compared to other “palliative” therapies such as vagus nerve stimulation.

As it may be important to understand the underlying circuits of epileptic propagation and its involved brain areas, with its possible different targets for acute seizure interruption, a review of different forms of epileptic seizures and syndromes is given in the introduction. Especially, the semiological seizure classification is addressed as

potential tool to choose candidates for deep brain stimulation. Indeed, different seizure semiology reflects involvement of different activated brain areas and cerebral circuits. This knowledge may be as important as the understanding of the organization of the basal ganglia, with its different structures involved in a system of endogenous control of epilepsy.

To understand better the possible control of epileptic seizures by the basal ganglia three main questions are presented and discussed in this thesis:

1. Is it possible to confirm the inhibitory role of the basal ganglia in human epilepsies, with impact on the selection of optimal candidates for deep brain stimulation in epilepsy ?
2. What are the optimal deep brain stimulation parameters in epilepsy for interruption of epileptic seizures ?
3. Are there electrophysiological hallmarks that heralds the onset of epileptic seizures into the basal ganglia ?

I. INTRODUCTION

A. The epilepsies

Epilepsy is defined by the occurrence of recurring seizures. An epileptic seizure is characterized by sudden onset of rhythmic and synchronized discharges of several neurons, in restricted brain areas or the whole brain. The semiology of seizures is diverse and reflects activation of different cerebral circuits. It depends of: (i) the dimension, (ii) the localization and (iii) the seizure spread to other brain areas. The seizure leads typically to an activation (hallucinations, motor symptoms) and seldom to inhibition of different areas (scotoma, dysphasia, paresis). The seizure frequency is very variable and can range from one in a lifetime to several hundreds a day or even evolve into status epilepticus, with lack of seizure termination (Hufnagel and Noachtar, 2003). However, all seizures are characterized by the hypersynchronous electrical neuronal activity, independent of the underlying etiology.

The prevalence of epilepsies range from 0,5 - 1%. After cerebrovascular disorders, epilepsy is the second most common neurological disorder. The incidence is 5-7 per 10.000 persons per year and is age dependent (Hufnagel and Noachtar, 2003). The rate of primary manifestation is highest in the first two years and declines to the end of the second decade. After the 40th year, it raises again with a second peak after the sixth decade. Idiopathic generalized epilepsies show a classical phase of manifestation in child- and adulthood. Focal epilepsies may become manifest at every age. In infants malformations, neurometabolic and perinatal brain damage are the main causes of epilepsies. Temporal lobe epilepsies manifest often between the age of 5-15 years. In the second to fifth decade, traumas, withdrawal of alcohol, infections and neoplasmas are the main causes. Stroke is the main etiology of new onset epilepsies after the sixth decade.

In human epilepsies, a differentiation is made of the ictal phase (up to several minutes), with alteration of neurological function due to the seizure activity. The postictal phase follows the ictal phase and is characterized by restitution of physiological function. The interictal phase is the time which preceeds the next seizure and may last from a few minutes to several years.

The International League Against Epilepsy (ILAE) recommends to distinguish between focal and primary generalized seizures. Seizures with a focal origin are mainly caused by structural lesions of the brain, whereas primary generalized seizures are often

determined genetically. In seizures with focal origin, the seizure onset is restricted to a circumscribed brain area and propagation takes place through recruiting of surrounding neurons. Seizure spread by propagation to neighbored and distant brain areas may induce changes in seizure semiology.

Seizures, in which such propagation is limited to a restricted brain area are called *simple partial seizures*, when consciousness is not altered. The seizure becomes only recognizable, when symptomatic brain regions, with recognizable brain function, is affected.

When both hemispheres or the speech dominant hemisphere are involved, consciousness is lost during these *complex partial seizures*. Propagation to the whole brain and involvement of motor areas resulting in *secondary generalized tonic clonic seizures*. Primary generalized seizures were not believed to have a focal origin and fast (10-20ms) involvement of synchronized discharges in both hemispheres occurs.

Conclusion: Epileptic seizures are the predominant symptom of epilepsy. It is the second most common neurological disorder. Because of the unpredictability of epileptic seizures, it possess a great burden in daily and quality of life for the patients.

1. Epileptic seizures

1.1. Classification of epileptic seizures

The International League Against Epilepsy (ILAE) introduced a seizure classification in 1981 based on clinical semiology, interictal EEG findings, and ictal EEG patterns (Epilepsy, 1981) (see table 1). The assumption behind such a classification based on electroclinical features, is the existence of a strict one-to-one correlation between clinical-ictal semiology and interictal EEG findings. However, detailed analysis of clinical semiology and EEG findings shows that this assumption is, particularly for infants (Acharya et al., 1997), frequently incorrect (Manford et al., 1996). For this reason a classification on seizure semiology was proposed (Lüders et al., 1998; Noachtar et al., 1998). Such a semiological seizure classification stresses the differentiation between epileptic seizures and epileptic syndromes and provides common terms for typical ictal symptoms and types, that are independent of the underlying EEG pattern, as well as other laboratory information.

Table 1: Classification of seizures of the ILAE 1981 (Commission on classification 1981)

<p>I. Partial seizures</p> <p>A. simple partial seizures (without alteration of cognition)</p> <ol style="list-style-type: none"> 1. with motor symptoms 2. with somatosensory symptoms 3. with autonomic symptoms 4. with psychic symptoms <p>B. complex partial seizures (with alteration of consciousness)</p> <ol style="list-style-type: none"> 1. simple partial seizures evolving into complex partial seizures 2. complex partial seizure (alteration of consciousness at the beginning) <p>C. partial seizures (simple partial or complex partial) evolving into secondary generalized seizures.</p> <p>II. Generalized seizures</p> <p>A. Absence seizures</p> <ol style="list-style-type: none"> 1. typical absence 2. atypical absence <p>B. Myoclonic seizures</p> <p>C. Clonic seizures</p> <p>D. Tonic seizures</p> <p>E. Primary tonic-clonic seizures</p> <p>F. Atonic seizures</p> <p>III. Unclassified seizures</p> <p>adapted from (Epilepsy, 1981)</p>
--

1.2. Semiological seizure classification

Careful clinical observations and detailed reports of seizure semiology by the patient or other observers have been used since the 18th century to classify epileptic seizures and epileptic syndromes. A detailed analysis of seizure semiology is still essential for the proper management of epileptic patients. Seizures comprise the main symptomatology of patients with epilepsy, and their control is the target of all treatments. The quality of a patient's life depends in large part on the type of seizures, as well as the frequency. A clear definition of the seizure type is also important for classifying the correct epileptic

syndrome. Syndrome and etiology of the epilepsy are essential factors determining the prognosis, as well as the most effective pharmacological treatment (Benbadis and Lüders, 1996). Furthermore, selection of candidates for deep brain stimulation may be in the future dependent of seizure semiology, localization, seizure evolution and ictal phenomena.

Epileptic seizures are characterized by a variety of signs and symptoms. A seizure is analyzed according to the four categories of seizure symptomatology (Lüders et al., 1998):

- (1) sensorial sphere;
- (2) autonomic sphere;
- (3) consciousness;
- (4) motor sphere.

Sensorial sphere: Only a few seizure types involve one of these categories exclusively. One example is an aura, which affects the sensorial sphere without any objective signs. Aura refers to an epileptic seizure during which exclusively subjective symptoms occur without objective signs that can be documented by an observer. Auras are the first clinical expression of a seizure, and therefore, they frequently provide extremely useful localizing information about the seizure-onset zone (Palmini and Gloor, 1992).

Autonomic sphere: Autonomic seizures refer to seizures, in which the predominant symptomatology is an objectively documented alteration of the autonomic system. Autonomic seizures are very rare. They show clear EEG seizure patterns but affect only the autonomic system, such as tachycardia or ictal pallor. Pure ictal tachycardia without any other clinical symptoms is highly correlated with a temporal, rather than extratemporal, EEG seizure pattern (Weil et al., 2005).

Consciousness: Many seizures are associated with a disturbance of consciousness. However, only in some seizures this reflects the predominant feature of the seizure. The term “dialeptic seizure” for ictal episodes was proposed, in which the main manifestation is an alteration of consciousness, independently of whether the patient has focal or generalized epilepsy (Lüders et al., 1998; Noachtar et al., 1998). Dialeptic seizures consists of an episode of alteration of consciousness, during which a patient cannot react to external stimuli at all, or only to a limited extent, and which they do not recall later. The main feature is the behavioural arrest with staring. Dialeptic seizures occur in several generalized and focal epilepsies (Noachtar et al., 2000). In generalized

epilepsies, with the typical 3-Hz per second spike and wave discharges in the EEG, they are also often called “absence” seizures.

Motor sphere: Seizures in which the main manifestations are motor phenomena are called “motor seizures”. Motor seizures are divided into two major groups on the basis of the type of motor symptomatology: *simple* and *complex motor seizures*. *Simple motor seizures* are characterized by unnatural, relatively simple movements that can be reproduced by electrical stimulation of the primary and supplementary sensorimotor areas. *Complex motor seizures* consist of motor seizures during which the patient performs movements that imitate natural movements, are relatively complex, and tend to involve different body segments, moving in different planes.

Others: Seizures that cannot be assigned to any of the four groups outlined above, are included in the group labeled “special seizures”. Most of these seizures characteristically have a “negative” influence on motor (atonic, akinetic) or cognitive (aphasic) activity.

See also table 2: Semiological seizure classification.

Table 2: Semiological seizure classification (adapted from (Lüders et al., 1998))

I. Epileptic seizure			
	Aura		Somatosensory aura ^a Visual aura ^a Auditory aura ^a Olfactory aura Gustatory aura Autonomic aura Epigastric aura Psychic aura
	Autonomic seizure ^a		
	Dialeptic seizure		
	Motor seizure ^a	Simple-motor seizure ^a	Myoclonic seizure ^a Epileptic spasm ^a Tonic-clonic seizure Tonic seizure ^a Clonic seizure ^a Versive seizure ^a
		Complex-motor seizure ^b	Hypermotor seizure ^b Automotor seizure ^b Gelastic seizure
	Special seizure		Atonic seizure ^a Astatic seizure Akinetic seizure ^a Negative myoclonic seizure ^a Hypomotor seizure ^b Aphasic seizure ^b
II. Paroxysmal event			

^a Left/right/axial/generalized/bilateral asymmetric.

^b Lateralizing signs occurring during this type of seizure type are listed separately.

The semiological seizure classification identifies in detail the somatotopic distribution of the ictal semiology as well as the seizure evolution. That gives important clues for the identification of the seizure onset zone as well as the brain areas which are involved during seizure propagation. This is a clinical approach which is not based on concomitant EEG findings as it is the case in the seizure classification of the ILAE (Epilepsy, 1981). This might be important in the selection of optimal candidates for DBS in epilepsy, as the semiological seizure classifications gives clinical informations of different seizure spread patterns. Such semiological clues might overlap with basal ganglia circuits and therefore patients with different seizures might have different optimal targets for DBS. The simple motor seizures reflect activation of the primary and premotor areas. Ictal phenomena of motor seizures could be reproduced using subdural stimulation of these motor areas (Lüders et al., 1998). Since the basal ganglia and especially the subthalamic nucleus (STN) and the Substantia nigra pars reticulata (SNr) have strong connections with the primary motor cortex it is possible that patients with seizures involving these frontal areas are likely to be better candidates for seizure suppression by stimulation of the STN or SNr than others.

1.3. The epileptogenic zone

At the cellular level, the primary mechanisms which lead to the synchronous repetitive depolarization of neuronal cells, is still not fully understood. It has been suggested that an imbalance of excitatory and inhibitory neuronal activation would be critical and cause of neuronal excitation evolving into epileptic seizures. Reality may be far more complicated, even if it has been shown, that increase of excitatory neurotransmitters (like glutamate or aspartate) or reduced inhibitory transmitters (like gamma-aminobutyric-acid (GABA)) play an important role (Baulac et al., 2001; Klepper et al., 2001; Wallace et al., 2001).

The epileptogenic zone is the region from which the epileptic seizure originates (Lüders and Awad, 1992). An epileptic discharge that is limited to the seizure-onset zone does not necessarily lead to clinical symptoms, probably because the epileptogenic zone does not overlap with the symptomatogenic zone (Lüders and Awad, 1992). The term “symptomatogenic zone” refers to the area of the cortex that produces certain clinical symptoms as a result of epileptic activation. For example, seizures that originate in the frontal convexity remain asymptomatic as long as they do not spread into the

symptomatogenic zones. If the epileptic activation reaches the primary motor area, versive or focal clonic seizures occur (Noachtar et al., 2003).

1.4. Localizing significance of different seizure types

The knowledge of the seizure focus may be important not only for resective epilepsy surgery but also for alternative treatment strategies. To date, it is unknown which seizures would be best interrupted by electrical stimulation at different deep brain targets. It is possible that in the future, seizure propagation determines the optimal stimulation target. Therefore localization significance of different seizure types is mandatory. Analysis of epileptic seizures documented by means of simultaneous video and EEG recordings have dramatically improved our knowledge of epileptic seizure semiology and its localizing significance. This knowledge is important for the definition of epileptic syndromes as well as for the presurgical investigations. Whether it plays also a crucial role in determining optimal candidates for alternative surgical treatments like deep brain stimulation needs to be further elucidated. Table 3 gives an overview of the localizing significance of different seizure types with emphasis on frequent and less frequent localizations:

Table 3: Localizing significance of different seizure types

SEIZURE TYPE	FREQUENT LOCALIZATION		LESS FREQUENT LOCALIZATION	REF
Aura	Somato-sensory	Contralateral somatosensory cortex	Supplementary sensorimotor area or the secondary sensory area	a,b
	Visual	Striate and parastriate cortex		a
	Auditory	Heschl Gyrus	Temporal association cortex	a,c
	Olfactory	Amygdala	Orbitofrontal part of gyrus rectus	d
	Gustatory	Temporal lobe	Frontal lobe	e
	Psychic	Neocortical temporal lobe	Mesial temporal lobe	f
	Epigastric	Insula		g,h,i
	Autonomic	Basal frontal region and cingulate gyrus		a
Autonomic seizure		Temporal lobe		j
Dialeptic seizure		Focal or generalized, involvement of the thalamus		k,l,m
Motor seizure	Simple motor			
	Myoclonic	Primary motor cortex or premotor areas		n
	Epileptic spasm	does not allow localization		o
	Tonic-clonic	primary motor and the supplementary sensorimotor areas		p
	Tonic	primary motor and the supplementary sensorimotor areas	reticular formation of the brainstem and the thalamus (in Lennox Gastaud Syndrome)	q
	Clonic	Contralateral primary motor or premotor areas		r
	Versive	Frontal eye field that is contralateral to the side to which the eyes turn		a
	Complex motor			
	Hypermotor	Mesial frontal or supplementary sensorimotor area		s,t
	Automotor	Anterior cingulate gyrus, temporal lobe	Frontal lobe, especially orbitofrontal	u,v,w
	Gelastic	Hypothalamus		x
Special Seizure	Atonic	nucleus reticularis gigantocellularis (brainstem)	Negative motor areas	y, z
	Astatic	See tonic clonic, myoclonic and atonic		
	Akinetic	Negative motor areas		z
	Negative myoclonic	Not yet been defined		
	Hypomotor	Mostly temporal and generalized		
	Aphasic	Cortical language areas in the speech dominant hemisphere		

a (Penfield and Jasper, 1954)
 b (Morris et al., 1988)
 c (Luders, 1991)
 d (Acharya et al., 1998)
 e (Palmini and Gloor, 1992)
 f (Ebner, 1994)
 g (Rasmussen, 1982)
 h (Palmini and Gloor, 1992)
 i (Henkel et al., 2002)
 j (Weil et al., 2005)
 k (Kostopoulos, 2001)
 l (Noachtar et al., 2000)
 m (Lee et al., 2002)
 n (Janz and Christian, 1957)
 o (Fogarasi et al., 2002)
 p (Trinka et al., 2002)
 q (Bleasel and Lüders, 2000)
 r (Noachtar and Arnold, 2000)
 s (Morris et al., 1988)
 t (Williamson et al., 1985)
 u (Ebner et al., 1995)
 v (Manford et al., 1996)
 w (Talairach et al., 1973)
 x (Berkovic et al., 1988)
 y (Lai and Siegel, 1988)
 z (Lüders et al., 1995)

1.5. Localizing significance of different seizure evolutions

Epileptic seizures frequently evolve from one seizure type into another. That reflects the seizure spread with involvement of different brain areas. It is a well-established fact that the initial seizure symptoms provide information on the location of the seizure-onset zone. The evaluation of seizure evolutions is important as there are typical seizure sequences, which point to different epilepsy syndromes. For example, early clonic seizures following manual hand automatisms occur significantly more frequently in patients with neocortical temporal lobe epilepsy than in patients with mesial temporal lobe epilepsy. In contrast, patients with mesial temporal lobe epilepsy showed hand dystonia significantly more often in the course of their seizures than patients with neocortical temporal lobe epilepsy (Pfander et al., 2002). These may be important information, as different distinct epileptic circuits may be sensitive to different new therapeutic approaches such as deep brain stimulation.

1.6. Ictal lateralizing phenomena

Most patients with medically intractable focal epilepsy who are considered for epilepsy surgery show ictal lateralizing phenomena such as dystonic hand posturing, version, ictal vomiting, unilateral clonic seizures, postictal aphasia, and preserved

responsiveness during automatisms (Table 4). These phenomena have often not only lateralizing values, but reflect also the spread of epileptic activity in different brain areas.

Ictal dystonia

For example ictal limb dystonia (ID) is one of the best lateralizing signs and occurs contralateral to the seizure focus in TLE (Kotagal et al., 1989). It is regarded as a sign of involvement of the basal ganglia, as it was shown that ID is associated with a relative, short-term increase in the perfusion of putamen and caudate nucleus (striatum) contralateral to the dystonic limb (Mizobuchi et al., 2004; Newton et al., 1992; Shin et al., 2002). Furthermore, in patients with ID, interictal hypometabolism was observed in the striatal region ipsilateral to the seizure focus and contralateral to the dystonic limbs evidenced by fluorodeoxyglucose positron emission tomography (FDG–PET) (Dupont et al., 1998).

Ictal version

Contralateral head versions were shown to typically occur prior to secondary generalization in patients with focal (mostly temporal) epilepsy (O'Dwyer et al., 2007; Wyllie et al., 1986a). This appears to be due to the propagation of the seizure to the frontal eye field as electrical stimulation of this structure also elicits versive movements of the eyes and head to the opposite side (Godoy et al., 1990). If defined as forced and involuntary head movement resulting in unnatural positioning (Wyllie et al., 1986b), versive head movement displays a high positive predictive value for localization of a contralateral seizure onset (Bleasel et al., 1997; Chee et al., 1993; Steinhoff et al., 1998). In seizures with secondary generalization, the most common headturning pattern consists of an ipsilateral head turn occurring early in the seizure evolution and before contralateral versive head movement with regard to the hemisphere of seizure onset (Abou Khalil and Fakhoury, 1996). The controversy over the lateralizing significance of head movements may be related to the observation that in many patients in addition to contralateral head version, there is also ipsilateral head turning and no systematic difference has been made as to the sequence of the occurrence and character of the movement (Bleasel et al., 1997; Chee et al., 1993; Ochs et al., 1984; Robillard et al., 1983; Steinhoff et al., 1998). In the study of O'Dwyer, utilizing a quantitative method of movement analysis shows that ipsilateral head movements followed by contralateral head movements, occurring before secondary generalization have an excellent PPV (100%) for lateralization of the seizure onset (O'Dwyer et al., 2007).

Table 4: Lateralizing seizure phenomena

Lateralizing seizure phenomena	Hemisphere	Authors
Head and eye version	Contralateral	(Bleasel et al., 1997; Wyllie et al., 1986a)
Dystonic hand posturing	Contralateral	(Bleasel et al., 1997; Kotagal et al., 1989)
Figure 4 sign	Contralateral	(Kotagal et al., 2000)
Automatisms with preserved responsiveness	Nondominant	(Ebner et al., 1995; Noachtar et al., 1992)
Ictal speech	Nondominant	(Gabr et al., 1989)
Postictal aphasia	Dominant	(Gabr et al., 1989)
Ictal vomiting	Nondominant	(Krämer, 1997; Kramer et al., 1988)
Ictal spitting	Nondominant	(Voss et al., 1999)
Periictal urinary urge	Nondominant	(Baumgartner et al., 2000)
Postictal nose rubbing	Ipsilateral	(Leutmezer and Baumgartner, 2002)
Postictal coughing	Nondominant	(Wennberg, 2001)
Unilateral clonic seizure	Contralateral	(Jackson, 1890)
Unilateral tonic seizure	Contralateral	(Werhahn et al., 2000)
Unilateral eye blinking	Ipsilateral	(Benbadis et al., 1996; Henkel et al., 1999; Wada, 1980)

Conclusion: The semiological seizure classification of epileptic seizures, the course of seizure evolution and lateralizing signs takes into account the underlying affected brain regions and circuits which may be better localized and identified. This is mandatory for the selection of candidates for “novel” therapeutic approaches, like for deep brain stimulation and more generally for our understanding of the pathophysiology of seizures.

2. Epileptic syndromes

An epileptic syndrome is defined by the epileptic seizures occurring in a characteristic manner together with specific etiological, genetical, pathophysiological and phenomenological factors. In 1989 the ILAE defined different epileptic syndromes, which were differentiated in focal, generalized, neither focal nor generalized and special syndromes. Another discrimination factor was the underlying etiology. Idiopathic seizures are characterized by a genetic etiology with an age-specific onset. Symptomatic seizures have a known underlying etiology. When such an etiology is absent and they are not idiopathic they are called kryptogenic seizures. Actually, a revised form of classification of epileptic seizures and syndromes is in process (see also table 5: Classification of epileptic seizures and syndromes by the ILAE (www.ilae.org)). All available informations as imaging studies (MRI, PET, SPECT), seizure semiology and genetic analysis are included in the definition of epileptic syndromes.

Table 5 : Classification of epileptic syndromes by the ILAE

Classification of seizures	
GENERALIZED SEIZURES	
Tonic clonic (in any combination)	
Absence	1. Typical 2. Atypical 3. Absence with special features
Myoclonic absence	
Eyelid myoclonia	
Myoclonic	1. Myoclonic 2. Myoclonic atonic 3. Myoclonic tonic
Clonic	
Tonic	
Atonic	
Epileptic spasms	
FOCAL SEIZURES	
Descriptors of focal seizures	
1) According to severity	
a. Without impairment of consciousness/responsiveness	
i. With observable motor or autonomic components	
ii. Involving subjective sensory or psychic phenomena only	
b. With impairment of consciousness/responsiveness	
c. Becoming secondarily generalized	
2) According to putative site of origin	
a. With frontal lobe semiology	
b. With temporal lobe semiology	
c. With parietal lobe semiology	
d. With occipital lobe semiology	
e. With multi-lobar semiology	
f. Without localizing features	
3) According to elemental sequence of clinical features	

Electro-clinical syndromes and other epilepsies.

Electro-clinical syndromes

Neonatal period

Benign familial neonatal seizures (BFNS)

Early myoclonic encephalopathy (EME)

Ohtahara syndrome

Infancy

Migrating partial seizures of infancy

West syndrome

Myoclonic epilepsy in infancy (MEI)

Benign infantile seizures

Dravet syndrome

Myoclonic encephalopathy in nonprogressive disorders

Childhood

Febrile seizures plus (FS+) (can start in infancy)

Early onset benign childhood occipital epilepsy (Panayiotopoulos type)

Epilepsy with myoclonic astatic seizures

Benign childhood epilepsy with centrotemporal spikes (BCECTS)

Autosomal-dominant nocturnal frontal lobe epilepsy (ADNFLE)

Late onset childhood occipital epilepsy (Gastaut type)

Epilepsy with myoclonic absences

Lennox-Gastaut syndrome

Epileptic encephalopathy with continuous spike-and-wave during sleep (CSWS)
including: Landau-Kleffner syndrome (LKS)

Childhood absence epilepsy (CAE)

Adolescence - Adult

Juvenile absence epilepsy (JAE)

Juvenile myoclonic epilepsy (JME)

Progressive myoclonus epilepsies (PME)

Autosomal dominant partial epilepsy with auditory features (ADPEAF)

Other familial temporal lobe epilepsies

Epilepsy with generalized tonic-clonic seizures alone

Less Specific Age Relationship

Familial focal epilepsy with variable foci (childhood to adult)

Reflex epilepsies

Distinctive Constellations

Mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE with HS)

Rasmussen syndrome

Gelastic seizures with hypothalamic hamartoma

Epilepsies that *do not* fit into any of these diagnostic categories can be distinguished first on the basis of the presence or absence of a known structural or metabolic condition (presumed cause) and then on the basis of the primary mode of seizure onset (generalized versus focal).

Epilepsies attributed to structural-metabolic causes (by cause)

Malformations of Cortical development
Tuberous sclerosis complex
Tumors
Infections
Trauma
Peri-natal insults
Stroke
Etc

Epilepsies of unknown cause**Conditions with epileptic seizures that are traditionally not diagnosed as a form of epilepsy *per se*.**

Benign neonatal seizures (BNS)
Febrile seizures (FS)

In the following section, a short description of the focal epileptic syndromes which appear in the paper “Does ictal dystonia have an inhibitory effect on seizure propagation in focal epilepsies?” and in the PhD work is given.

2.1. Mesial temporal lobe epilepsy (mTLE)

Auras occurs in 5% of all patients with mTLE. It is often followed by dialeptic seizures and / or automotor seizures with oral and manual automatisms. Unilateral ictal dystonia occurs when seizure propagates to the basal ganglia. Ictal or postictal aphasia results, when the speech dominant hemisphere is involved. Secondary generalization is seen after seizure spread in the frontal lobe.

2.2. Neocortical temporal lobe epilepsy (nTLE)

may be distinguished from mTLE when auras include complex visual hallucinations, simple or complex acoustic hallucinations, vertigo or speech arrest (by involvement of the speech dominant hemisphere). Secondary generalization may occur after seizure spread in the frontal lobe.

2.3. Frontal lobe epilepsy (FLE)

May originate from the central region resulting in contralateral clonic convulsions, tonic phenomena or negative motor phenomena (Noachtar 1998). The involved topographic region of the central gyrus determinates which body part is affected. The seizure acitivity can spread as “Jacksonian March” from one body part to another. Seizures

from the supplemental motor parts are short (5-3 s) and are leading to tonic posturing with sudden on- and offset. Hypermotor seizures with bizarre automatisms and heavy motor involvement are seldom but occurs often during sleep. Frontolateral onset leads to an isolated conjugated bulbous deviation to the contralateral side. Seizure duration is short, patients are amnesic for the episode. Premotor origin is characterized by complex automatisms like body rocking, in some cases versive movements and bilateral increase of muscle tone occurs. Fronto orbital originating seizures have a diffuse beginning and ending, sometimes olfactory auras or epigastric auras occurs. Mostly complete amnesia for the event and high tendency of complex motor and whole body automatisms, early ictal urination and seizure spread to the temporal lobe is present.

2.4. Parietal lobe epilepsy (PLE)

have often versive movements, bilateral increase of the muscle tone, contralateral hyp- or paresthesias and acoustic sensations. They are characterized by seizure spread to the occipital lobe, temporal lobe or frontal lobe.

2.5. Occipital lobe epilepsy (OLE)

With a seizure onset zone in the occipital lobe results in visual hallucinations in form of flashlights or scotomias. When associative visual fields are involved this results in more complex visual hallucinations like seeing colours, micropsia, macropsia or strange complex scenes.

Conclusion. Epileptic syndromes are defined by all available informations including genetic data, etiology, imaging data and seizure semiology. In some of these syndromes the involvement of the basal ganglia has been described (see section of the Basal Ganglia). This may give additional clues for the selection of patients for DBS in epilepsy (see Discussion).

3. Status epilepticus

Status epilepticus is a medical emergency associated with significant morbidity and mortality. Based on clinical studies showing that single seizures rarely last longer than 5 minutes (Theodore et al., 1994), and on experimental evidence of irreversible neuronal damage caused by prolonged seizures (Meldrum, 1983), it has been suggested that the

operational definition of generalized tonic-clonic status epilepticus should be more than 5 minutes of continuous seizures or two or more discrete seizures between which recovery of consciousness is not regained. Status epilepticus escapes the control of seizure termination. It is currently under debate if seizure termination is due to depletion of activity of the seizure focus or structures maintaining epileptic activity or due to activation of an endogenous inhibitory system (Lado and Moshe, 2008; Ziemann et al., 2008). In principle, status epilepticus may occur in every epileptic syndrome and in every seizure type. Especially patients with ring chromosome 20 are suffering from many seizures often evolving into status epilepticus. In these patients a bilateral decrease in 18[F]fluoro-L-DOPA uptake in both putamen and caudate nucleus has been shown and it was suggested that the dysfunction of the striatal dopaminergic neurotransmission may impair seizure interruption (Biraben et al., 2004). If such involvement of the dopaminergic system are also responsible for the occurrence of status epilepticus in other patients or epileptic syndromes was to date not investigated.

Conclusion: Status epilepticus is a medical emergency, and can be considered as seizure activity that escapes endogenous control mechanisms. In patients with ring chromosome 20, a decrease in uptake of L-DOPA was described in the striatum. If such alterations of the basal ganglia are also involved in other forms of status epilepticus, is to date unknown.

4. Intractable epilepsy

Being able to define and study intractable epilepsy allows one to identify potential underlying causes, some perhaps modifiable, that could result in prevention of intractability and provide insight into the mechanisms and therefore help in the development of new therapeutic approaches. This is especially true for the development of new deep brain stimulation therapies. To date, candidates for such a new treatment are not only pharmacological intractable but also intractable for resective surgery treatments. Common components for a definition of intractability emerge from a number of recent studies in which intractability have been revised (Arts et al., 2004; Berg et al., 2003; Berg et al., 2001; Kwan and Brodie, 2000).

1. *AED failure.* The concept of “medically refractory” is defined with respect to a minimum number of administered drugs which were ineffective. As it is not

possible to test all available drugs in all possible combinations, some minimum threshold number of AED failure must be specified. There seems to be a growing consensus that failure of two drugs places a person in a category where it becomes highly unlikely that further AEDs will be successful to control seizures (Arts et al., 1999; Dlugos, 2001; Wiebe et al., 2001).

2. *Seizure occurrence.* It is under debate, if there is a minimum frequency at which seizures must occur to be considered intractable (Berg, 2001; Engel, 2004). Others define a minimum seizure remission in order not to qualify as intractable (Arts et al., 1999; Dlugos, 2001; Kwan and Brodie, 2000).
3. *Time dimension.* For seizure frequency, the seizures must be observed over some period of time. This period might be very variable. Another question is the timing during the course of the disorder. Evaluation is possible in a certain time of remission, or time after last follow up. Neither of these approaches considers the evolution of the seizure disorder up until that time.

An alternative approach might be to consider a constellation of criteria. Once those criteria will be met, the individual is considered intractable, regardless of when during the disorder the criteria are met and regardless of prior or subsequent outcome (Berg, 2001). It is important to note that epilepsy is a very heterogenous disorder with different clinical expressions, different underlying etiologies, different natural histories, and different implications for management and treatments (Berg and Kelly, 2006). For selection of candidates for “alternative” therapies, definition of “weak” criteria of intractability might result in a high probability of “false positive” selected patients.

Which patients are defined as intractable from a “classical” point of view and might be therefore a good candidate for new therapy options like DBS in epilepsy? Patient with focal epilepsies are considered as candidates for such therapies, when they are pharmaco-resistant without any option of resective surgical therapy after a presurgical EEG-video-monitoring. This can be caused by multiple seizure onset zones or involvement of eloquent cortex. In generalized epilepsies this might be patients with underlying syndromes who are associated with epileptic encephalopathies or catastrophic epilepsies, such as West, Lennox Gastaut, Dravet, and Landau-Kleffner syndromes. The seizures are highly refractory from the start and it is rare that these syndromes remit. If these patients are optimal candidates for deep brain stimulation and where they should be stimulated is unknown.

Conclusion: Patients with intractable epilepsies are a heterogenous population with different underlying epileptic syndromes. The selection of optimal candidates for new therapeutic approaches is mandatory, as patients with different syndromes may respond different successful to new therapeutic options.

5. Treatment of epilepsy

Regarding any form of treatments, primary therapy goals needs to be distinguished from secondary therapy goals. Primary therapy goals are to obtain seizure freedom. When this can not be achieved, a reduction of seizure frequency with as less as possible secondary side-effects should be obtained. Secondary therapy goals are the improvement of the psychosocial situation, especially reintegration into work. Another important goal is the prevention of secondary burden through injuries during the seizures and progression of illness with further decrease of memory function, as it is the case in hippocampal sclerosis, as well as the prevention of sudden unexpected death during a seizure (SUDEP). Treatment of associated disturbances such as psychiatric disorders is also mandatory. Nevertheless, all pharmacological and surgical treatments should be aimed at obtaining seizure freedom as this is crucial for an increase of the quality of life.

5.1. Pharmacological therapy

Initially, epilepsy therapy should be started as monotherapy according to a focal or generalized origin. Different medications can be choosen as first choice (see table 6).

Table 6: First choice of antiepileptic drugs (ordered alphabetically)

<u>Epilepsies with focal origin</u> <u>First choice:</u> Carbamazepine Gabapentine Lamotrigine Levetiracetam Oxcarbazepine Phenytoine Topiramate Valproid acid	<u>Second choice:</u> Clobazam Gabapentin Pregabalin Tiagabin Zonisamide
<u>Idiopathic generalized epilepsies</u> <u>First choice:</u> Lamotrigine Levetiracetam Phenytoine Topiramate Valproid acid When one of these five AEDs are contraindicated or incompatible Phenobarbital can be used.	<u>Second choice:</u> Clobazam Phenytoine

When monotherapy fails, another antiepileptic drug (AED) should be initiated as monotherapy or combined with a second AED (see table 6). In the combination or “add-on” therapy, a drug should preferentially be chosen with a different mechanism of action. However, that may result in an increase of side effects (Schmidt, 1982). The chance of seizure freedom with the second AED in monotherapy decrease to 10-15% and with the third AED to 4% (Kwan and Brodie, 2000) and is less likely with every new drug independent of the mechanism of action.

Pharmacoresistance is defined by insufficient seizure control with respect to a minimum number of AEDs tested (Kwan and Brodie, 2001). In clinical practice, this is the case after failure of 2-3 AEDs in mono- or add-on therapy with maximal tolerable

dosages. Therefore an evaluation for resective surgical therapy should be initiated in patients with focal epilepsies in a specialized EEG-Video-Monitoring Unit.

5.2. Resective surgical therapy

The basic requirements for a surgical treatment is the exact diagnosis of epilepsy. This also includes that non epileptic seizures are ruled out. Furthermore, it must have been proven that pharmacological treatment is not successful, i.e., that the compliance of the patient was correct and that the AEDs used fit to the epileptic syndrome of the patient. An AED is regarded as not successful after the dosage was increased up to intolerable side effects. In general within two years, especially for TLE, it is possible to prove that a pharmacological treatment was not successful. It has been shown that in TLE the resective surgical treatment is more efficient than a pharmacological treatment (Wiebe et al., 2001). That implements that the presurgical evaluation should be initiated without further delay to avoid neuropsychological and psychosocial burden (Jokeit, 2001)

Requirements for a resective surgical treatment are:

- proven diagnosis of epilepsy
- pharmacoresistance
- disability of the seizures
- resectable focus
- motivation of the patient
- no progressive etiology (exception Rasmussen encephalitis)
- high probability that seizure freedom increases the quality of life.

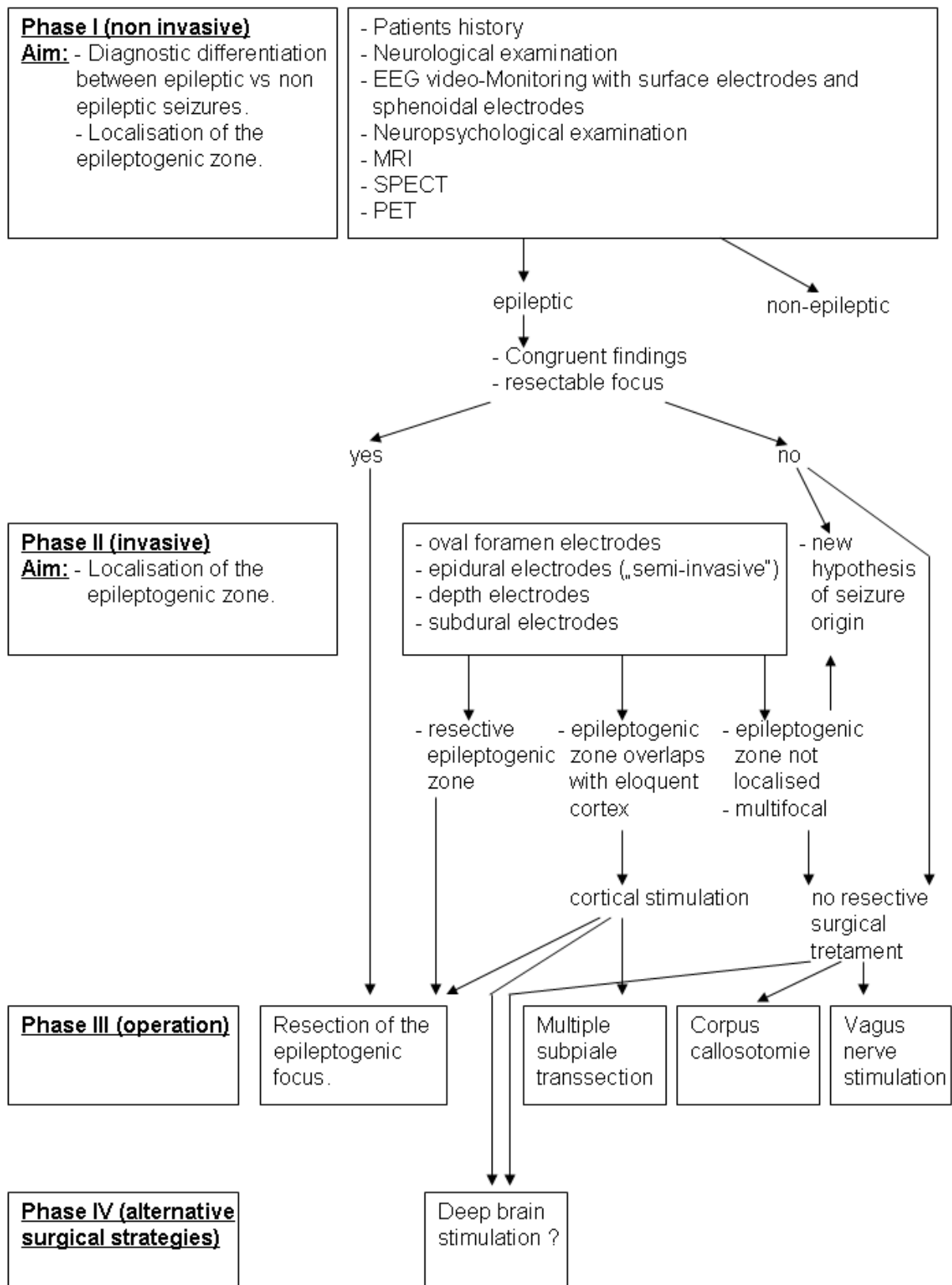
It has been shown that the prognosis is better when seizure freedom is achieved early. Single seizures may lead to impaired cognition in patients with left sided TLE (Jokeit et al., 2001). Especially in children, it is well accepted that early surgical treatment may have the opportunity to limit neuropsychological and psychosocial disadvantages as it is the case when the time-course to achieve seizure freedom is delayed (Lindsay et al., 1984). The success of a resective surgical treatment depends on how good the epileptogenic zone can be identified and fully removed, without injuries of functional important cortex areas (Awad et al., 1991). If it is not possible to resect the epileptogenic zone totally, a palliative improvement of seizure severity and frequency can be the aim, even if the results are less favorable (Wyllie et al., 1987).

Another conceptional approach of epilepsy surgery is to interrupt the seizure spread, although the results are less positive compared to a complete resection of the

epileptogenic zone (Fish et al., 1991). The transection of the corpus callosum (callosotomy) may be helpful to diminish seizures with severe falling as in the Lennox-Gastaud Syndrome. Similarly, subpial transections may interrupt seizure spread in Landau-Kleffner syndrome (Morrell et al., 1989). When non-invasive Video-EEG-Monitoring and the analysis of MRI, seizure semiology, EEG and neuropsychology reveals not congruent findings, an invasive EEG monitoring with subdural implanted electrodes or depth electrodes may help to identify the epileptogenic zone properly. Hereby, a cortical stimulation of the implanted electrodes is possible to distinguish seizure onset zones from eloquent cortex, whereas a resective surgical therapy would lead to functional impairment (Rosenow and Luders, 2001). Such overlap of eloquent cortex with seizure onset zones may be one of the reasons to consider new therapeutic approaches like deep brain stimulation. In focal epilepsies, other candidates for such therapies are patients in whom bilateral or multiple seizure onset zones have been detected by invasive EEG monitoring. Therefore, candidates for deep brain stimulation may suffer from different seizure types and epileptic syndromes and do not constitute a homogeneous population.

An overview of the presurgical proceedings is given in table 7.

Table 7: Presurgical epilepsy proceedings



5.3. Multiple subpial transection

The technique of multiple subpial transection was developed for patients in whom the epileptogenic zone is overlapping with eloquent cortices and resection of the focus is not possible (Morrell et al., 1989). The concept is to cut the horizontal cortical connections which are responsible for seizure propagation and to preserve the vertical descending axons to minimize the postoperative functional deficit (Kaufmann et al., 1996). In patients with multiple subpial transection plus resection, excellent outcome (>95% reduction in seizure frequency) was obtained in 87% of patients for generalized seizures, 68% for complex partial seizures, and 68% for simple partial seizures. For the patients who underwent multiple subpial transection without resection, the rate of excellent outcome was only slightly lower, at 71% for generalized, 62% for complex partial, and 63% for simple partial seizures (Spencer et al., 2002).

5.4. Callosotomy

Transection of the corpus callosum (callosotomy) may be considered for patients with medically intractable generalized epilepsies, suffering from a combination of different seizures. These include often tonic, atonic, generalized tonic clonic, absence and seldom focal seizures (Wyler, 1993). A realistic aim of that kind of surgery is the reduction of severe seizures, not the achievement of seizure freedom. Callosotomy often leads to a reduction of tonic and atonic seizures, known to be associated with falls and secondary injuries (Gates et al., 1984). Most of these patients suffer from mental retardation and have Lennox Gastaut Syndrome. A stepwise approach is considered, with a 2/3 transection of the anterior part of the corpus callosum in the first step. When lacking a clear benefit, a complete callosotomy can be performed without risk of a so-called “disconnection syndrome” (Wilson et al., 1982).

5.5. Neurostimulation

5.5.1. Vagus Nerve Stimulation (VNS)

Vagus nerve stimulation is to date the only approved stimulation therapy by the FDA (Amar et al., 2008) as it was proven to lead to a reduction in seizure frequency in generalized as well as in focal epilepsies. A seizure reduction up to 50% is reported in the 30 to 50% of the patients treated with VNS for several months or years (Ben Menachem et al., 1999). In about 10% of patients, a seizure reduction of more than 80% was observed (Ramsay et al., 1994). The antiepileptic effect is thought to be

transmitted through the nucleus tractus solitarius and parabrachial nucleus which projects to the limbic, autonomic, and reticular structures of the forebrain (Henry, 2002). It has been correlated to changes in the the noradrenergic and serotonergic neurotransmission systems of the brain and spinal cord, the amygdala, insula, hypothalamus, periaqueductal grey matter, and the thalamus (Vonck et al., 2001). These widespread, bilateral, and multisynaptic projections account for the possible multiple therapeutic mechanisms leading to a change in neurotransmission systems which takes place over months. Therefore, this technique is not an acute interruption of ongoing seizures but implements a chronic change which leads to the described changes. VNS is reasonable in patients who are not candidates for a resective surgical treatment. During the stimulation period hoarseness, local paresthesias, dyspnea and coughing may occur, but can be reduced by lowering the stimulation intensity. It has also been shown that VNS is leading to antidepressant and activation processes, which is probably due to the changes in serotonergic and noradrenergic neurotransmissions. This lead to initiate trials in pharmacoresistant depressive patients (Schlaepfer et al., 2008). As side effects are very low, it was proposed to perform VNS prior to callosotomy. However, seizure freedom is rarely achieved with VNS probably because candidates are mainly patients suffering from severe epileptic syndromes with a long history of seizures (Amar et al., 2008). Because surgery and preclinical evaluation are easy for VNS and because this therapy has lower rates of complications, new stimulation paradigms for deep brain stimulation which are certainly more risky, required better results than VNS. As VNS therapy is to date the only approved electrical stimulation therapy for epilepsy by the FDA, new therapies should be compared with this “gold standard” and aim to lead to seizure freedom. Seizure freedom is achieved in VNS therapy in very few patients but is important as it would result in substantially increase of quality of life.

5.5.2. Stimulation of the epileptic focus

Stimulation of the epileptic focus has been performed in the hippocampus or the cortex. Hippocampal stimulation was carried out in 10 patients who had undergone implantation of subdural or depth electrodes in the temporal region for investigation prior to temporal lobectomy. Bipolar high frequency stimulation at 130 Hz was applied continuously for 2-3 weeks. In 7 patients, complex partial and secondarily generalized seizures were

abolished after 6 days of stimulation. In three other patients one was seizure free after an 18 months follow-up whereas the others experienced seizure reduction of 73% and 86% (Velasco et al., 2001b). In another open case serie, three patients had a seizure reduction of 50% after a 3- to 6-month follow up period (Vonck et al., 2002). Two additional trials of hippocampal stimulation were conducted, leading to opposite results. In one double-blind study, the seizure outcome was significantly improved in all 9 patients over a long-term follow-up (Velasco et al., 2007a), which showed more than 95% seizure reduction in the 5 patients with normal MRI, and 50-70% seizure reduction in the 4 patients who had hippocampal sclerosis. It was suggested that beneficial effects of stimulation were associated with a high GABA tissue content and a low rate of cell loss (Cuellar-Herrera et al., 2004). By contrast, seizure frequency was reduced by only 15% in average in the 4 patients of the double-blind, multiple cross-over, randomized study of Tellez-Zenteno (Tellez-Zenteno et al., 2006). Currently, a randomized controlled trial of hippocampal stimulation for temporal lobe epilepsy (METTLE) is recruiting patients to determine whether unilateral hippocampal electrical stimulation is safe and more effective than simply implanting an electrode in the hippocampus without electrical stimulation, or treating with medical therapy alone, in patients with unilateral or bilateral mesial temporal lobe epilepsy (MTLE)

(<http://www.clinicaltrials.gov/ct2/show/NCT00717431?term=mettle&rank=1>).

The study is currently recruiting participants.

A prospective randomized controlled study of neurostimulation in the medial temporal lobe for patients with medically refractory medial temporal lobe epilepsy is also currently recruiting patients for a controlled randomized stimulation versus resection (CoRaStiR) study. Patients will be prospectively randomized to 3 different treatment arms:

Treatment group 1: patients who undergo medial temporal lobe resection. Treatment group 2: patients who receive immediate hippocampal neurostimulation. Treatment group 3: patients who are implanted with an intracranial electrode but in whom hippocampal neurostimulation is delayed for 6 months. Twelve months after inclusion unblinding will occur. Patients in group 2 and 3 will have the option to choose between continuing neurostimulation treatment or resective surgery

(<http://www.clinicaltrials.gov/ct2/show/NCT00431457?term=corastir&rank=1>).

This study is currently recruiting participants.

Cortical stimulation is generally used to map functions in eloquent brain. It is known that cortical stimulation can evoke focal after-discharges that may evolve into clinical seizures. It has been shown that afterdischarges elicited by electrical stimulation via subdural electrodes can be interrupted by the application of brief bursts of 50 Hz electrical stimulation through subdural electrode contacts (Lesser et al. 1984). An implantable, local closed-loop responsive neuro-stimulation system (RNS) has been developed (Neuropace, Inc., Mountain View, CA, USA) which consists in a cranially-implanted pulse generator, one or two quadripolar subdural strip or depth leads which are in connection with an external programming device (Fountas and Smith, 2007). Seizure detection, cortical stimulation, and clinical data obtained with the RNS system were recently provided for the first 4 patients. Based on the patients' seizure diaries and clinical follow-up (22-25 months), the implanted devices functioned at a high sensitivity for clinical seizure detection and reduction in seizure frequency, ranged from 50 to 75%. No adverse stimulation-induced side effects were noted, and no hardware malfunctions requiring explantation occurred. Generator replacements for battery depletion were required at 11, 17, and 20 months in 3 patients (Anderson et al., 2008). In the long-term safety and efficacy of the RNS system in adults with medically intractable partial onset seizures, the responder rate in 50 subjects was 27% for complex partial seizures, 65% for generalized tonic clonic seizures and 24% for total disabling seizures (simple partial motor, complex partial and generalized tonic clonic seizures. For the secondary evaluation over the most recent 84 days participation, the responder rate was 48% for all 60 patients. There were no serious unanticipated device-related adverse events, and responsive neurostimulation was well tolerated (Sun et al., 2008). Currently a RNS long-term treatment clinical investigation study is enrolling participants by invitation only to assess the ongoing safety and to evaluate the long-term efficacy of the Responsive Neurostimulator (RNS™) system as an adjunctive therapy in reducing the frequency of seizures in individuals 18 years of age or older with partial onset seizures that are refractory to two or more antiepileptic medications (<http://www.clinicaltrials.gov/ct2/show/NCT00572195?term=rns+stimulation&rank=1>).

5.5.3. Deep brain stimulation

Cooper was the first to propose stimulation of anteriomedial cerebellar cortex in the early 70s on the basis that stimulation of the cerebellum could improve generalized

seizure activity and focal limb seizures (Cooper et al., 1973). Uncontrolled human studies have shown suppression of a variety of seizures (Chkhenkeli et al., 2004), but no randomized controlled studies have been reported. Several deep brain targets have been considered so far among which the anterior and centromedian nuclei of the thalamus and the subthalamic nucleus appear as the most documented ones.

Thalamus

Different nuclei of the thalamus have been studied during the last 20 years to understand the physiopathology of epilepsy because many interaction pathways exist between these nuclei and the cortex. Several thalamic targets have been stimulated to suppress seizures, mainly the centromedian nucleus (CM) and the anterior nucleus (AN). There is limited proof from animal studies that stimulation of these structures can influence seizure threshold. However, there is clinical evidence that continuous stimulation of these targets in epileptic patients reduces seizure frequency and severity.

The CM is part of the reticulothalamocortical system mediating cerebral cortex excitability (Jasper, 1991), and has been suggested to participate in the modulation of vigilance states (Velasco et al., 1979).

Stimulation of the centromedian (CM) thalamus for epilepsy treatment in humans was first reported by Velasco et al (Velasco et al., 1987). In five patients with different epileptic syndromes they reported 60% to 90% improvement with high frequency stimulation of this part of the thalamus. Longer follow-up of 7 to 33 months revealed substantial reduction of generalized tonic clonic and atypical absence seizures (Velasco et al., 1995). The positive results on these seizure types were confirmed in Lennox Gastaud syndrome which showed the most significant suppression (Velasco et al., 2000b; Velasco et al., 2001a). The anticonvulsant effect of CM stimulation appears to persist for several months after discontinuating the stimulation. In contrast, CM stimulation was not effective in the management of patients with complex partial seizures and focal spikes in the temporal regions. A placebo controlled double-blind study was performed to assess the efficacy of CM stimulation. In six patients, there was an overall reduction of 30% of generalized seizures when the stimulator was on and a 8% reduction when the stimulator was off compared to baseline (Fisher et al., 1992). However, there was no statistical significant difference between the on and the off phases. The major difference between the two studies were the CM localisation

(physiological index of the Velasco group and anatomical stereotactic methods on the basis of identification of the anterior and posterior commissures in the Fisher group) and study design. In addition, the types of seizures was different : The Velasco's group reported subsequently a double-blind cross-over study in 13 patients and found that seizures were significantly reduced in the on and off phases. Two explanted patients had seizure recurrence compared to baseline levels, 4 and 6 month after explantation (Velasco et al., 2000b). In conclusion, there is yet no sufficient evidence to assess that chronic CM stimulation is safe and efficient. Further clinical double-blind studies as well as experimental approaches are necessary to determine the efficacy of CM stimulation with physiological localization of the stimulation electrodes and determination of long-lasting effects.

Another target for thalamus stimulation is AN. The AN of the thalamus receives projections from the hippocampus via the fornix, the mamillary bodies and the mamillo-thalamic fascicle of Vicq d'Azir and has outputs to the cingulate cortex and, via the cingulum, to the entorhinal cortex and back to the hippocampus. It appears to be in close interaction with the circuit of Papez which is often involved in some forms of epilepsies (e.g. temporal lobe epilepsies). AN therefore is central in the network which underlies limbic seizures and, as such, represents an attractive target for DBS in epileptic patients. For AN stimulation there have been several case series reported. Chronic stimulation of the AN in six patients with complex partial seizures without localizable focus reduced seizure frequency by more than 60% in five patients (Rosenow et al., 2002). In another study there was an improvement in seizure activity in three of five patients (Sussman, 1988). However, Lozano and Hamani reported a significant seizure reduction of 54% after insertion of the electrode, *without stimulation*, in five patients. There was no additional seizure reduction with the stimulation on or off (Lozano and Hamani, 2004). It remains unclear if the beneficial effects were produced exclusively by microthalamotomy, by stimulation, or by any implantation-stimulation interaction. This lead to the implementation of a prospective, randomized, double-blind trial using existing technology to test whether bilateral stimulation of the anterior nucleus of the thalamus can safely and effectively reduce seizure frequency in patients with epilepsy (SANTE clinical trial). This study includes enrollment of 158 patients at 17 sites in the U.S. A minimum of 102 patients will be implanted and monitored for 13 months following implant, with long-term follow-up until the device is approved or the study is stopped. Patients in the active group, who receive neurostimulation, will be monitored

for a reduction in seizure rates compared to the control group, who will not receive neurostimulation during the three-month double-blind phase. After the double-blind phase, all patients will receive neurostimulation. Candidates for the trial are adults with partial-onset epilepsy for whom at least three antiepileptic drugs have proven ineffective. They have had an average of six or more seizures per month. Candidates continue to receive their epilepsy medications while participating in the trial (<http://www.clinicaltrials.gov/ct2/show/NCT00101933?term=epilepsy+stimulation&rank=1>). The study is ongoing but not recruiting participants.

Subthalamic nucleus

Based on experimental studies and the first case series of deep brain stimulation in epilepsy, it has been shown that the basal ganglia are involved in the control of epileptic seizures. The results of open cases studies with stimulation of the subthamamic nucleus as well as other related nuclei in humans, are presented in the following section on the Basal Ganglia.

Conclusion: Deep brain stimulation (DBS) has been considered as an alternative therapy for some patients with to date intractable epilepsy, since subcorticals networks are assumed to control cortical excitability. Several clinical studies have targeted the thalamus and the basal ganglia structures with encouraging, yet incomplete, data. The current data suggests that DBS in epilepsy can be carried out safely in several brain structures. Further studies will be required to determine the optimal targets and the optimal parameters for the treatment of epilepsy according to the semiology of the seizures and epileptic syndrome.

B. The basal ganglia

6. Organization of the basal ganglia

The basal ganglia play a major role in the control of motor function, emotional and cognitive aspects (Packard and Cahill, 2001). The dysfunctioning of different parts of the basal ganglia is leading to some severe disabling motor diseases as Parkinson`s Disease, Chorea Huntington and hemiballism (Albin et al., 1989). The basal ganglia are integrating structures, modifying informations arising from the cerebral cortex, thalamus, hippocampus and amygdala. Their output structures control the excitability of brainstem areas, thalamic motor circuits, premotor, prefrontal and limbic circuits of the cerebral cortex. For the development of new therapeutic approaches, as DBS, the anatomical and physiological functions of the basal ganglia with its several components have a great importance. That is particularly true for the knowledge of the underlying circuits, which may be influenced to suppress seizures. Additionally, potential side-effects, through changes in pathological or physiological circuits, must be taken into account.

The term “basal ganglia” summarizes different subcortical structures and nuclei. These comprise the caudate nucleus and putamen (striatum), globus pallidus, subthalamic nucleus and substantia nigra (see figure 1).

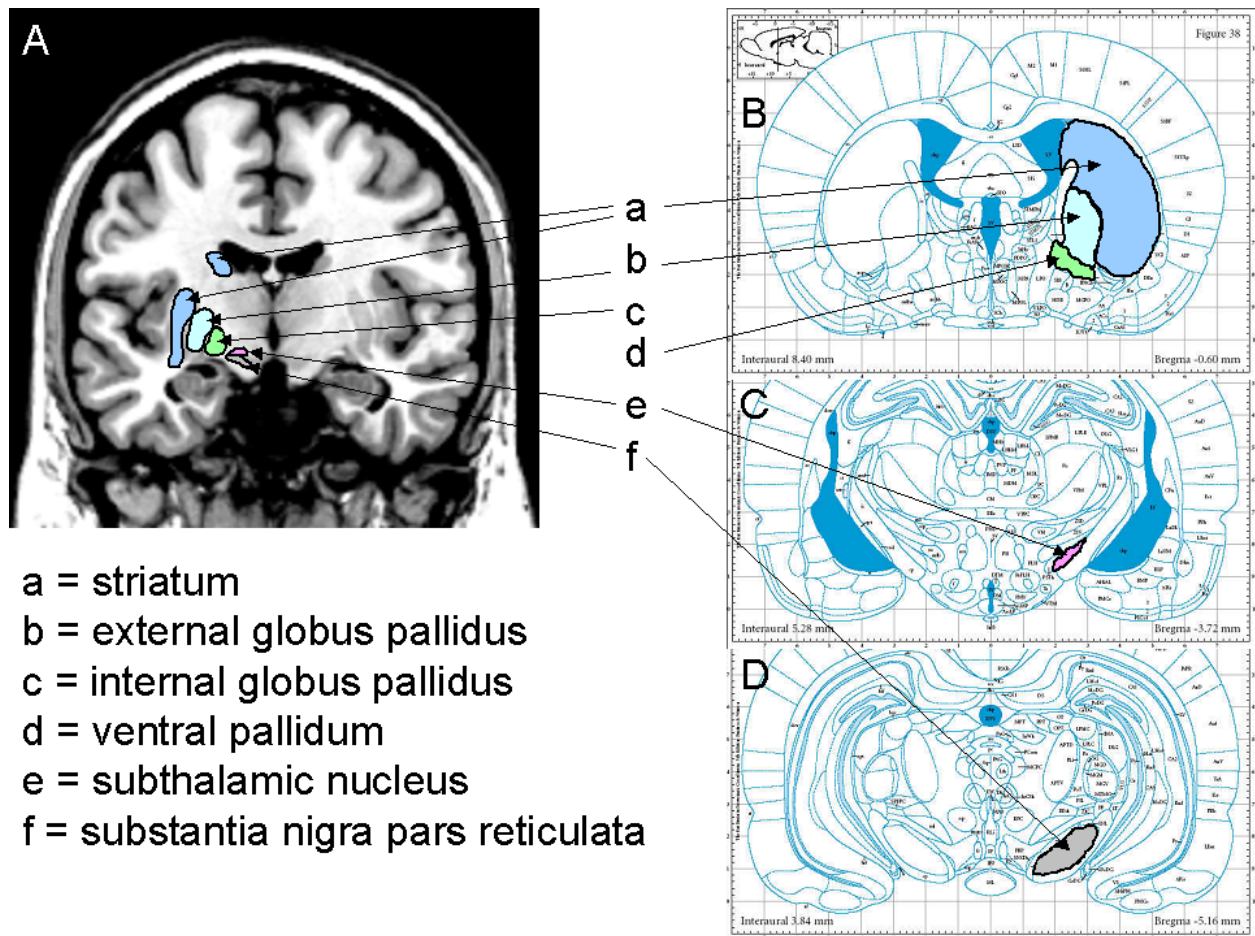
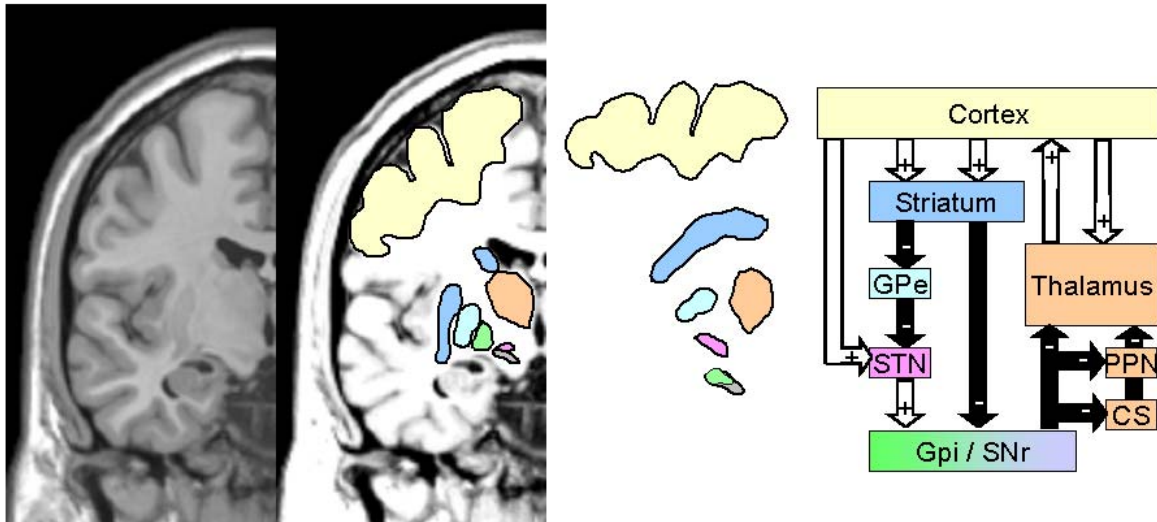


Figure 1: Overview of the basal ganglia in humans and rodents. Fig 1 A shows a coronar section of a human cerebral MRI indicating basal ganglia structures (a-c, e, f). Fig 1 B, C, D shows coronar sections of the rat brain (adapted from Paxinos and Watson, fifth edition 2005 (Paxinos and Watson, 2005)). Basal ganglia structures are indicated with a, b, c, d, e, f. The striatal complex in rodents is not divided into putamen and caudate like it is in humans (no internal capsule). The main output structures are the substantia nigra pars reticulata + entopeduncular nucleus in rodents and internal globus pallidus + substantia nigra pars reticulata in humans.

The principle organisation of the BG was first proposed by Alexander and Crutcher (1990) (Alexander and Crutcher, 1990). The unidirectional character of the major connections imposes on this system a definite functional polarity, the information being transmitted from an input stage to an output stage (see figure 2). The cerebral cortex determines the organisation of different functionnally separated pathways of the basal

ganglia, which is also represented in the thalamus. Parallel and serial cortico-striato-pallido-thalamo-cortical loops are involved, subserving sensorimotor, associative as well as limbic functions.



*Figure 2: Classical model of the basal ganglia with the distinct direct and indirect pathway. White arrows are excitatory, black arrows inhibitory. **GPe**=external Globus pallidus, **STN**=Subthalamic nucleus, **GPI**=internal globus pallidus, **SNr**=Substantia nigra pars reticulata, **CS**=superior colliculus, **PPN**=Pedunculo-pontine nucleus.*

Input of the basal ganglia: The main input structure of the BG is the striatum where the informations from the cerebral cortex, the intralaminar thalamic nuclei, the complex of the ventro-anterior, -medial and –lateral thalamus, the hippocampus and amygdala are processed (Hoshi et al., 2005; Kita and Kitai, 1990; Mink, 1996). The STN also receives direct projections from the frontal cortex (mainly motor and premotor areas) (Kunzle, 1978; Maurice et al., 1998a; Maurice et al., 1998b; Monakow et al., 1978; Ryan and Clark, 1992), of the parafascicular thalamus (Feger et al., 1994; Groenewegen et al., 1990; Mouroux et al., 1997; Sugimoto et al., 1983), and of the ventral pallidum (Maurice et al., 1997) and could be considered as the second major input structure of the BG. All the input to the BG are excitatory and glutamatergic (Di Chiara et al., 1979; Pollack, 2001).

Output of the basal ganglia: The output structures of the BG are the substantia nigra pars reticulata (SNr) and the internal part of the globus pallidus (GPi). The SNr and the GPi integrate information originating from most of the striatal regions (the caudate, putamen and core of the nucleus accumbens), as well as from the subthalamic nucleus (STN). They send projections to the thalamus (especially ventromedial (VM) thalamus of SNr projections and parafascicular thalamus of GPi projections) and ponto-mesencephalic structures like the superior colliculus, and the pedunculopontine nucleus of the tegmentum (Chevalier et al., 1985; Depaulis et al., 1990; Deransart et al., 1998b; Di Chiara et al., 1979; Parent, 1990). Altogether the thalamic nuclei targeted by the basal ganglia open this system onto a large portion of the frontal pole of the cortex, including motor, premotor, prefrontal and limbic areas (Chevalier et al., 1984; Deniau and Chevalier, 1984; Krout et al., 2001). Via the ascending projections of the brain stem nuclei (i.e., pedunculopontine nucleus), the basal ganglia exert a widespread influence on the cerebral cortex (Chevalier et al., 1984; Grantyn and Grantyn, 1982).

6.1. Organization of basal ganglia circuits

With its numerous connections, the basal ganglia receive inputs from forebrain structures known to be involved in the generation of seizures like the cerebral cortex, the thalamus, the amygdala and the hippocampus. The cortical informations are transmitted from the input to the output structures via three different pathways. :

1. A trans-striatal “direct” pathway, which connects the striatum direct with the output structures. When activated, this direct pathway results in a strong disinhibition of the thalamus and brainstem structures. Indeed, the neurons which project directly from the striatum to the SNr, are activated by the mainly cortical glutamatergic excitatory inputs. Because of their inhibitory (GABAergic) projection to the SNr they suppress the tonic inhibition of the thalamus and brainstem neurons, leading to a strong disinhibition or “relative” activation of the thalamus and brainstem structures.
2. A trans-striatal “indirect” pathway connecting the striatum with the output structures via the GPe and STN. In this pathway, the neurons from the cortex activate the striatum, which leads via its inhibitory GABAergic neurons to an inhibition of the GPe. The GABAergic neurons from the GPe influence the activity of the STN which leads to a disinhibition of the glutamatergic neurons of the

STN resulting in an activation of SNr neurons (Bevan et al., 2002; Maurice et al., 1998b). Recent studies indicating that cortical rhythmic activity leads to oscillations in the STN and the GPe, whereas the time-phase of these oscillations is controlled by reciprocal excitatory and inhibitory connections between both nuclei (Magill et al., 2000; Magill et al., 2001; Plenz and Kital, 1999).

3. A “hyperdirect” pathway connecting the cortex directly with the STN and the output structures (SNr and GPi). The excitatory corticosubthalamic neurons are at the origin of a direct activation of the STN. That leads to an activation of the SNr via its excitatory glutamateric neurons (Albin et al., 1989). Therefore the STN is a key relay structure of both the indirect trans-striatal and the “hyperdirect” pathway projecting to the output structures of the BG.

As these three different pathways are transmitting their information with different time delays, the result is a complex response of the SNr. An activation of the cortex is leading to a precece activation, or not, by the “hyperdirect” pathway, followed by an inhibition, or not, via the direct trans-striatal pathway and followed, or not, by an excitatory responses of the indirect trans-striatal pathway (Fujimoto and Kita, 1993; Kita, 1994; Ryan and Sanders, 1994) (see figure 3).

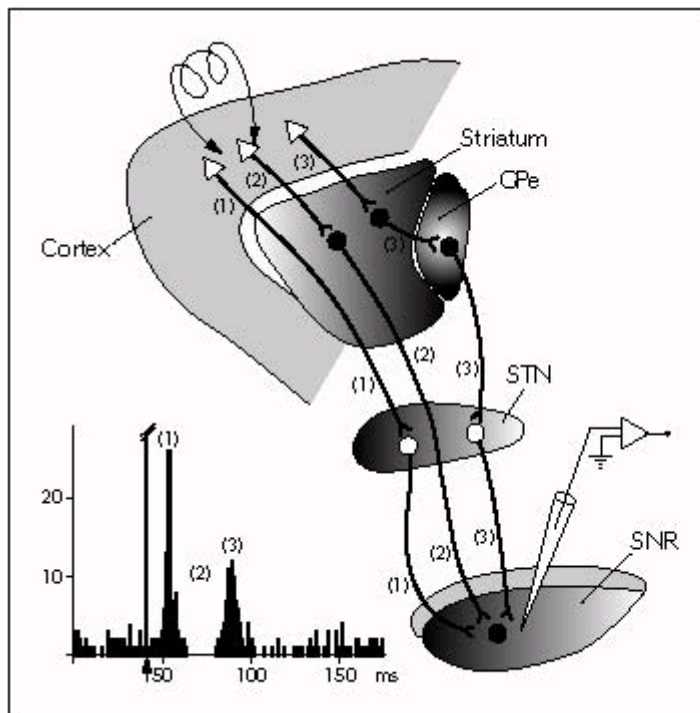


Figure 3: Typically triphasic excitatory-inhibitory-excitatory responses evoked in SNr cells following cortical stimulation. The short latency excitation results from activation in the fast cortico-subthalamo-nigral circuit (1), the inhibitory response results from activation of the direct cortico-striato-nigral circuit (2) and the late excitatory response results from the so-called indirect cortico-striato-pallido-subthalamonigral circuit (3), from (Slaght et al., 2002b).

Different modulations of these three pathways with their responses are possible (Maurice et al., 1999). The cell populations of the striatum, which are at the origin of the direct and indirect trans-striatal pathway, shares common inputs via their cortico- and thalamo-striatal inputs (Kawaguchi et al., 1990; Wu et al., 2000). The differences in the delay of both pathways suggests that the indirect pathway limits the duration of the inhibition caused by the direct pathway.

6.2. Organization of functional loop systems within the basal ganglia

Five different anatomical loop systems were identified, according to their cortical origin. Motor, oculomotor, dorsolateral prefrontal, lateral orbitofrontal and anterior cingulate loops. These are summarized as three functional systems comprising a sensorimotor, associative and limbic system (Alexander et al., 1986). It is possible that in the future

these different systems may contribute to different stimulation sites in DBS for epilepsy, according to the origin of the seizure onset zone and involvement of different functional cortex areas. Corticostriatal fibers arise from all cortical regions including the neocortex, mesiotemporal lobe and hippocampus (Goldman and Nauta, 1977; Kemp and Powell, 1970; Selemon and Goldman-Rakic, 1985). Main part of these corticostriatal projections evolve from the sensorimotor cortex (Groenewegen et al., 1997). Afferent fibers from the sensorimotor, associative and limbic cortex overlap in part in the striatum. However, these three functional characteristics are determining different parts of the striatum and are retained through the fiber course in the basal ganglia and the thalamus (Groenewegen et al., 1999). In the SNr this cortical mosaic is retained in an onion-like representation (Deniau et al., 1996). This functional anatomy in rodents is similar in primates (Kunzle, 1977; Parent and Hazrati, 1995).

The influence of the basal ganglia in modifying sensorimotor actions are numerous. It has been proposed that the STN has a key function in adapting motor function by modifying the disinhibiting signals of the striatum, leading to a “scaling” of movements (Mink and Thach, 1993). Furthermore, numerous studies suggest that the indirect trans-striatal pathway is influencing the profile of the activity of the output structures of the BG by parallel processing (Chevalier and Deniau, 1990; Chevalier et al., 1985; Deniau and Chevalier, 1985; Mailly et al., 2001). The interaction between different channels in the basal ganglia, may result in a selection of actions (Gurney et al., 2001; Redgrave et al., 1999). The activation of the trans-subthalamic pathway may limit the time of inhibition of the direct pathway and / or resulting in contrasting effects of the SNr by increasing the activity of SNr neurons. It has been proposed that an increase of the inhibition of the output structures is associated with the termination of movements and / or inhibition of not selected ones. The dysfunctioning of different pathways of the basal ganglia could therefore be at the origin of different movement disorders (Chesselet and Delfs, 1996). The negative motor symptoms in Parkinson`s disease are caused by an overactivity of the firing rate of STN neurons, which can be counteracted by the inhibitory actions of high frequency DBS of the STN (Lin et al., 2008). In contrast, unilateral infarction of the STN is leading to hemiballism with uncontrolled excessive movements of the contralateral limbs.

The basal ganglia may contribute to the spread of epileptic seizures, since the processing channels are not functionally segregated. One of the additional levels of

“communications” is provided by the dendritic arborisation of the SNr cells, which shares the inputs of neurons located in adjacent projecting fields (Slaght et al., 2002b). Furthermore, as epileptic seizures have often a complex activation of different parts of the brain leading to semiological different seizures, this may contribute to an activation of different channels of the basal ganglia. Therefore, seizure interruption by DBS or by some endogenous mechanisms of the basal ganglia should be seizure specific, target specific and intratarget specific to the functional loop activated by seizure spread.

Conclusion: As a major principle of organization of the basal ganglia, the unidirectional character of the major connections imposes on this system a definite functional polarity, the information being transmitted from an input stage to an output stage. The striatum and STN are the “input nuclei” whereas SNr and GPi the “output stations”. Due to their organisation with close connections, especially with cortical structures involved in ictiogenesis, their modulation appears likely to interfere with seizure occurrence.

7. Involvement of the basal ganglia in the control of epileptic seizures

7.1. Animal studies

7.1.1. Pharmacology

Pharmacological manipulations of the basal ganglia were shown to modulate seizures in several animal models of seizures or epilepsy. These modulatory effects can be observed at different levels of the BG. The common endpoint of all antiepileptic effects appears to result from an inhibition of the SNr which could lead in turn to a disinhibition of the thalamus or the superior colliculus and then to an inhibition of cortical excitability.

Striatum

Because the striatum receives important dopaminergic projections (Nauta and Domesick, 1984) and activation of such neurotransmission was shown to generally result in seizure suppression (al-Tajir and Starr, 1991; Ogren and Pakh, 1993), several authors have tested the effects of dopaminergic agonist directly into the striatum. Turski et al. presented evidence that bilateral application of picomole amounts of apomorphine (a dopamine agonist) into the striatum confers protection against seizures produced by pilocarpine (a cholinergic agonist) in rats. The anticonvulsant effect of apomorphine is topographically confined to the caudate-putamen, nucleus accumbens, and olfactory

tubercle. Bilateral application of nanomolar amounts of haloperidol (a dopamine antagonist) into the striatum or systemic application of haloperidol both lower the threshold for pilocarpine-induced seizures (Turski et al., 1988).

D1 receptors are located on neurons of the direct striato–nigral pathway, whereas D2 receptors are located on striatal cells belonging to the indirect pathway (Gerfen et al., 1990). D1 and D2 receptors belong to two different families of dopamine receptors and their activation by specific ligands results in opposite cellular effects. Activation of D1 receptors has excitatory effects (Jensen et al., 1996). On the contrary, activation of D2 receptors results in cell inhibition mediated by a decrease in adenylate cyclase activity through Gi proteins (Huff, 1996). Although there has been some controversies about this segregation of striatal outputs (Lester et al., 1993; Surmeier et al., 1992), recent results obtained with different technical approaches appear to confirm this hypothesis (Huang and Walters, 1996; Le Moine and Bloch, 1995; Robertson and Jian, 1995). Altogether, these data suggest that a release of dopamine in the striatum leads to inhibition of SNpr neurons by both pathways: dopamine acting on D1 receptors activates the direct inhibitory GABAergic striato–nigral pathway, whereas acting on D2 receptors it reduces the activity of the striato–pallidal pathway inducing an activation of the GABAergic pallido–sub-thalamic projection and then an inhibition of the subthalamo–nigral excitatory projection. Although the cellular details of activation of either D1 or D2 receptors in the striatum are not fully understood yet, several data have shown that intrastriatal application of D1 agonists increases the activity of the direct pathway (Akkal et al., 1996; Morari et al., 1996), whereas application of D2 agonists decreases the activity of the indirect pathway (Akkal et al., 1996; Starr, 1995; Yang and Mogenson, 1989). The role of the regulation of the dopaminergic system has been shown to have effects in both directions, seizure aggravation or seizure suppression, in a model of absence seizures in rats (GAERS). An increase in striatal dopaminergic transmission results in a dose-dependent suppression of absence seizures, whereas a decrease in dopamine transmission favours their occurrence (Deransart et al., 2000).

Subthalamic nucleus

The subthalamic nucleus (STN) plays a crucial role as a regulator of basal ganglia outflow by providing excitatory glutamatergic input into the two output nuclei of the basal ganglia, SNr, and entopeduncular nucleus (GPe in humans). In GAERS, an involvement

of nigral glutamatergic inputs in the control of seizures was demonstrated for the first time by Deransart et al. (Deransart et al., 1996). Indeed, blockade of nigral N-methyl-D-aspartate receptors in the SNr suppressed spontaneous generalized non-convulsive seizures in the rat, whereas blockade of non N-methyl-D-aspartate receptors was without effect. Furthermore, inhibition of the subthalamic projection by bilateral injections of a GABAergic agonist in the STN similarly suppressed absence seizures in the GAERS (Deransart et al., 1996), flurothyl seizures (Veliskova et al., 1996) and amygdala-kindled seizures (Deransart et al., 1998a). Bilateral, but not unilateral, injection of muscimol into STN protected against limbic motor seizures evoked either by intravenous bicuculline or by focal application of bicuculline into the anterior piriform cortex (area tempestas) (Dybdal and Gale, 2000).

Substantia nigra

It was shown in the 80's that pharmacological inhibition of the SNr decreased seizure activity in different models of epilepsy (for review, see (Depaulis et al., 1994). Iadarola and Gale were the first in 1982 to demonstrate that pharmacological potentiation of GABAergic transmission within the SNr, by bilateral microinjections by muscimol, a GABA agonist, suppressed seizures in different models of generalized convulsive seizures in the rat (Iadarola and Gale, 1982). These effects were confirmed in other models by other research groups in focal as well as in generalized models of epilepsy. Indeed, bilateral activation of GABAergic transmission by muscimol, or by gamma-vinyl GABA, an inhibitor of GABA transaminase, within the SN suppressed seizures in models like maximal electroshock seizures (Miller et al., 1987; Platt et al., 1987), systematically and intracerebrally applied chemical convulsants (Iadarola and Gale, 1982; Xu et al., 1991), fluorothyl inhalation (Xu et al., 1991 (Okada et al., 1986), kindling (Loscher et al., 1987; McNamara et al., 1984), systemic pilocarpine (Turski et al., 1986), or chemically-induced absence seizures (Depaulis et al., 1989; Iadarola and Gale, 1982). This was further confirmed in models of epilepsy like the genetic absence epilepsy rats from Strasbourg (GAERS) (Depaulis et al., 1988) where this suppressive effect on EEG discharges was demonstrated for the first time. Less data were obtained in models of focal seizures. When focal seizures were induced by stimulation at low frequency of the homolateral premotor cortex, unilateral injection of muscimol in the SNr decreased the threshold for seizures (Ono and Wada, 1987). On the contrary, in the model of kindling, bilateral injection of muscimol or gamma-vinyl GABA resulted in a

suppression of both afterdischarges and motor components whether the seizures resulted from stimulation of the amygdala, the lateral entorhinal cortex or olfactory structures (McNamara, 1994). In such model, the antiepileptic effects were obtained during acquisition of kindling as well as in fully kindled rats (Loscher et al., 1987)(Shin et al., 1987). However, muscimol injection, but not GABA uptake blockers (nipecotic acid or a spider venom neurotoxin FrPbA2), into the SNr abolished seizures induced by bicuculline injection in the dorsal hippocampus formation (Rodrigues et al., 2004). It is important to note that such suppression of seizures by inhibition of the SNr was not universal. Generalized tonic seizures induced by high doses of penylenetetrazol (PTZ) as well as tonic audiogenic seizures known to involve brainstem structures were not suppressed by bilateral activation of GABAergic transmission within the SNr (Depaulis et al., 1990b). This suggests that the so-called “nigral control of epilepsy” may depend on the underlying circuitry of seizure generation or propagation. This nigral control of epilepsy was suggested to mainly interfere with epileptic circuits involving forebrain structures (Depaulis et al., 1994; Deransart et al., 2001). All these pharmacological aspects mentioned here, referring to the SNr. However, the described effects may be also evoked by the SNc (Danover et al., 1998).

7.1.2. Electrophysiology

Striatum

Interictal or afterdischarges were recorded in different animal models of focal seizures in the ipsilateral striatum (Faeth et al., 1954; Neafsey et al., 1979; Udvarhelyi and Walker, 1965).

Striatal output neurons do not fire during absence seizures probably because of an increase in membrane Cl conductance, which is temporally correlated with bursts of action potentials in striatal GABAergic interneurons (Slaght et al., 2004). It was shown with intra- and extracellular recordings that interictal action potential discharge in striatal output neurons irregularly, which was transiently interrupted during SWDs. This lack of firing was associated with subthreshold rhythmic depolarizations superimposed on a tonic hyperpolarization during the cortical SWDs. It was discussed, that this effect could be explained by a cessation of excitatory synaptic activity in striatal output neurons resulting from a transition in firing of the cortical afferents (Slaght et al., 2004). The strong connectivity between cortical neurons and striatal output neurons is increased by

findings that suggest that synaptic oscillations in striatal output neurons during SWDs mainly result from rhythmic synchronized discharges in their cortical afferents (Charpier et al., 1999; Kawaguchi et al., 1995; Kincaid et al., 1998). These findings reinforce the hypothesis that electrical stimulation of deep brain structures may influence the cortex via antidromic pathways. A rebound of excitation of striatal output neurons was observed at the end of cortical SWDs, which is consistent with the decrease of SNr activity at the end of cortical paroxysms (Deransart et al., 2003) and could contribute to the seizure termination.

Subthalamic nucleus

Paz et al have shown in GAERS that the propagation of cortical paroxysms through the cortical-subthalamo-pallidal pathway generates a bursting pattern in the STN that might produce a powerful phasic synaptic excitation of the basal ganglia output nuclei (Paz et al., 2005). This pattern of electrical events in the STN is very similar to that observed after electrical stimulation of the motor cortex (Kita, 1994; Kitai and Deniau, 1981). The synchronized rhythmic bursting of STN neurons during absence seizures together with the lack of action potential firing of striatal projection neurons suggests a change between excitation and inhibition in the basal ganglia output nuclei. That might lead to a reinforcement of synaptic excitation originating from the STN (Paz et al., 2005). The termination of seizures could be initiated by the recovery of the irregular, desynchronized, firing in STN neurons at the end of SWDs, together with the rebound of excitation in striatal projection neurons (Slaght et al., 2004). That would lead to a rebalancement between excitation and inhibition in the basal ganglia output nuclei, and could initiate the postictal decrease in the activity of nigrothalamic neurons (Deransart et al., 2003) and so play an important role in the participation of seizure termination (Paz et al., 2005).

The involvement of basal ganglia was also shown in focal models of epilepsy. In amygdala kindled seizures the development of kindling is associated with recruitment of SNr neurons into a seizure propagating network (Bonhaus et al., 1991). In a model of penicillin-induced focal cortical epileptiform discharges it was suggested that the SN may be a prominent element of the pathway involved in the spread and generalization of cortical epileptiform activity (Kaniff et al., 1983).

Substantia nigra

It was shown that the SNr controls the thalamus and superior colliculus neuronal activity (Chevalier and Deniau, 1990). This is especially correct for the ventro-medial (VM), parafascicular / centromedian (PF/CM), which receives direct and indirect projections of the SNr and are not directly involved in the generation of SWD as it is the case for the relais nuclei of the thalamus like ventral posterior (VP), ventral posterior lateral (VPL). In a genetic model of absence epilepsy (GAERS) single-unit analysis showed that the firing rate in the SNr decreased rapidly during the last second of the seizure (Deransart et al., 2003). Pharmacological blockade of glutamatergic transmission in the SNr increased the rate of discharge in VM thalamic cells and led to an irregular tonic firing pattern correlated with an interruption of cortical SWDs (Paz et al., 2007). This blockade of ictal activity was associated in cortical neurons with a membrane hyperpolarization and a decrease in input resistance (Paz et al., 2007). The rebound of excitation of striatonigral neurons at seizure termination (Slaght et al., 2004) would be responsible for the decrease of firing in nigrothalamic neurons (Deransart et al., 2003). Thus the subsequent tonic firing in the VM thalamocortical neurons through a disinhibiting process, might contribute to the cortical desynchronization (Glenn and Steriade, 1982).

7.1.3. Metabolism

Several authors suggested that the involvement of basal ganglia circuits by seizure propagation and / or triggering of the control circuits, may result in long term modifications of the dopamine neurotransmission system. Indeed, in fully amygdala-kindled rats, a decrease in presynaptic dopamine turnover has been demonstrated in the the ipsilateral nucleus accumbens by microdialysis (Rada and Hernandez, 1990), as well as an increase in D2 receptor binding and mRNA expression (Gelbard and Applegate, 1994). Most modifications concerning the dopaminergic system have been reported in models of induced convulsive seizures and the motor patterns of the convulsions may also interfere with the dopaminergic neurotransmission (Deransart and Depaulis, 2002).

Measurements of glucose uptake have been performed to detect alterations in brain metabolism during seizures. An increase in glucose uptake as a sign of increased activation was seen in different models of epilepsy. In kindled rats, glucose uptake increased in the SNr after the appearance of generalized motor seizures (Engel et al.,

1978). An additional increase was observed in the globus pallidus after systemic administration of soman, penicillin, pentylentetrazol, picrotoxin or bicuculline (Ben-Ari et al., 1981). After status epilepticus, evoked by pilocarpine injection a rise of glucose metabolism was also seen in the caudate (Fernandes et al., 1999). However, when the status was induced by kainic acid no changes in the SNr were observed, but prominent increases were observed in the ventral putamen and ncl. accumbens (Ben-Ari et al., 1981). Interestingly it could be shown, that the involvement of the basal ganglia depends on the seizure type. In the continuous amygdala kindling model, seizures with mild behavioural changes showed an increase in the ncl. accumbens. Generalized seizures in this model were associated with increase in glucose metabolism in the striatum and the SNr. However these data do not allow further conclusion whether these changes are indicators of an active generating process or changes of passive propagation. Furthermore the 2-deoxy-glucose procedure has not a sufficient time resolution to determine the time course of seizure propagation. This is different when local cerebral blood flow is measured using the quantitative [^{14}C]iodoantipyrine autoradiographic technique. In sub-clinical seizures of amygdala kindled rats an increase of blood flow was seen in the stimulated target at early ictal time (injection of the tracer 15 sec before seizure induction) and the SN (Chassagnon et al., 2006). Compared to human SPECT studies, this work confirms that some ictal hyperperfused areas belong to the spreading network rather than to the epileptogenic zone, as it was seen that clinical evident seizures (stage 1 seizures) lead to an increase in several subcortical structures like the piriform cortex, substantia nigra, ventral tegmental area, cerebellum and bilaterally in several limbic and subcortical structures, excepted in hippocampus and pallidum (Chassagnon et al., 2006). These findings show that in focal epilepsies the SN is involved early after amygdala stimulation, and that even subclinical seizures are propagated to remote subcortical structures.

7.1.4. Deep brain stimulation of the basal ganglia

Because of the very coherent multidisciplinary data suggesting a critical role of the basal ganglia in the control of epileptic seizures, there have been several experimental attempts to “reinforce” the inhibitory control of the basal ganglia by electrical stimulation of different brain structures.

Stimulation of the caudate nucleus

In different animal models, an inhibition of epileptic activity was reported following low-frequency (5-25 Hz) electrical stimulations of the caudate nucleus (La Grutta et al., 1971; La Grutta and Sabatino, 1988; Psatta, 1983). This effect was suggested to be mediated through an hyperpolarization of cortical neurons by activation of the striatum (Klee and Lux, 1962). The positive effects in suppression of limbic seizures may be due to the influence of subcortical loops including the substantia nigra (Amato et al., 1981). This is furthermore highlighted by the effect, that especially low frequency stimulation (4-8 Hz), which is presumed to be activating, lead to a decrease of epileptic activity. By contrast, high-frequency stimulations (>30 Hz) of the striatum, which are regarded as mainly inhibiting, increased seizures in the aluminium-hydroxide model of motor seizures in the monkey (Oakley and Ojemann, 1982). This is coherent with the suppression of seizures seen in epileptic patients following similar stimulations (Chkhenkeli and Chkhenkeli, 1997).

Stimulation of the subthalamic nucleus

It was first shown in the GAERS that bilateral 130 Hz stimulation of the STN leads to an acute interruption of generalized absence seizures (Vercueil et al., 1998). This antiepileptic effect was also reported in the model of fluorothyl induced seizures, (Lado et al., 2003) and unilateral STN DBS showed significant suppression of the secondary generalization of seizures induced by systemic kainic acid injections (Usui et al., 2005). These studies were performed, using the parameters which were efficacious in the treatment of Parkinson`s Disease (i.e., 130 Hz, 60 μ s of pulse). However, no parametric studies for these antiepileptic effects were ever conducted and neither chronic nor continuous stimulation were tested. The mechanisms involved by the anticonvulsant effect of STN stimulation was studied by Zhang et al. (Zhang et al., 2008) in epileptic animals (after systemic administration of kainic acid) and non epileptic controls. Electrical stimulation 130 Hz for 1 h of the STN induced increases in GABA content in the SNr of each group, while GABA remained stable in the GP. The extracellular GABA level in the epileptic group was significantly higher than that of the normal group. The GABA-elevating effects in the SNr were slightly greater at 260 Hz than 130 Hz. In addition, the frequency of 130 Hz provoked the maximum increase in Glu contents both in the GP and SNr, whereas 260 Hz had less effect (Zhang et al., 2008). Such an increase in normal rats of extracellular glutamate levels in the GP and the SNr, whereas

GABA was increased only in the SNr, following STN stimulation with 130 Hz was also reported by Windels and colleagues (Windels et al., 2000) in normal rats. When applying electrical stimulation at the STN at various frequencies (10, 60, 130, and 350 Hz) in normal rats, the results show that, for Glutamate, the amplitude of increase detected in GP and SNr is maximal at 130 Hz and is maintained at 350 Hz. No modifications of GABA were observed in GP whatever the frequency applied, whereas, in SNr, GABA increased from 60 to 350 Hz (Windels et al., 2003). More recently new insights in the mechanism of DBS were obtained using an optogenetic approach which allows to inhibit or excite targeted neurons in the STN selectively. It could be shown, that neither inhibition nor excitation of the STN neurons had positive effects on relief of the parkinsonian symptoms in parkinsonian rats. Control of afferent axons in the STN led to the suspected positive effects. Furthermore selective optic stimulation of layer V neurons in the primary motor cortex M1 showed similar therapeutic effects. These M1 layer V neurons could be antidromically recruited by optical stimulation of the STN (Gradinaru et al., 2009). If such effects are restricted to the pathophysiology of Parkinson's disease or whether they could be applied also for other animal models is to date not answered. However, clinical data suggests that such a mechanism of controlling layer V neurons in the primary cortex could also play a positive role in DBS for seizure suppression (see chapter IV Discussion, selection of optimal candidates for DBS in epilepsy by localization of the seizure focus).

Stimulation of the substantia nigra pars reticulata

In the model of fluoroethyl-induced seizures, bilateral stimulation of the SNr at 130 Hz produced a significant increase in the seizure threshold for clonic fluoroethyl seizures (Velisek et al., 2002). Unilateral SNr DBS was less effective than STN stimulation in suppression of secondary generalization of limbic seizures (Usui et al., 2005). It was also shown that DBS of SNr, if correctly timed with the onset of amygdala kindling, may exert long lasting effects on the networks and may prevent the recurrence of kindled seizures (Shi et al., 2006). In a model of temporal lobe epilepsy induced by injection of kainate acid into the hippocampus in mice, bilateral stimulation of the SNr at 130 Hz, interrupted spontaneous seizures (Deransart, 2004). Overall, it is important to note that these antiepileptic effects (increase in thresholds, blockade of ongoing seizure) were mainly observed when the electrical stimulation was applied at seizure onset.

Conclusion: Altogether, experimental data obtained from animal studies support the existence of an endogenous system controlling epileptic seizures. This remote control system appears to be independent from the networks generating seizures and involve the basal ganglia. In most of the animal model of epileptic seizures investigated so far, all the manipulations in the BG inducing a decreased activity in the SNr have antiepileptic effects. The SNr appears as a key structure in this control and was recently targeted in clinical studies.

7.2. Clinical studies

Based on the experimental data (see above), and the neurosurgical experience of DBS in Parkinson`s disease, the first target of DBS in epilepsy was the STN. The increasing evidence of the role of the basal ganglia was supported by clinical studies investigating pharmacological, electrophysiological and imaging aspects.

7.2.1. Pharmacology

Dopamine is a key neurotransmitter in basal ganglia circuits. A dopamine deficiency is resulting in the development of idiopathic Parkinson`s Disease. Epidemiologic studies suggest that the coincidence of idiopathic Parkinson`s Disease and epilepsy compared to an age-matched normal population is remarkably low (Bodenmann et al., 2001; Hauser et al., 1991; Li et al., 1985). For many years, cases have been reported showing an inverse relationship between epilepsy and parkinsonism, with seizure reduction or even seizure freedom as the parkinsonian state developed (De Angelis and Vizioli, 1984; Vercueil, 2000). This may be due to differences in the influence of intracortical inhibition, leading to synchronization of large-scale activities which is reduced through dopamine deprivation (Brown and Marsden, 1984). However it is also possible that the drug treatment for idiopathic Parkinson`s Disease, mainly dopaminergic drugs, may suppress seizures. Indeed, Levodopa was studied in patients with progressive myoclonic epilepsy (Mervaala et al., 1990) or photosensitivity (Quesney et al., 1981). In the study by Mervaala, apomorphine blocked the epileptic photosensitivity in all patients

and also reduced intention myoclonus in a patient with Baltic progressive myoclonus epilepsy. There is a common deficit of dopaminergic inhibitory neurotransmission at the level of the striate cortex in patients with progressive myoclonus epilepsy, regardless of the nature of the specific underlying neuropathologic process (Mervaala et al., 1990). Apomorphine, a mixed dopamine agonist, transiently blocked the response of photosensitivity in patients with generalized seizures. However, the rate of generalized SWD were not influenced. Nevertheless, in the daily clinical practice, dopamine agonists are not used for treatment of epilepsy, even if numerous animal studies had shown a beneficial effect (see above chapter 7.1.1. Involvement of the basal ganglia in the control of epileptic seizures → Animal studies → *Pharmacology* → Striatum). Changes in dopaminergic tone, as evidenced by clinical imaging studies in humans (see “Imaging” thereafter), and in animal studies by pharmacological alterations (Deransart et al., 2000), have also been reported recently in the literature to play a crucial role in seizure modulation.

7.2.2. Electrophysiology

There is good evidence from electrophysiological recordings in human patients, that the epileptic activity is transmitted to the basal ganglia (Rektor et al., 2002; Vercueil and Hirsch, 2002; Semah et al. 2002). However, no epileptic interictal or ictal discharges were noticed in the putamen in patients with TLE investigated with depth electrodes. The spread of epileptic activity to other cortical structures was associated with slowing of basal ganglia EEG activity (Rektor et al., 2002). Epileptiform activity has been recorded directly from the STN in association with scalp recordings in patients, who underwent stereotactical implantation of depth electrodes in the STN for the first clinical trials of DBS in epilepsy (Benabid et al., 2002; Chabardes et al., 2002; Dinner et al., 2002; Loddenkemper et al., 2001). In a patient with temporal lobe epilepsy and subthalamic stimulators implanted to treat Parkinson's disease, temporal and frontotemporal spikes were observed in the EEG. Temporal spikes spread to the STN in 40% of cases, involving simultaneously all contacts. Frontotemporal spikes showed more frequent STN propagation (70%), shorter delays, and progressive spread from ventral to dorsal contacts than temporal spikes. These results suggest that a direct fronto-subthalamic pathway might account for the fast propagation of the frontotemporal spikes to the ventral STN (Urrestarazu et al., 2009). These data suggest that especially seizure arising from the frontal lobe with its strong connections to the basal ganglia

might be prone for deep brain stimulation in epilepsy. Kuba et al. investigated ictal EEG in the putamen and the temporal and frontal lobes during contralateral ictal limb dystonia (ID) with invasive intracerebral and/or subdural electrodes, in patients with temporal lobe epilepsy. Slow EEG-activity was recorded in the putamen during ID. Several cortical regions were involved in the ictal discharge, within both the contralateral temporal and frontal lobes. Although there are some non-specific changes in the putamen contralateral to ID, the changes were never epileptic in type (Kuba et al., 2003). The putamen probably collaborates in the genesis of ID, but does not generate the epileptic discharge during its course.

7.2.3. Imaging

With the opportunity of functional brain imaging using different binding tracers in the field of nuclear medicine, the involvement of the basal ganglia in some epileptic syndromes or seizures, has been increased during the last years.

Imaging of cerebral blood flow and glucose metabolism

Different investigators showed that ictal dystonia is associated with a relative, short-term increase in the perfusion of the basal ganglia contralateral to the dystonic limb (Mizobuchi et al., 2004; Newton et al., 1992; Shin et al., 2002). Such ictal increase in cerebral blood flow measured with an increased uptake of the SPECT tracer indicates not only the seizure onset zone, but also the involvement of activated and hyperperfused subcortical structures. Furthermore, in patients with ictal dystonia, interictal hypometabolism was observed in the striatal region using [18F] fluorodeoxyglucose positron emission tomography (FDG-PET) (Dupont et al., 1998). Such changes show that these structures are altered in their metabolic function during the interictal period. They don't reflect an activation or involvement in seizure spread patterns but a general involvement of such subcortical structures in the process of the epileptic disorder. To date it remains unknown if such an involvement reflects the cause or consequence of the disorder. More recently, a negative correlation between the occurrence of dystonia and bilateral tonic or clonic behaviors was shown in a group of patients with temporal lobe epilepsy (Cleto Dal-Col et al., 2008). The presence of dystonia (associated with basal ganglia involvement) could be the expression of involvement of intrinsic mechanism of seizure termination. Glucose metabolism in the caudate and lentiform nuclei did not show any correlation with seizure duration or rate of

secondary generalization in a group of intractable frontal and temporal epilepsies (Benedek et al., 2004). Comparing pre- and postoperative FDG-PETs showed that postoperative glucose metabolism decreased in the caudate nucleus in the hemisphere ipsilateral to the hippocampal seizure focus. This may be related to a permanent loss of afferents from resected anterior-mesial temporal structures (Joo et al., 2005).

Imaging of the dopaminergic system

The first clinical description of the involvement of the basal ganglia on the severity of an epileptic syndrome was done by Biraben et al. who reported a bilateral decrease in ^{18}F fluoro-L-DOPA uptake in both putamen and caudate nucleus in patients with ring chromosome 20. These patients have long-lasting generalized seizures evolving very often into a status epilepticus and it was suggested that the dysfunction of the striatal dopaminergic neurotransmission may impair seizure interruption (Biraben et al., 2004). Such a decrease in ^{18}F fluoro-L-dopa uptake in the basal ganglia was also described in patients with refractory epilepsy (Bouilleret et al., 2005). Additionally to the patients with ring chromosome 20, patients with resistant generalized “absence-like” epilepsy and with drug-resistant temporal lobe epilepsy with hippocampal sclerosis, showed a decreased uptake of ^{18}F -fluoro-L-DOPA. The decreased ^{18}F -fluoro-L-DOPA uptake provided direct evidence that the BG, and especially the striatum, is involved in human epilepsy. In TLE patients, ^{18}F fluoro-L-dopa uptake was reduced to the same extent in caudate and putamen in both cerebral hemispheres as well as in the SN. These dopaminergic functional alterations occurred without any glucose metabolism changes in these areas. This study provided support for dopaminergic neurotransmission involvement in temporal lobe epilepsy (Bouilleret et al., 2008). Furthermore the extrastriatal dopaminergic system is altered in focal epilepsies with reduced D2/D3-receptor binding in the epileptogenic temporal lobe (Werhahn et al., 2006). Mutations of the neuronal nicotinic acetylcholine (nACh) receptor identified in patients with autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) lead to increased sensitivity to ACh. As activation of presynaptic nicotinic receptors increases the release of dopamine in the striatum and the prefrontal regions, Fedi et al. tested the hypothesis, that the mutation of the nACh receptor affects dopaminergic transmission. A reduced D(1) receptor binding was found in these patients in the putamen, and may represent increased extracellular dopamine levels or, more likely, receptor downregulation. The authors concluded that alterations in mesostriatal dopaminergic circuits may contribute to

nocturnal paroxysmal motor activity in autosomal dominant nocturnal frontal lobe epilepsy (Fedi et al., 2008). In idiopathic generalized epilepsies an involvement of the basal ganglia was also noted. In a volumetric MRI study, patients, with tonic clonic seizures as the only seizure type, exhibited elevated frontal lobe fraction of cerebral spinal fluid and reduced fraction of gray matter in the frontal, parietal, temporal cortex, thalamus, and cerebellum. The thalamus and cerebellum also showed reduced volumes, as did the caudate and putamen (Ciumas and Savic, 2006). In juvenile myoclonic epilepsy, the dopamine signaling seemed impaired in the target regions for dopaminergic neurons (the striatum and frontal lobe), and can be related to several interictal dysfunctions in juvenile myoclonic epilepsy (Ciumas and Savic, 2006; Ciumas et al., 2008). In TLE patients with refractory epilepsy glucose metabolism was unchanged in the caudate and putamen (Bouilleret et al. 2008). These data shows that epilepsy is not only related to the epileptogenic cortical focus but reflects a network disorder in which the harmony of cortical and subcortical pathways are interrupted or disturbed.

7.2.4. Deep brain stimulation

Stimulation of the caudate nucleus

The first to suggest a potential effect of striatal stimulation in epileptic patients were Sramka and colleagues (Sramka et al., 1980; Sramka et al., 1976) and Chkhenkeli and his group (Chkhenkeli and Chkhenkeli, 1997). A decrease in focal and generalized interictal discharges was observed among 57 patients who were stimulated with low frequency (4-6 Hz) in the CN (Chkhenkeli and Chkhenkeli, 1997). Unfortunately, the effects on seizures frequency of this open study were not assessed. Interestingly, epileptic activity was worsened by stimulating the CN at high frequencies. As low frequency stimulation is regarded as mainly excitatory, and high frequency stimulation as inhibitory, these data are in good agreement with the concept of the nigral control of epilepsy, since activation of the striatum inhibits SNr via its direct GABAergic projections, whereas its inhibition leads to the reverse effect. Although one would expect low frequency stimulations to inhibit the SNr through the direct striatonigral pathways, activation of the striatum through the indirect striato-nigral pathway would lead to an activation of the SNr. It is possible that the direct pathway dominates this effect as the transmission is faster compared to the indirect pathway. It is also possible that the obtained effects are due to an antidromic effect resulting in seizure suppression

at a cortical level. Nevertheless, these data confirm the influence of basal ganglia activity in the modulation of epileptic seizure activity.

Stimulation of the subthalamic nucleus

Human studies of STN stimulation for epilepsy mainly come from two groups. In 1998 the Grenoble group carried out the first case of STN stimulation in a patient with cortical dysplasia and intractable seizures (Benabid et al., 2002). Four more patients underwent STN stimulation (Chabardes et al., 2002). Three patients responded with seizure reductions of 71 to 84%. The most effective target was thought to be the inferior part of the STN close to the SNr. The Cleveland clinic also reported the effects of STN stimulation in four epileptic patients (Loddenkemper et al., 2001). Stimulation was beneficial in two patients with 42% to 75% reduction of seizure frequency, along with reduction of seizure severity and duration. Continuous and intermittent stimulation appeared to be equally effective, using stimulation parameters similar to those used for STN stimulations in Parkinson disease (130Hz, 60µs). One study assessed the effect of STN stimulation in a patient with progressive myoclonic epilepsy. Bilateral monopolar DBS reduced the intensity and frequency of seizures by 50% (Vesper et al., 2007). In these open case series the safety of the technique was shown as well as the potential benefit. For better evaluation and interpretation of these encouraging results, controlled studies are required in larger number of patients. To this aim, a double-blind cross-over study is in progress in Grenoble to evaluate the effect of STN/SNr stimulation in patients with ring chromosome 20 epilepsy (STIMEP, France). These patients show a dopaminergic deficiency in the striatum compared to normal subjects (Biraben et al., 2004) and suffer from long lasting seizures often evolving into status epilepticus.

Conclusion: Consistent with the large body of both experimental and clinical evidence regarding the involvement of the basal ganglia, the SNr appears as a key target for DBS approaches. However no study investigated so far the specific DBS parameters and modalities to be applied to this structure. We investigated in a pre-clinical approach, the optimal stimulation parameters in absence-epilepsy rats from Strasbourg. Whether DBS parameters and modalities of the SNr are specific to such neurological disorder was thus further addressed.

II. QUESTIONS AND OBJECTIVES

The accumulated data concerning epileptic seizures, the basal ganglia and the involvement of the latter in some epileptic syndromes as well as the first case reports on electrical stimulation of different structures to suppress epileptic seizures gave hope to develop new therapeutic options in the treatment of epilepsy. This is also reflected by the increasing number of reviews in the current literature concerning this topic (Benabid, 2007; Ellis and Stevens, 2008; Saillet et al., 2009; Theodore and Fisher, 2004).

However, to date it is not a therapeutic option to be established in patients with some specific and clearly delineated syndromes. Therefore the primary encouraging results from the first pilot studies were not satisfactory enough. This may be at least partly due to the very heterogenous population studied. A number of unsolved questions raised we tried to answer in this thesis :

1. Does seizure spread to the basal ganglia inhibits secondary generalization in focal epilepsies?

To date it remains unknown, if ictal involvement of the basal ganglia has an influence on single seizure evolution, severity and duration. Some studies have addressed the involvement of basal ganglia activity using invasive EEG recordings with depth electrodes or imaging studies in nuclear medicine with SPECT and PET tracers (Biraben et al., 2004; Bouilleret et al., 2008; Newton et al., 1992; Rektor et al., 2002). However, these techniques are seldom used in a large population of epileptic patients as they are cost intensive and can be only performed in highly specialized centers. Ictal dystonia leads to a short-term increase in the perfusion of the basal ganglia contralateral to the dystonic limb in humans and is thought to reflect propagation to and activation of the basal ganglia (Joo et al., 2004; Mizobuchi et al., 2004; Newton et al., 1992). Endogenous ictal activation of the basal ganglia as assessed by ictal dystonia is thus thought to have an inhibitory effect on the time-course of seizure activity, especially on secondary generalization. Therefore we wanted to assess the endogenous control of basal ganglia involvement using clinical evidence based on the semiological seizure classification. On the other hand, version is a sign of seizure spread to the frontal eye field. We therefore investigated different seizure evolutions with different spread of seizure activity and comparing the rate of secondary generalization.

Elaboration of optimal deep brain stimulation parameters in epilepsy

2. What are the optimal single stimulation parameters for acute seizure interruption?

As deep brain stimulation has been applied very successfully in the treatment of movement disorders, and especially Parkinson's Disease, most of the animal and first clinical trials, used the stimulation parameters which were used for DBS in Parkinson's Disease. However, there is no scientific evidence that these parameters would be effective and optimal in the stimulation of epileptic patients. Therefore, we were interested to test which parameters are the best in interrupting single seizures, with a maximal margin to behavioural and motor side effects. For this purpose it was necessary to investigate animals with a high recurrence of endogenous epileptic seizures. Furthermore it was mandatory to have animals with intact basal ganglia functioning and without possible neuronal cell loss, as it is the case in models resulting from status epilepticus. We used the model of GAERS as these have a high rate of recurring epileptic seizures, even if absence seizures are no candidates for alternative therapeutic options in humans, as these are generally good responders to antiepileptic medication. The substantia nigra was used as the targeted structure, as it has been shown to play a key role in the control of absence-seizure in GAERS and it has been reported that the electrode contacts between STN and SNR at the border of the SNR were the most effective in the first five patients stimulated in Grenoble (Chabardes et al., 2002). The first task was thus to investigate the optimal single stimulation parameters for acute seizure interruption in GAERS through bipolar intranigral depth electrodes.

3. What are the optimal repeated stimulation parameters for sustained seizure suppression?

After establishing of the optimal parameters of single seizure interruption, with special emphasis on the location, polarity, pulse width, frequency and intensity, these parameters were further investigated in different repeated stimulation protocols in order to delineate the optimal repeated stimulation parameters for sustained seizure suppression in GAERS.

4. Is it possible to characterize markers that heralds epileptic seizures into the basal ganglia?

There are two different strategies to achieve a sustained seizure suppression. One is, that the stimulation is leading to changes of different neurotransmitters within the basal ganglia and/or the cerebral cortex, which makes the occurrence of epileptic seizures less likely. Another one is to stimulate and interrupt each seizure before, or as soon as possible, after its appearance. That requires to establish “markers” that heralds epileptic seizures. In the present work, we investigated if such markers can be found in the EEG signal recorded at the site of stimulation, i.e., the SNr. To this aim, coherence analyses of the EEG-signal within both SNr were performed before absence seizures in GAERS. Several attempts using different mathematical modulations have been reported to establish such seizure predicting tools but none has been successful in clinical practice. Most of these studies were performed using cortical or surface electrodes. As it might be important to minimize the numbers of implanted electrodes in humans we focussed our attention to possible markers preceeding the occurrence of epileptic seizures as recorded by local field potentials from stimulation electrodes implanted in the substantia nigra of the GAERS.

The answers are presented in the result section, followed by a general discussion and some perspectives.

The descriptions of the detailed methods are given in each article. As the experimental data were obtained using GAERS as an animal model of epilepsy, the following insert thereafter give a detailed description of this model.

The GAERS model

Progress in our understanding of the role of basal ganglia in the control of seizures has been enhanced by the use of a genetic model of generalized non convulsive seizures (Genetic Absence Epilepsy Rats from Strasbourg or GAERS). In this model the seizures are characterized by generalized spike-and-wave discharges (SWD) recorded on the cortical electroencephalogram, concomitant with behavioural arrest (Danober et al., 1998; Marescaux et al., 1992). This model shows many of the features of absence epilepsy in human and is suppressed by all anti-absence drugs. The cortex, and the reticular nucleus and the ventrobasal relay nuclei of the thalamus play a predominant role in the development of SWD, whereas limbic structures (e.g. hippocampus, amygdala) are not involved. Recently it has been shown that absence seizures in GAERS arise from the facial somatosensory cortex. Using in vivo intracellular recordings. Polack et al., found, that epileptic discharges are initiated in layer 5/6 neurons of this cortical region (Polack et al., 2007). The "focal" theory in genetic models of absence epilepsy was initially driven by findings in the Wistar Albino Glaxo/Rijswijk (WAG/Rij) rat (Coenen and Van Luijckelaar, 2003; Meeren et al., 2005; Meeren et al., 2002), who provided additional evidence for a leading role of the cerebral cortex. In this model, nonlinear correlation analysis of SWDs demonstrated the existence of a cortical "focus" within the perioral region of the somatosensory cortex (Meeren et al., 2005; Meeren et al., 2002).

As seizures occur spontaneously every minute and last about 20 s, this model allows investigators to test the effectiveness and time-course of pharmacological treatments (Danober et al., 1998; Loscher and Schmidt, 1988). Furthermore this model seems optimal for validation of new treatment strategies as subcortical structures are preserved intact compared to models after initiation of status epilepticus when neuronal cell loss occurs.

In this model the involvement of the basal ganglia circuits, which play a major role in the modulation of absence seizures, has been investigated (Deransart and Depaulis, 2002; Deransart et al., 1998b). The role in this control mechanism of the direct GABAergic projection from the striatum to the substantia nigra and of the indirect pathway, from the striatum through the globus pallidus and the subthalamic nucleus, was shown using pharmacological manipulations.

Activation of the direct pathway or inhibition of the indirect pathway suppressed absence seizures through disinhibition of neurons in the deep and intermediate layers of the superior colliculus. Dopamine D1 and D2 receptors in the nucleus accumbens, appeared to be critical in these suppressive effects (Deransart and Depaulis, 2002; Deransart et al., 1998b). The involvement of the STN to suppress epileptic seizures was shown using both ways (pharmacological and electrical) of reduction of the excitatory influence of the STN in this model (Deransart et al., 1996; Vercueil et al., 1998). Furthermore it has been described, that the firing rate of cells in the SNr decreases before the end of the absence seizures (Deransart et al., 2003).

In conclusion the model of GAERS represents a model of absence epilepsy with similar electrophysiological and pharmacological features as in humans. Even if the aim of development of new strategies to interrupt epileptic seizures is not a primary goal in absence epilepsies, because these seizures can be controlled by antiepileptic drugs, the choice of this model is justified by several facts: 1) Seizures occur spontaneously and can be studied by electrophysiological approaches in vivo. 2) Seizure frequency is high which enables a testing of several stimulation parameters in a short time for acute as well as chronic protocols. 3) The involvement of the basal ganglia as well as the possibility to record seizures from these structures has been largely documented in this model

III. RESULTS

1. B. Feddersen, J. Remi, M. Kilian, L. Vercueil, C. Deransart, A. Depaulis, S. Noachtar, Does ictal dystonia have an inhibitory effect on seizure propagation in focal epilepsies?
Submitted to Epilepsia as a full-length original research article.
2. B. Feddersen, L. Vercueil, S. Noachtar, O. David, A. Depaulis, C. Deransart. Controlling seizures is not controlling epilepsies: a parametric study of deep brain stimulation for epilepsy.
Neurobiology of Disease 2007; 27: 292-300.
3. B. Feddersen, R. Meier, A. Depaulis, C. Deransart. EEG Changes Between Left and Right Substantia Nigra Heralds the Occurrence of Generalized Seizures in a model of GAERS.
In preparation, to be submitted to Epilepsia as a short communication.
4. M. Langlois, S. SAILLET, B. Feddersen, L. Minotti, L. Vercueil, S. Chabardès, O. David, A. Depaulis, P. Kahane, C. Deransart. Deep brain stimulation in epilepsy: experimental and clinical data.
In: Deep Brain Stimulation. Mark H. Rogers and Paul B. Anderson Eds. Nova Science Publishers, Inc. 2009, in press.

Main findings:

ARTICLE 1

B. Feddersen, J. Remi, M. Kilian, L. Vercueil, C. Deransart, A. Depaulis, S.

Noachtar, Does ictal dystonia have an inhibitory effect on seizure

propagation in focal epilepsies?

Submitted to Epilepsia as a full-length original research article.

see “Scientific production”, page 122.

In this work, we investigated the secondary generalization of seizures with different semiologies. We compared patients who had focal seizures with (i) dystonia, (ii) dystonia *and* version, and (iii) version only. Ictal dystonia has been suggested to reflect spreading activity through the basal ganglia, whereas ictal version is thought to occur when epileptic activity spreads into the frontal eye field. In our study, seizures with version generalized more often (95%, 82 of 86 seizures) than seizures without version (10%, 25 of 244 seizures, $p < 0.0001$). Furthermore, the rate of secondary generalization was significantly lower for seizures characterized by ictal dystonia *and* version (62%, 13 of 21 seizures) than for seizures with isolated version (95%, 82 of 86 seizures, $p < 0.001$). However, this rate was similar between seizures with (8%, 6 of 72 seizures) or without ictal dystonia (3%, 5 of 160 seizures; $p > 0.05$). Unilateral ictal dystonia is associated with inhibitory mechanisms potentially related to the basal ganglia, which may exert an inhibiting effect on secondary seizure generalization if epileptic activity spreads to the frontal eye field. Without such a coactivation and higher susceptibility of secondary generalization, ictal dystonia did not lead to a decrease in secondary generalization (no difference between seizures with and without ictal dystonia). These data show that different seizure spread patterns may have the ability to inhibit further seizure evolution. In addition, they support the view that the basal ganglia system could be involved in remote control mechanisms.

ARTICLE 2

B. Feddersen, L. Vercueil, S. Noachtar, O. David, A. Depaulis, C.

Deransart. Controlling seizures is not controlling epilepsies: a parametric study of deep brain stimulation for epilepsy.

Neurobiology of Disease 2007; 27: 292-300.

see “Scientific production”, page 138.

In this study, we investigated the optimal stimulation parameters to interrupt spontaneous seizures in rats with genetic absence epilepsy (GAERS). It was shown that acute 5-s stimulations were successful to interrupt ongoing seizures with lowest thresholds in the substantia nigra pars reticulata compared to other structures within its vicinity (substantia nigra pars compacta, zona incerta and cerebral peduncle). The most effective stimulations were bipolar, monophasic and bilateral with 60- μ s pulse width and 60-Hz frequency. Combination of these parameters allow optimal in seizure interruption with the lowest antiepileptic thresholds and the highest thresholds for behavioral side-effects. Repeated stimulations, whatever the duration of the ON-OFF intervals that were investigated were ineffective to suppress the occurrence of spike-and-wave discharges. On the contrary, seizure-triggered stimulations were effective when a minimal interval of 60 s was applied. It is noteworthy that seizure aggravation was seen as rebound and habituation effects in repeated stimulation protocols. These data claims for further experimental investigations of chronic protocols using either open- or closed-loop stimulation procedures.

ARTICLE 3

B. Feddersen, R. Meier, A. Depaulis, C. Deransart. EEG Changes Between Left and Right Substantia Nigra Heralds the Occurrence of Generalized Seizures in a model of GAERS.

In preparation, to be submitted to Epilepsia as a short communication.
see “Scientific production”, page 149.

In this study, we investigated the changes in neuronal synchronization that may occur between the SNr in GAERS before the occurrence of spike and wave discharges (SWD). These episodes were compared to episodes of wakefulness or sleep and without SWD in order to verify whether the differences were specific to SWD or rather reflect a change of vigilance state. Our data show that the coherence between the two bipolar SNr electrodes increased 12 to 8 s before the onset of SWD at frequencies between 10 – 40 Hz (35 Hz, -10 sec, > 5 SD, $p < 0.001$), without changes in power in these bands. Such changes were not observed during wake or sleep periods. This early coupling of the two SNr suggests that changes in the dynamics of the basal ganglia may “predispose” the cortex to seize. These changes may also help to develop a close-loop device allowing detection and stimulation through the same electrode.

ARTICLE 4

M. Langlois, S. Sallet, B. Feddersen, L. Minotti, L. Vercueil, S. Chabardès, O. David, A. Depaulis, P. Kahane, C. Deransart. Deep brain stimulation in epilepsy: experimental and clinical data.

In: Deep Brain Stimulation. Mark H. Rogers and Paul B. Anderson Eds. Nova Science Publishers, Inc. 2009, in press.

see “Scientific production”, page 159.

In this review the main findings of the existing data of deep brain stimulation in epilepsy are summarized. These include animal data as well as the data of the first case series in humans.

IV. DISCUSSION

1. Question 1: Which epileptic syndromes and seizures are optimal for deep brain stimulation in epilepsy?

To date it remains unknown which patients should be considered for “alternative” therapies like DBS and who will benefit from such therapeutic options. Patients with focal seizures that are pharmacoresistant and for which the epileptogenic zone overlaps with eloquent cortex and/or are bilateral may represent the most appropriate candidates. Patients with generalized seizures that are difficult to control by antiepileptic drugs, (e.g., Lennox-Gastaut Syndrome) may also be appropriate candidates (Langlois et al., 2009).

In order to address this issue, we will consider the following questions:

Can epileptic candidates for DBS be selected:

- According to their seizure semiology?

Careful assessment of seizure semiology allows to map brain areas who are involved in seizure spread. Activation of specific brain areas by seizures or by external electrical stimulation leads to specific clinical manifestations. Most of the clinical characteristics which appear during some forms of epileptic seizures are elicited by electrical stimulation via subdural grid electrodes during investigations of invasive presurgical epilepsy monitoring (Godoy et al., 1990; Lüders et al., 1989). Therefore the careful assessment of the seizure semiology gives helpful informations about the involved cortical areas which might be affected by electrical stimulation of the basal ganglia.

It remains debatable whether dystonia in human patients reflects an activation or an inhibition of the basal ganglia circuits due to seizure spread. However, electrophysiological recordings in animal models strongly suggest that when epileptic activity spreads to the basal ganglia, it may suppress the physiological firing rate of some circuits, which results in the termination of epileptic seizures (Deransart et al., 2003; Paz et al., 2005). This might be also the mechanism of suppression of secondary generalization in patients with ictal dystonia and concomitant ictal version. Whether these patients are better candidates for DBS is an important issue.

We investigated the role of ictal dystonia, considered as involving basal ganglia circuits, and ictal version which reflects activation of the frontal eye field, on the rate of secondary generalization. We have shown that ictal dystonia is associated with less secondary seizure generalization and have suggested that this may be due to the involvement of the basal ganglia. This inhibiting effect is prominent when the epileptic activity spreads to the frontal eye field. Without such a coactivation of the frontal lobe with high probability of secondary generalisation, such effects were not observed. Therefore patients showing ictal dystonia do not appear better candidates than others, from a semiological point of view.

Patients with activation of the frontal lobe and especially of the frontal eye field have a high rate of secondary generalisation. Co-involvement of the basal ganglia lead to a decrease of such secondary generalisation. As the probability of further seizure spread is very high in patients with ictal version these might be good candidates for DBS in epilepsy. It is likely that a high level of epileptogenicity and therefore synchronized power is necessary for stimulation of subcortical structure to be successful in acute seizure interruption. Furthermore, it is known that the thalamic nuclei, targeted by the basal ganglia, have a strong connectivity onto a large portion of the frontal pole of the cortex, including motor, premotor, prefrontal and limbic areas (Chevalier et al., 1984). That might open the opportunity of acute seizure interruption by implementing an electrical stimulus to abort the synchronized epileptiform activity at brain areas involved in seizure onset or propagation through orthodromic pathways. Antidromic interruption of such seizure activity may be especially successful in STN stimulation as this structure receives direct projections from the frontal cortex (mainly motor and premotor areas) (Gradinaru et al., 2009). Therefore patients with seizure spread into the frontal lobes with activation of motor and premotor areas resulting in a semiology of motor seizures (myoclonic, tonic, clonic, tonic-clonic and versive seizures) might be optimal. Especially as a functional loop of the basal ganglia comprises the sensorimotor system with strong corticostriatal connections from the sensorimotor cortex. Patients with different seizure origin might be recommended for DBS in epilepsy when a fast seizure spread in the frontal lobe occurs which can be seen by evolving seizure semiology in motor seizures. Such a fast seizure spread might be necessary to have the opportunity that seizures can be interrupted at an early stage of the seizure course.

- According to the seizure focus?

It seems reasonable that the selection of candidates for DBS in epilepsy takes into account both the localization of the seizure onset zone and the pathway(s) of seizure spread. Seizure spread of different seizure onset zones may involve different circuits of the basal ganglia. Therefore, structures within these circuits may be prone to DBS according to the seizure onset zone. To answer this question, it is interesting to consider the epileptic patients that were already treated by DBS in the STN in different hospitals throughout the world. At the Grenoble hospital, a 67% to 80% reduction in seizure frequency was observed in three patients, with the seizure focus in the central cortical region (Chabardes et al., 2002). These three patients, considered as good responders, had mainly motor seizures. Two other patients were poor responders and had (i) a Dravet Syndrome with absence seizures and generalized tonic clonic seizures (seizure reduction of 41,5%) or (ii) an autosomal dominant nocturnal frontal lobe epilepsy with a seizure focus in the left insula and hypermotor seizures (no change in seizure frequency). At the American University of Beirut, a patient with Lennox Gastaut syndrome showed a complete suppression of generalized tonic-clonic seizures and a reduction of myoclonic seizures and atypical absences of over 75% after 1 year follow up (Alaraj et al., 2001). In the group of five patients stimulated at the Cleveland Clinic, STN-DBS was beneficial in two of them with reduction of focal seizure frequency of 42% and 75%, along with reduction of seizure severity and duration. Unfortunately the semiology and epileptic syndrome were not described in detail ("intractable focal epilepsy") (Loddenkemper et al., 2001; Vesper et al., 2007). Vesper et al reported a 50% seizure reduction of a patient with STN DBS, suffering from progressive myoclonus epilepsy, in Kehl-Kork, Germany (Vesper et al., 2007). Altogether, these data suggest that patients with seizures that primarily involved frontal cortical structures with widespread epileptic activation involving especially the motor and pre-motor areas are better responder to STN DBS. This is in agreement with anatomical findings indicating a high connectivity of the SNr and STN with the frontal lobes (Maurice et al., 1998a; Ryan et al., 1992). This is underscored by recent findings on the mechanism of DBS which have shown, that stimulation of layer V neurons of the motor cortex lead to the same effects as stimulation of the STN to improve parkinsonian symptoms in rats (Gradinaru et al., 2009). In another study, functional recovery was paralleled by a disruption of aberrant low-frequency synchronous corticostriatal oscillations, leading to a restoration of

normal locomotion in animal models of PD (Fuentes et al., 2009). These results may explain the positive effects (seizure reduction of 81%) in the first patient stimulated in Grenoble at the STN showing seizures arising from the primary motor cortex due to cortical dysplasia (Benabid et al., 2002). Although quite speculative it might be suggested that the cortical areas which are involved to improve PD symptoms by DBS, might also be involved by DBS of the same target in another disease like epilepsy.

- According to their deficit in dopaminergic functions?

Several data from animal models have shown a decrease in seizure severity associated with an increase of dopaminergic activity (Deransart et al., 1998b). Although many antiepileptic drugs like Valproate and Ethosuccimide have been reported to interfere with dopaminergic function (Huang et al., 2006; Ichikawa et al., 2005; Jadhav et al., 1981; Snead, 1982; Westerink and Korf, 1976), no antiepileptic drugs have been developed on such a rationale based on dopamine modulation. Inversely, reduction of dopaminergic functions was shown to aggravate seizures (Deransart and Depaulis, 2002). Yet, no seizures are induced by such treatment.

In human patients, it has been shown that the dopaminergic system is involved in several epileptic syndromes such as ring chromosome 20 epilepsies (Biraben et al., 2004), refractory temporal lobe epilepsy (Bouilleret et al., 2008; Ciumas et al., 2008), juvenile myoclonus epilepsies (Ciumas et al., 2008) and autosomal dominant nocturnal frontal lobe epilepsies (ADNFLE) (Fedi et al., 2008). In the latter, a decrease of D1 dopamine receptor binding sites was shown in the putamen. In TLE patients, [(18)F]fluoro-L-dopa uptake was reduced to the same extent in caudate and putamen in both cerebral hemispheres as well as in the SNr. These dopaminergic functional alterations occurred without any glucose metabolism changes in these areas (Bouilleret et al., 2008). Patients with juvenile myoclonus epilepsies had a reduced binding potential of 18-F-DOPA-PET in the substantia nigra and midbrain, and normal values in the caudate and putamen (Ciumas et al., 2008). These results show the involvement of different dopaminergic neurons within the basal ganglia in different epileptic syndromes. However, although it has been used as a criterion of inclusion in the cross-over study testing the efficacy of STN stimulation (Stimep), it

remains speculative whether patients with a deficit of dopaminergic transmission are better candidates for DBS of the basal ganglia.

The significance of such decrease in dopamine markers, as the cause or the consequence of epileptic seizures remains to be determined. However, dysfunction of the dopaminergic transmission and, more generally, the basal ganglia, is unlikely to be the cause of epilepsy. Indeed, it has been shown that lesions, alterations or induced dysfunction of the basal ganglia are not epileptogenic and that these structures do not generate seizures (Deransart and Depaulis, 2002). It is more likely, that they influence seizure severity and are involved in the termination of seizures (Deransart et al., 2003).

Whether DBS could act by restoring dopamine function in the patients mentioned above appear unlikely. The effect of DBS on dopamine levels were not investigated in epilepsy, neither in animal models nor in patients. In patients with pronounced Parkinson disease (PD), a recent functional imaging study showed that despite effective bilateral STN stimulations, a continuous decline of dopaminergic function is observed (Hilker et al., 2005). This decline was similar to previously reported data from longitudinal imaging studies in PD. Even, if electrical stimulation of different BG structures would result in equilibrating dopamine levels, it is unlikely that this would result in seizure freedom. Rather, a reduction of seizure severity (seizure duration, rate of secondary generalization) or increase of the quality of life may be obtained. In conclusion to date a dopaminergic deficit reflects the involvement of subcortical structures in some forms of epilepsy. As it has been shown that electrical stimulation of these structures would not lead to an increase of dopamine levels, the selection of patients only based on a reduction of dopamine levels in the basal ganglia for deep brain stimulation in epilepsy may not be sufficient.

Conclusion: the following table 8 lists all possible clues of recommendation for the selection of patients for DBS including semiology, dopaminergic deficit and by the seizure focus.

Epileptic syndromes	Semiology	Dopaminergic deficit	Seizure focus	Recommended for DBS ?	Existing effective therapy	
					Pharmacology	Resective surgery
Focal epilepsies						
mesial temporal lobe epilepsy	+	+	-	-	+/-	+
Neocortical temporal lobe epilepsy	+	0	-	-	+/-	+
Frontal lobe epilepsy	+	+	+	+	+/-	+/-
Parietal lobe epilepsy	+	0	-	-	+/-	+/-
Occipital lobe epilepsy	+	0	-	-	+/-	+/-
Generalized Epilepsies						
Childhood / Juvenile Absence	+	0	-	-	+	-
Dravet Sy	+	0	-	-	+/-	-
Juvenile myoclonus	+	+	-	-	+	-
Progressive myoclonus	+	0	-	-	-	-
Lennox Gastaud Sy	+	0	-	-	-	-

+ = yes; - = no; 0 = unknown; +/- = in some cases yes, in some no

Table 9 shows the data of the patients stimulated in the STN/ SNr to reduce epileptic seizures.

Epileptic syndromes	Semiology	Dopaminergic deficit	Seizure focus	Seizure reduction	Reference
Focal epilepsies					
Frontal lobe epilepsy	+	+	+		
Pat. 1	R tonic (-clonic); right	No data	Left central	80,7%	Chabardes et al., 2002
Pat. 2	clonic	No data	Right central	67,8%	Chabardes et al., 2002
Pat. 3	L>R tonic (-clonic) R tonic → fall	No data	Left central	67%	Chabardes et al., 2002
Generalized Epilepsies					
Dravet Sy	+	o	-		
Pat. 1	Absence Sz, GTCS		Generalized	41%	Chabardes et al., 2002
Progressive myoclonus	+	o	-		
Pat. 2	myoclonic		Generalized	50%	Vesper et al., 2007
Lennox Gastaud Sy	+	o	-		
Pat. 3	GTCS, myoclonic, atypical absences		Multifocal generalized	75%	Alaraj et al., 2001

+ = yes; - = no; o = unknown; -/+ = in some cases yes, in some no

According to table 9, patients should be regarded as optimal candidates for DBS when all conditions/requirement/factors are positive. This appears to be the case in particular for patients with focal frontal lobe epilepsy. Regarding other syndromes with various forms of seizures like in Lennox Gastaud, it is uncertain if DBS can be recommended as it may be effective in only some forms of seizures as it would emphasise rather a palliative approach compared to the goal of seizure freedom. This would result in an insufficient control of seizures with a minor impact on quality of life. However, as it is the case for VNS, DBS can be combined with AED therapy to decrease the probability of seizure occurrence.

Conclusion: Optimal candidates of DBS in epilepsy might be patients with involvement of the primary and premotor areas of the frontal lobe which can be assessed by seizure semiology and / or seizure focus. Whether a dopaminergic deficit will be a relevant criterion for optimal patient selection warrants further experimental and clinical investigations.

2. Question 2: “What is the optimal target for deep brain stimulation in epilepsy?”

With the new interest of several groups in the use of DBS to control epileptic seizures, the question of the optimal target is quite debated. During the recent years, different targets have been investigated in the thalamus (Centromedial and anterior nuclei), the caudate nucleus and the STN by different investigators. In the following section the existing evidence of the optimal target in DBS for epilepsy is discussed according to anatomical seizure onset considerations and according to the mechanism of action.

2.1. Anatomical considerations

2.1.1. Stimulation of the focus

Direct stimulation of the epileptic focus appears as the shortest way of action to interrupt ongoing seizure activity. Indeed, inhibition of epileptiform activity was observed during the application of a regional electrical current when afterdischarges were induced by cortical stimulation in patients with subdural grid electrodes (Lesser et al., 1999). However, for patients with seizure onset zone overlapping with eloquent

cortex direct stimulation of the focus, appears less feasible as it would result in additional burden for the patient. Furthermore the Responsive Neurostimulation Study (RNS) has shown a responder rate of only 48% for seizure onsets in the neocortex and in the hippocampus (Morrell, 2008). Hippocampal stimulations to reduce mostly mesio-temporal seizures was conducted in several studies (Tellez Zenteno, 2006; Velasco et al., 2007a; Velasco et al., 2000a). In a first study by the Velasco group a seizure abortion was reported in 7 of 10 patients where the stimulated electrode was placed within the hippocampus (Velasco et al., 2000). In another study a seizure reduction of 50% was reported in three patients after a mean follow up of 5 months (Vonck et al., 2002). However, these open unblinded trials were followed by two double-blind trials showing that in 9 patients more than 95% seizure reduction in the 5 patients with normal MRI, and 50-70% seizure reduction in the 4 patients who had hippocampal sclerosis (Velasco et al., 2007b). A seizure reduction by only 15% in average was observed in the 4 patients of the double-blind, multiple cross-over, randomized study of Tellez-Zenteno (Tellez-Zenteno et al., 2006). These data do not show a clear benefit in seizure reduction by hippocampal stimulation. Especially in unilateral temporal lobe epilepsy “alternative” therapies need to show better results compared to resective therapies, as these can be performed safely with good seizure outcomes. For other localisations direct stimulation of the focus may be impossible, when the seizure onset zone overlaps with eloquent cortex.

2.1.2. Thalamus stimulation

2.1.2.1. Anterior nucleus

The anterior nucleus (AN) of the thalamus has outputs to the cingulate cortex and, via the cingulum, to the entorhinal cortex and back to the hippocampus. Its close interaction with the circuit of Papez which is often involved especially in temporal lobe epilepsies and limbic seizures favours the AN as an attractive target for DBS in epileptic patients. Four open-label trials were reported showing that seizure frequency was reduced from 20 to 92% and being statistically significant in 12 of the 18 patients (Hodaie et al., 2002; Kerrigan et al., 2004; Lim et al., 2007; Osorio et al., 2007). Whether AN stimulation could be more effective in temporal lobe epilepsy (Zumsteg et al., 2006) and whether other components of the circuit of Papez, namely the mamillary bodies and mamillo-thalamic tract (Duprez et al., 2005; van

Rijckevorsel et al., 2005) are possible targets for DBS are important issues for clinical trials for further discussion see (Saillet et al., 2009).

2.1.2.2. Centromedian nucleus

The Centromedian (CM) nucleus is part of the reticulothalamocortical system mediating cerebral cortex excitability (Jasper, 1991). As this structure is interconnected with limbic structures, the basal ganglia and the cortex, the CM appears as an interesting target in DBS for epilepsy. In five patients with different epileptic syndromes the Velasco group reported 60% to 90% improvement with high-frequency stimulation of this target (Velasco et al., 1987). Longer follow-up of 7 to 33 months revealed substantial reduction of generalized tonic clonic and atypical absence seizures (Velasco et al., 1995). The positive results on these seizure types were confirmed in Lennox Gastaut syndrome which showed the most significant suppression (Velasco et al., 2000b; Velasco et al., 2001a). In contrast, CM stimulation was not effective in the management of patients with complex partial seizures. A placebo controlled double-blind study was performed to assess the efficacy of CM stimulation. In six patients, there was an overall reduction of 30% of generalized seizures when the stimulator was on and a 8% reduction when the stimulator was off compared to baseline (Fisher et al., 1992; Slaght et al., 2002a). To date it remains questionable if the CM is an optimal target for DBS in epilepsy. The cumulated data suggest that this target might be most effective in the suppression of generalized seizures involving the frontal cortex.

2.1.3. Stimulation of the basal ganglia

The present study as well as several experimental and clinical studies have provided a strong rationale for the basal ganglia as a target for DBS in epilepsy. BG are probably the target with the most important reciprocal projections with seizure onset zone (Slaght et al., 2002a) suggesting that it would be most successful for seizure interruption by a single stimulation.

2.1.3.1. Caudate nucleus

The caudate nucleus seems to be an interesting target, as part of the striatum is the main input target of the basal ganglia. Here the informations from the cerebral cortex, the intralaminar thalamic nuclei, the complex of the ventro-anterior, -medial and –

lateral thalamus, the hippocampus and amygdala are processed (Hoshi et al., 2005; Kita and Kitai, 1990; Mink, 1996). A decrease in focal and generalized interictal discharges was observed among 57 patients who were stimulated with low frequency (4-6 Hz) in the CN (Chkhenkeli and Chkhenkeli, 1997). Unfortunately, the effects on seizure frequency in this open study was not assessed. Whether these effects were mediated through orthodromic or antidromic pathways remains speculative. Further studies are mandatory in animal models to investigate the mechanisms of such a stimulation, especially to evaluate the differences in cortical excitability during such CN stimulations. The strong connectivity and involvement of the striatum is highlighted by several imaging studies using nuclear tracers. A decrease of dopamine receptor binding in the striatum has been seen in different forms of epilepsies, such as ring chromosome 20 epilepsies (Biraben et al., 2004), refractory temporal lobe epilepsy (Bouilleret et al., 2008), and autosomal dominant nocturnal frontal lobe epilepsies (ADNFLE) (Fedi et al., 2008), as discussed above. Such a process might show the disconnection of afferent fibers.

2.1.3.2. Subthalamic nucleus

The STN also receives direct projections from the frontal cortex (mainly motor and premotor areas) (Kunzle, 1978; Maurice et al., 1998a; Monakow et al., 1978; Ryan and Clark, 1992), of the parafascicular thalamus (Feger et al., 1994; Groenewegen and Berendse, 1990; Sugimoto and Hattori, 1983), and of the ventral pallidum (Maurice et al., 1997) and could be considered as the second major input structure of the BG. To date, 12 patients suffering from different forms of epilepsy received high frequency STN stimulation at different institutions (Chabardes et al., 2002; Loddenkemper et al., 2001; Vesper et al., 2007). Overall, seizure occurrence was reduced by at least 50% in 7/12 cases, and the stimulation was well tolerated (see above). Although the STN has a strong input to the SNr, its input from the cerebral cortex makes it possible that DBS interrupt seizures by antidromic mechanisms.

2.1.3.3. Substantia nigra pars reticulata

To determine the optimal parameters of basal ganglia DBS, we have chosen to stimulate the SNr (Publication #2) as it is considered as the major output structures of the basal ganglia (Chevalier et al., 1985; Depaulis et al., 1990a; Di Chiara et al., 1979). In addition, in the five patients stimulated in Grenoble, the most effective

electrode contacts were located in the inferior part of the STN, at the close proximity of the SNr. This region is different from the STN target used in patients with Parkinson disease, which is located more laterally and more dorsally. In our animal study in GAERS, lower antiepileptic thresholds were obtained when stimulations were applied within the boundaries of the SNr as compared to stimulations within the SNc, zona incerta and white matter surrounding the SNc, or the cerebral pedunculus (Feddersen et al., 2007). When compared to antiepileptic threshold obtained for STN stimulation ($100 \pm 26 \mu\text{A}$) in an initial study performed by Vercueil et al. using the same modes and parameters (monophasic, bipolar, bilateral, $60\mu\text{s}$ and 130Hz) (Vercueil et al., 1998), the antiepileptic threshold for SNr stimulation appeared 3 times lower ($32.9 \pm 7.1 \mu\text{A}$) (Feddersen et al., 2007). Such a difference is in agreement with pharmacological data showing that similar doses of GABA agonists are more effective in the SNr compared to the STN (Deransart et al., 1996) and the synergy of both direct and indirect striato-nigral projections in the control of seizures (Deransart and Depaulis, 2002).

2.2. Considerations according to the seizure onset zone

The seizure onset zone is the part of the brain where the seizure starts. That might become apparent in different clinical symptoms, when it overlaps with eloquent cortex (symptomatogenic zone). The effects of DBS must reach that seizure onset zone, when antiepileptic effects should be obtained, whether via antidromic and/or orthodromic ways. Therefore different seizure onset zones might be reached from different optimal stimulation targets. Recently it has been reported, that DBS of the STN acts on afferent neurons from layer V of the primary motor cortex, in an animal model of PDs (Gradinaru et al., 2009). Transferring of these results in the field of STN DBS in epilepsy, may explain why patients with a seizure focus in the primary motor cortex responded best (see above). The increasing knowledge of the functional loops according to their cortical origin will stratify the choice of the optimal target depending on the seizure focus in the future. Hereby, antidromic as well as orthodromic ways should be taken into consideration.

2.3. Considerations according to the mechanism of action of deep brain stimulation

An important point that requires to be addressed when discussing the optimal target is related to the mechanisms of action of DBS. Indeed, the recent studies that have examined this question have focused on the DBS of STN (Gradinaru et al., 2009; Hammond et al., 2008). In the case of Parkinson disease, it has been suggested that high-frequency stimulations (HFS) “normalize” spontaneous pathological patterns by introducing a regular activity in several nodal points of the network. According to this hypothesis, the best target for HFS should be in a region where the HFS-driven activity spreads to most of the identified dysrhythmic neuronal populations, without causing additional side effects (Hammond et al., 2008). HFS, as an extracellular stimulation, is expected to involve subsets of both afferent and efferent axons, leading to **antidromic** spikes that collide with ongoing spontaneous ones and orthodromic spikes that evoke synaptic responses in target neurons (Hammond et al., 2008).

Using an optogenetic approach which offers the opportunity to inhibit or excite targeted neurons in the STN selectively, Gradinaru and Mogri et al. could show, that neither inhibition nor excitation of the STN neurons had positive effects on relief of the parkinson symptoms. Control of afferent axons in the STN lead to the suspected positive effects. Furthermore selective optic stimulation of layer V neurons in the primary motor cortex M1 showed similar therapeutic effects. These M1 layer V neurons could be antidromically recruited by optical stimulation of the STN (Gradinaru et al., 2009). In another study, functional recovery was paralleled by a disruption of aberrant low-frequency synchronous corticostriatal oscillations, leading to a restoration of normal locomotion in animal models of PD (Fuentes et al., 2009). These results may explain the positive effects in patients showing seizures arising from the primary motor cortex (Benabid et al., 2002; Chabardes et al., 2002). Themes of synchrony and oscillations driven by particular cell and fiber types will likely be common to other brain stimulation-responsive disease such as epilepsy (Gradinaru et al., 2009). Further evidence of retrograde cortical activation derives from preliminary data of cortical potentials evoked by STN stimulation. Evoked potentials were found by timelocking EEG activity to the onset of electrical stimulation delivered to the STN (Loddenkemper et al., 2001). Latencies as long as 400ms after

different types of stimulation were reported (Montgomery and Baker, 2000). An interpulse interval of 1 msec led to a 50% increase in amplitude relative to the result of single stimulation, typically seen in stimulation of axons (Montgomery and Baker, 2000). An antidromic activation of the cortical inhibitory interneurons via antidromic activation of the corticosubthalamic axons could be one mechanism to decrease cortical excitability and susceptibility to seizures (Loddenkemper et al., 2001).

To date there is good evidence that acute seizure interruption may act through both antidromic and orthodromic pathways (Deransart and Depaulis, 2002; Gradinaru et al., 2009; Loddenkemper et al., 2001). However, it still remains unknown how DBS works in chronic conditions. Further studies are mandatory to investigate the effects of chronic stimulation to answer this question, specially taking into account long-term changes in both pathologic and non-pathologic neural networks. That might also change the selection criteria for patients.

Conclusion: The optimal target for DBS in epilepsy should take into account the seizure onset zone together with both maximal antidromic and orthodromic connectivity to the stimulated structure. In our experimental approach in GAERS the SNR appears as such a nodal point. However, whatever the targeted structure, optimal parameters to be applied have to be carefully determined.

3. Question 3: Which are the optimal parameters in deep brain stimulation

3.1. for acute seizure interruption?

Most of the first case series and animal studies of DBS in epilepsy were performed with the “classical” parameters used for patients with Parkinson’s Disease. In addition, the experimental studies used mainly single stimulation acutely applied to ongoing seizures. As these parameters and mode of stimulation were at least partly effective, they were not questioned or changed. From our own data (Publication #2) we concluded that 60 Hz frequency instead of 130 Hz frequency is sufficient to suppress seizures with an optimal therapeutical index to avoid behavioural and motor side effects (Feddersen et al., 2007). The optimal parameters for acute seizure interruption by a 5 s lasting seizure triggered stimulus were: bipolar, bilateral, monophasic stimulations of the SNr with 60-Hz frequency and 60- μ s pulse width.

Comparison of these parameters to those generally used in other studies is difficult as they apply to different pathologies (different animal models of epileptic seizures, Parkinson disease, pain and dystonia) and also different targets (STN versus SNr for instance). Hence, such comprehensive parametrical studies in animal models, have been largely neglected.

This discrimination from motor side effects (e.g. contralateral circling in animal models) is very important, as unlike Parkinsonian patients where stimulation threshold can be adjusted during or right after surgery by controlling motor symptoms, it is not possible in the case of epileptic patients. A compromise between safety and efficiency is thus mandatory in the case of DBS in epilepsy. In our experiments, a difference of up to 30% could be observed between antiepileptic thresholds and the intensity necessary to obtain the very first behavioral changes (Feddersen et al., 2007). In reference to parameters used in other animal models of epilepsy, the main difference seems to be related to the frequency of stimulation. This is noteworthy as a frequency dependence has been reported concerning the effect of STN-DBS on generalized clonic and tonic-clonic flurothyl seizures (Lado et al., 2003). Shi et al reported an antiepileptic effect of high frequency (130 Hz, 60 us) stimulation of the SNr on amygdala-kindled seizures (Shi et al., 2006). Our 60-Hz frequency is in full agreement with previous experimental studies showing that either electrophysiological or neurochemical effects could be obtained at this frequency in parkinsonian rats (Windels et al., 2003). It is well known that an increase of frequency, and pulse width may progressively decrease the intensity of the stimulus intensity necessary to reach the required clinical effect in parkinsonian patients (Rizzone et al., 2001). In epilepsy this is the case for acute seizure interruption, with the limitation of negative side effects. In our study the intensity for acute seizure interruption could be decreased by increasing the frequency and / or pulse width. However at some limits no differences between antiepileptic thresholds and side effect thresholds could be obtained. Therefore in the case of DBS in epilepsy, the goal is not a stimulation with intensities as minimal as possible, but furthermore as minimal and as *safe* as possible. The differences in optimal parameters as determined in our study as compared to classically used parameters for PD might also be due to the fact that the basal ganglia system in epilepsy are not to be considered *per se* as pathological as it is the case in PD. Even if dopaminergic changes have been reported in epileptic animals and patients (see above), these

have nothing in common with neurodegenerative process known to occurs in PD and less likely to display obvious symptomatic expression. Nevertheless, slight changes in dopaminergic tones are likely to occur in epileptic conditions and warrants further investigations.

3.2. for repeated seizure interruption?

Whereas chronic STN stimulation in epileptic patients were found to remain effective throughout time (Chabardes et al., 2002; Loddenkemper et al., 2001), our study clearly showed that repeated stimulations of the SNr did not result in a long term suppression of seizures, whatever the protocol (5 s ON and 15 s OFF, 5 s ON and 5 s OFF or continuous ON) used. At most, SWD were suppressed for up to 2 min and then occurred again, as during the reference period. This lack of lasting effect of repeated stimulations was already observed in the same animal model using STN stimulation (Vercueil et al., 1998).

However, our repeated stimulations are difficult to compare with the chronic 24h/day conditions in the clinic. Indeed, it is possible to that HFS stimulation of the STN or SNr become effective only after several days or weeks of continuous stimulations. This was suggested by a recent study (Shi et al., 2006) who observed a longlasting antiepileptic effect of high frequency (130 Hz, 60 us) stimulation of the SNr on amygdala-kindled seizures. It was shown that DBS, if well timed with the onset of amygdala kindling, may exert long lasting effects on the networks that may prevent the recurrence of kindled seizures.

To accurately address this point, a specific set-up is required that allows chronic stimulations over periods of days and weeks in the rat with spontaneous epileptic seizures. Experiments investigating for the consequences of such chronic HFS on spontaneous seizures are currently in progress in the laboratory (Sandrine SAILLET thesis). Whether such effects may induce long term changes in neurotransmitters plasticity within the basal ganglia and reduce the probability of epileptic seizures warrants also to be addressed. These are expected to rather result in a decreased occurrence of seizures than a shortening of single seizure duration.

In our study, seizure interruption was successful only when a minimal interval of 60 s was allowed before two 5-sec stimulations. Because of the high occurrence of SWDs in GAERS, seizure-triggered stimulations were found to be ineffective when

systematically applied to each seizures. These data suggest the existence of a refractory period after each stimulation, during which time the „control network“ cannot be activated anymore. This is in contrast with clinical data where no refractory period was observed in responsive epileptic patients as well as in *in vitro* slice preparation including the STN and related structures, suggesting that only imposing neurons to behave as stable oscillators is not a sufficient condition to suppress seizures (Garcia et al., 2005). Although this period may depend on the duration of the stimulation or when it is applied during the course of the SWD, the „epileptic control network“ thus appears likely to involve other mechanisms, as well as further downstream structures, as suggested earlier (Deransart and Depaulis, 2002).

Our acute stimulation may evoke fast changes in gating channels or neurotransmitters which makes the system unsusceptible for about 60 seconds. In a study using best estimates of anatomic and electrogenic model parameters for *in vivo* STN axons, the model predicts a functional block along the axon due to K^+ accumulation in the submyelin space (Bellinger et al., 2008). Extracellular accumulation of K^+ may impair the mechanism which is necessary to interrupt ongoing seizures by a stimulus. Such changes might explain the necessary minimal interval before the next stimulation is effective (time which is necessary for the extracellular accumulation of K^+ to be restored). This may also explain why higher intensities are necessary to overcome such a functional block of the axon to interrupt the pathological firing patterns of the epileptic seizures (which was the case in our parametrical study, personal observation). However, this supports that DBS, in our conditions, instead of providing long-lasting inhibition of the SNr, rather acutely disrupts synchronization of the thalamo-cortical loop. To be efficient, such stimulation has to be delivered through pulsatile stimulation protocols taking into account the refractory period of the control system to be triggered (Popovych et al., 2006). Further studies are mandatory in other models of epilepsy to confirm if such phenomenon is restricted to the model of GAERS, with many seizures appearing in clusters, when the animal is in a state of quiet wakefulness. Furthermore it highlights the need of a “closed loop” system of seizure detection and stimulation using the same electrodes.

Conclusion: Optimal parameters to acutely interrupt ongoing absence seizures in GAERS with a maximal discrimination to motor side effects might be bilateral, bipolar, monophasic, 60 us pulse width and 60 Hz frequency. Chronic stimulation might be most effective when applied intermittently and as less frequent as possible like it would be the case for closed loop stimulation with acute stimulation of every occurring seizure.

4. Seizure aggravation by substantia nigra pars reticulata stimulation

When seizure-triggered stimulations were used (publication #2), with a minimum delay of 60 s, occurrence of SWD was often observed between two stimulations. In fact, an increased occurrence of these “in between” seizures as well as an increase in their duration were observed. An aggravation of seizure frequency was also reported under chronic stimulations of the anterior thalamus, in rats with chronic seizures following acute status epilepticus induced by systemic kainic acid administration (Lado, 2006). It remains speculative whether the aggravation we have seen in GAERS relates to this observation using a very different model. It is possible that intranigral glutamate release would be increased during stimulation of the SNr and somehow contribute to these aggravating effects. Indeed, an increase in intranigral glutamate has been reported following STN stimulation (Zhang et al., 2008). Another possibility also relates to the dopaminergic neurotransmission. Increased dopaminergic transcripts for D3 receptors has been reported in GAERS and suggested to contribute to seizure aggravating effects (Deransart et al., 2003). DBS of the SNr is likely to modify the modality of dopamine release in stimulated animals, thus contributing to aggravating effects on seizure occurrence. Conversely, the possibility remains that the GAERS model is not the most suitable for such investigations due to its high occurrence of seizures. Nevertheless, this possibility of aggravation upon repeated stimulations has to be further investigated before clinical trials.

5. How can seizures be predicted to release a seizure triggered closed-loop stimulation?

During the last 20 years, a new field of research has evolved which aims at detecting epileptic seizures automatically on the EEG, but also at 'predicting' them in a time window that allows acute intervention or alarms the patient to avoid a risky situation. Predicting factors can only rarely be seen on the EEG (Gotman, 1985; Gotman, 1999) and more elaborate methods, involving signal analysis, appeared necessary to detect early changes in the dynamics of brain activity leading to a seizure. To this aim, different methods have been developed. *Linear* methods include the investigation of power changes in different frequency bands or the measurement of the energy of the signal (Esteller et al., 2005). Methods arising from *non-linear* system theory include the largest Lyapunov exponent (Iasemidis et al., 1990), mean phase coherence (Schelter et al., 2006) or the dynamical similarity index (Le Van Quyen et al., 2000; Le Van Quyen et al., 2001). In a comparative study, non-linear methods were shown comparably powerful as linear ones. Furthermore, both methods very much depended on the optimization of the analysis parameters to the data of each patient and were not transferable between patients with constant quality (Mormann et al., 2005). The interval by which a seizure could be predicted varied across methods, types of seizures and patients from seconds to a few hours (Lehnertz et al., 2007; Mormann et al., 2007). A novel method for the detection of SWD, based on the key observation that SWD are quasi-periodic signals was introduced by van Hese et al. The method consists of the following steps: (1) calculation of the spectrogram, (2) estimation of the background spectrum and detection of stimulation artefacts, (3) harmonic analysis with continuity analysis to estimate the fundamental frequency, and (4) classification based on the percentage of power in the harmonics to the total power of the spectrum. The method outperforms all tested SWD/seizure detection methods, showing a sensitivity and selectivity of 96% and 97%, respectively, on the first test set, and a sensitivity and selectivity of 94% and 92%, respectively, on the second test set (Van Hese et al., 2009). To establish a system where seizures are interrupted acutely by a short HFS of a few seconds, it is not necessary to have methods allowing prediction several hours before. To avoid additional electrodes we focussed our attention on changes of the SNr preceding seizures in GAERS. An increase in coherence between left and right SNr were seen several seconds before the first spike-and-wave discharges in

GAERS. These changes occur before seizure onset but not in the state of wakefulness or during sleep (Feddersen et al., in preparation). A decrease in the firing rate of SNr neurons was seen in this model at the end of SWD (Deransart et al., 2003; Paz et al., 2007). These data confirm the role of the BG in the modulation of seizures. The increase of coherence before the seizures stands in contrast to the inhibition of the BG at the end of seizures. It is unclear if an interruption of such an increase in coherence may have the ability to prevent the occurrence of epileptic seizures. However, these findings may lead to the development of new antiepileptic drugs acting on the BG or to develop a closed loop system whereas epileptic seizures can be detected and stimulated by the same electrode before the first appearance of epileptic seizures.

Using pathological firing of the BG as marker of stimulation release might be better feasible, if changes in coherence between both SNr, as it was seen in GAERS in our study could be also detected in human epilepsies.

Conclusion: Coherence between both SNRs is increased several seconds before the occurrence of SWD in GAERS, which might lead to a closed loop seizure detection and stimulation system in the future.

V. CONCLUSION

As about one third of epileptic patients are resistant to antiepileptic drugs, and only 30% are candidates for resective surgery it exists a great demand for the development of alternative surgical therapies. It has been shown in animal studies, that the basal ganglia and especially the SNr are involved in the control of epilepsy. In humans patients, at least for some epileptic syndromes, such an involvement of the basal ganglia was seen mainly in imaging studies. We investigated the influence of seizure spread into the basal ganglia, on the rate of secondary generalization. We showed that activation of the basal ganglia has an inhibiting effect on seizure propagation in focal epilepsies, when spread into the frontal lobe occurs. First case series, investigating deep brain stimulation of the basal ganglia to suppress epileptic seizures, showed encouraging results in at least some patients. However, more preclinical studies are mandatory to investigate the optimal stimulation parameters, as a complete seizure suppression could to date not be obtained. The aim of our experimental study was to determine the optimal stimulation parameters to control spontaneous seizures in a genetic model of absence epilepsy in the rat. The optimal parameters of single SNr stimulation were determined and were different to those classically used in DBS for patients with PD. When these parameters were used for repeated stimulations, no long term suppression and even increase of the number of seizures was observed. A delay of at least 60 sec was necessary between stimulations to be fully effective. Although single high frequency stimulation of the SNr can be used to suppress ongoing seizures, repeated high frequency stimulation are ineffective and could even aggravate seizures, thus supporting the need of closed loop stimulation procedures to chronically suppress seizures in therapeutical applications. A closed loop stimulation system would be only effective, when detectable changes heralds the seizure onset, to release the electrical high frequency stimulation for acute seizure suppression. In a genetic model of absence epilepsy such changes in the EEG-coherence between the left and right SNr could be identified.

VI. PERSPECTIVES

In the following sections studies and problems are listed, which needs to be solved before DBS in epilepsy may become a real therapy option for patients with pharmaco-resistant epilepsy, who are no candidates for a resective surgical procedure.

1. Animal studies

To date most animal studies investigated the effects of DBS of the BG only on acute seizure suppression, or over a relative short period (Feddersen et al., 2007). Further studies should be initiated to investigate the chronic effects of such stimulations over a few weeks or even months. Therefore animals should be equipped with a stimulation system which allows them to move freely in the cage. Long lasting changes in seizure activity should be assessed after several weeks clinically and with EEG. Such an approach would also provide new insights into the escape phenomenon (seizures that are not aborted by repeated stimulation protocols) and the aggravating effects of DBS we observed in GAERS (Feddersen et al., 2007). Both the escape and aggravating effects are themselves reminiscent of a pressure to seize phenomenon which may result from the progressive build up of changes preceding seizure onset and would somehow overcome the BG control system. However, because of the high recurrence rate of absence seizures in GAERS (Danover et al., 1998), the possibility also remains that other animal models with less frequent seizures will be more suitable for such studies.

Among the markers which may contribute to the build up of seizure onset, the dopaminergic neurotransmission, according to its widespread cortical projections and its ability to impinge on neuronal excitability through either phasic or tonic functioning, is likely to be involved (Thurley et al., 2008). Different models of epilepsy should highlight the effect of HFS of the SNr on neurotransmitters, especially on dopamine levels. This should be assessed using small animal PET. For instance, it would be interesting to use nuclear tracers as 18-F-Fallyprid for the assessment of D2 receptors, especially in chronic condition. Changes might contribute to the observed effect of seizure aggravation, as a decrease of dopamine has been shown to lead to seizure aggravation in GAERS (Deransart et al., 1998b).

As DBS of the BG in epilepsy may exert its effect through acute seizure suppression by disruption of the pathological firing rate (Feddersen et al., 2007), further studies should investigate the possibility of seizure prediction by changes in coherence using other animal models, especially on focal epilepsy like the model of mesiotemporal lobe epilepsy after intrahippocampal injection of kainate in mice (Heinrich et al., 2006; Suzuki et al., 1995). Hereby it is necessary to use models where the BG are kept intact and are not probably altered as it is the case in models with seizures occurring after status epilepticus (Turski et al., 1989).

2. Human studies

To date it remains unclear which patients may benefit most of DBS in epilepsy. Patients who are good candidates and may benefit most of such neurostimulation therapies should be identified. It is assumed that the best site of implantation of the HFS electrode may be in a region where the HFS-driven activity spreads to most of the identified, dysrhythmic, neuronal populations without causing additional side effects. Therefore it is necessary to image epileptic circuits in different epileptic syndromes with different seizure onset zones. Such imaging might open the opportunity to identify targets, which are involved in the spread of seizure activity and might be optimal targets for deep brain stimulation in epilepsy. The population of patients with pharmacoresistant epilepsy, who are no candidates for a resective surgical procedure, is very heterogeneous. An individualized approach of target selection, based on imaging studies might help to improve the rate of suppressed seizures.

The role of the dopaminergic system in some epileptic syndromes is not fully understood. Especially, if such changes in the basal ganglia and the decrease of dopamine levels in the striatum, reflects the disconnectivity of the impaired cortical areas to the basal ganglia or plays an independent role of seizure aggravation is questionable. These effects should be investigated in patients, in whom such an involvement of the basal ganglia was reported. It would be interesting to compare these findings in patients before after successful resective epilepsy surgery in patients, who are seizure free. An increase in the hypometabolism and decreased dopamine levels would emphasize the hypothesis of disconnectivity. If such changes could be reversed by a successful treatment, would point furthermore to the theory

that the basal ganglia structures are involved more intensively in the generation of epileptic seizures.

The role of the seizure focus on mechanism leading to the cessation of epileptic seizures is currently under investigation in our laboratory. Hereby seizures arising from the temporal lobe are compared with seizures arising from the frontal lobe in terms of seizure duration and secondary generalisation. This would increase the knowledge of mechanisms, which are responsible leading to seizure termination. A comparison to patients in whom such a seizure termination is missing, like it is the case in status epilepticus, will be a very interesting topic to investigate the role of the basal ganglia in such conditions.

Furthermore, it might be interesting to investigate the existing EEGs of the patients who underwent the first case series of STN stimulation in Grenoble and Cleveland in terms of coherence analysis between the left and right BG (Chabardes et al., 2002; Loddenkemper et al., 2001). The question should be answered, if such changes in coherence, as it was observed in GAERS, exist also in humans. That would facilitate the engineering and feasibility studies of a closed loop seizure detection and stimulation tool.

In conclusion, numerous studies in animals and in humans are necessary to increase the knowledge in the fascinating field of circuits involving cortical and subcortical areas, which are involved in the generation and termination of epileptic seizures. An individualized approach of target and parameter selection for each patient dependant on the seizure focus and seizure spread might increase the ability of successful seizure suppression.

REFERENCES

- Abou Khalil B, Fakhoury T. Significance of head turn sequences in temporal lobe onset seizures. 1996; 23: 245-250.
- Acharya JN, Wyllie E, Lüders HO, Kotagal P, Lancman M, Coelho M. Seizure symptomatology in infants with localization-related epilepsy. *Neurology* 1997; 48: 189-196.
- Acharya V, Acharya J, Luders H. Olfactory epileptic auras. *Neurology* 1998; 51: 56-61.
- Alaraj A, Commair Y, Mikati M, Wakim J, Louak E, Atweh S. Subthalamic nucleus deep brain stimulation. a novel method for the treatment of non-focal intractable epilepsy. Presented as a poster at Neuromodulation: defining the future. Cleveland, OH. June: 8-10. 2001.
- Albin RL, Young AB, Penney JB. The functional anatomy of basal ganglia disorders. *Trends Neurosci* 1989; 12: 366-75.
- Alexander GE, Crutcher MD. Functional architecture of basal ganglia circuits: neural substrates of parallel processing. *Trends Neurosci* 1990; 13: 266-71.
- Alexander GE, DeLong MR, Strick PL. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annu Rev Neurosci* 1986; 9: 357-81.
- Amar AP, Apuzzo ML, Liu CY. Vagus nerve stimulation therapy after failed cranial surgery for intractable epilepsy: results from the vagus nerve stimulation therapy patient outcome registry. *Neurosurgery* 2008; 62 Suppl 2: 506-13.
- Amato G, Sorbera F, Crescimanno G, La Grutta V. The role of the substantia nigra in the control of amygdaloid paroxysmal activity. *Arch Int Physiol Biochim* 1981; 89: 91-5.
- Anderson WS, Kossoff EH, Bergey GK, Jallo GI. Implantation of a responsive neurostimulator device in patients with refractory epilepsy. *Neurosurg Focus* 2008; 25: E12.
- Arts WF, Brouwer OF, Peters AC, Stroink H, Peeters EA, Schmitz PI, et al. Course and prognosis of childhood epilepsy: 5-year follow-up of the Dutch study of epilepsy in childhood. *Brain* 2004; 127: 1774-84.
- Arts WF, Geerts AT, Brouwer OF, Boudewyn Peters AC, Stroink H, van Donselaar CA. The early prognosis of epilepsy in childhood: the prediction of a poor outcome. The Dutch study of epilepsy in childhood. *Epilepsia* 1999; 40: 726-34.
- Awad IA, Rosenfeld J, Ahl J, Hahn JF, Luders H. Intractable epilepsy and structural lesions of the brain: mapping, resection strategies, and seizure outcome. *Epilepsia* 1991; 32: 179-86.
- Baulac S, Huberfeld G, Gourfinkel-An I, Mitropoulou G, Beranger A, Prud'homme JF, et al. First genetic evidence of GABA(A) receptor dysfunction in epilepsy: a mutation in the gamma2-subunit gene. *Nat Genet* 2001; 28: 46-8.
- Baumgartner C, Groppel G, Leutmezer F, Aull-Watschinger S, Patarraia E, Feucht M, et al. Ictal urinary urge indicates seizure onset in the nondominant temporal lobe. *Neurology* 2000; 55: 432-434.
- Bellinger SC, Miyazawa G, Steinmetz PN. Submyelin potassium accumulation may functionally block subsets of local axons during deep brain stimulation: a modeling study. *J Neural Eng* 2008; 5: 263-74.
- Ben-Ari Y, Tremblay E, Riche D, Ghilini G, Naquet R. Electrographic, clinical and pathological alterations following systemic administration of kainic acid, bicuculline or pentetrazole: metabolic mapping using the deoxyglucose

- method with special reference to the pathology of epilepsy. *Neuroscience* 1981; 6: 1361-91.
- Ben Menachem E, Hellstrom K, Waldton C, Augustinsson LE. Evaluation of refractory epilepsy treated with vagus nerve stimulation for up to 5 years [see comments]. *Neurology* 1999; 52: 1265-1267.
- Benabid AL. What the future holds for deep brain stimulation. *Expert Rev Med Devices* 2007; 4: 895-903.
- Benabid AL, Koudsie A, Pollak P, Kahane P, Chabardes S, Hirsch E, et al. Future prospects of brain stimulation. *Neurol Res* 2000; 22: 237-46.
- Benabid AL, Minotti L, Koudsie A, de Saint Martin A, Hirsch E. Antiepileptic effect of high-frequency stimulation of the subthalamic nucleus (corpus luyisi) in a case of medically intractable epilepsy caused by focal dysplasia: a 30-month follow-up: technical case report. *Neurosurgery* 2002; 50: 1385-91; discussion 1391-2.
- Benbadis SR, Kotagal P, Klem GH. Unilateral blinking: a lateralizing sign in partial seizures. *Neurology* 1996; 46: 45-48.
- Benbadis SR, Lüders HO. Epileptic syndromes: an underutilized concept. *Epilepsia* 1996; 37: 1029-1034.
- Benedek K, Juhasz C, Muzik O, Chugani DC, Chugani HT. Metabolic changes of subcortical structures in intractable focal epilepsy. *Epilepsia* 2004; 45: 1100-5.
- Berg AT. Epidemiology in Epilepsy. *Epilepsy Curr* 2001; 1: 56.
- Berg AT, Kelly MM. Defining intractability: comparisons among published definitions. *Epilepsia* 2006; 47: 431-6.
- Berg AT, Langfitt J, Shinnar S, Vickrey BG, Sperling MR, Walczak T, et al. How long does it take for partial epilepsy to become intractable? *Neurology* 2003; 60: 186-90.
- Berg AT, Shinnar S, Levy SR, Testa FM, Smith-Rapaport S, Beckerman B. Early development of intractable epilepsy in children: a prospective study. *Neurology* 2001; 56: 1445-52.
- Berkovic SF, Andermann F, Melanson D, Ethier RE, Feindel W, Gloor P. Hypothalamic hamartomas and ictal laughter: evolution of a characteristic epileptic syndrome and diagnostic value of magnetic resonance imaging. *Ann Neurol* 1988; 23: 429-439.
- Biraben A, Semah F, Ribeiro MJ, Douaud G, Remy P, Depaulis A. PET evidence for a role of the basal ganglia in patients with ring chromosome 20 epilepsy. *Neurology* 2004; 63: 73-7.
- Bleasel A, Kotagal P, Kankirawatana P, Rybicki L. Lateralizing value and semiology of ictal limb posturing and version in temporal lobe and extratemporal epilepsy. *Epilepsia* 1997; 38: 168-174.
- Bleasel A, Lüders HO. Tonic seizures. In: Lüders HO and Noachtar S, editors. *Epileptic seizures: pathophysiology and clinical semiology*. New York: Churchill Livingstone, 2000: 389-411.
- Bodenmann P, Ghika J, Van Melle G, Bogousslavsky J. [Neurological comorbidity in parkinsonism]. *Rev Neurol (Paris)* 2001; 157: 45-54.
- Bonhaus DW, Russell RD, McNamara JO. Activation of substantia nigra pars reticulata neurons: role in the initiation and behavioral expression of kindled seizures. *Brain Res* 1991; 545: 41-8.
- Bouilleret V, Semah F, Biraben A, Taussig D, Chassoux F, Syrota A, et al. Involvement of the basal ganglia in refractory epilepsy: an 18F-fluoro-L-DOPA PET study using 2 methods of analysis. *J Nucl Med* 2005; 46: 540-7.

- Bouilleret V, Semah F, Chassoux F, Mantzarides M, Biraben A, Trebossen R, et al. Basal ganglia involvement in temporal lobe epilepsy: a functional and morphologic study. *Neurology* 2008; 70: 177-84.
- Brown RG, Marsden CD. How common is dementia in Parkinson's disease? *Lancet* 1984; 2: 1262-5.
- Chabardes S, Kahane P, Minotti L, Koukksie A, Hirsch E, Benabid AL. Deep brain stimulation in epilepsy with particular reference to the subthalamic nucleus. *Epileptic Disord* 2002; 4 Suppl 3: S83-93.
- Chassagnon S, Andre V, Koning E, Ferrandon A, Nehlig A. Optimal window for ictal blood flow mapping. Insight from the study of discrete temporo-limbic seizures in rats. *Epilepsy Res* 2006; 69: 100-18.
- Chee MW, Kotagal P, Van Ness PC, Gragg L, Murphy D, Luders HO. Lateralizing signs in intractable partial epilepsy: blinded multiple-observer analysis. *Neurology* 1993; 43: 2519-2525.
- Chesselet MF, Delfs JM. Basal ganglia and movement disorders: an update. *Trends Neurosci* 1996; 19: 417-22.
- Chevalier G, Deniau JM. Disinhibition as a basic process in the expression of striatal functions. *Trends Neurosci* 1990; 13: 277-80.
- Chevalier G, Vacher S, Deniau JM. Inhibitory nigral influence on tectospinal neurons, a possible implication of basal ganglia in orienting behavior. *Exp Brain Res* 1984; 53: 320-6.
- Chevalier G, Vacher S, Deniau JM, Desban M. Disinhibition as a basic process in the expression of striatal functions. I. The striato-nigral influence on tecto-spinal/tecto-diencephalic neurons. *Brain Res* 1985; 334: 215-26.
- Chkhenkeli SA, Chkhenkeli IS. Effects of therapeutic stimulation of nucleus caudatus on epileptic electrical activity of brain in patients with intractable epilepsy. *Stereotact Funct Neurosurg* 1997; 69: 221-4.
- Chkhenkeli SA, Sramka M, Lortkipanidze GS, Rakviashvili TN, Bregvadze E, Magalashvili GE, et al. Electrophysiological effects and clinical results of direct brain stimulation for intractable epilepsy. *Clin Neurol Neurosurg* 2004; 106: 318-29.
- Ciomas C, Savic I. Structural changes in patients with primary generalized tonic and clonic seizures. *Neurology* 2006; 67: 683-6.
- Ciomas C, Wahlin TB, Jucaite A, Lindstrom P, Halldin C, Savic I. Reduced dopamine transporter binding in patients with juvenile myoclonic epilepsy. *Neurology* 2008; 71: 788-94.
- Cleto Dal-Col ML, Bertti P, Terra-Bustamante VC, Velasco TR, Araujo Rodrigues MC, Wichert-Ana L, et al. Is dystonic posturing during temporal lobe epileptic seizures the expression of an endogenous anticonvulsant system? *Epilepsy Behav* 2008; 12: 39-48.
- Coenen AM, Van Luijckelaar EL. Genetic animal models for absence epilepsy: a review of the WAG/Rij strain of rats. *Behav Genet* 2003; 33: 635-55.
- Commission CoCaTotILAE. Proposal for a revised clinical and electroencephalographic classification of epileptic seizures. *Epilepsia* 1981; 22: 489-501.
- Cooper IS, Amin I, Gilman S. The effect of chronic cerebellar stimulation upon epilepsy in man. *Trans Am Neurol Assoc* 1973; 98: 192-6.
- Cuellar-Herrera M, Velasco M, Velasco F, Velasco AL, Jimenez F, Orozco S, et al. Evaluation of GABA system and cell damage in parahippocampus of patients with temporal lobe epilepsy showing antiepileptic effects after subacute electrical stimulation. *Epilepsia* 2004; 45: 459-66.

- Danover L, Deransart C, Depaulis A, Vergnes M, Marescaux C. Pathophysiological mechanisms of genetic absence epilepsy in the rat. *Prog Neurobiol* 1998; 55: 27-57.
- De Angelis G, Vizioli R. [Parkinson's disease and epilepsy: hypothesis of biological incompatibility]. *Rev Neurol (Paris)* 1984; 140: 440-2.
- Deniau JM, Menetrey A, Charpier S. The lamellar organization of the rat substantia nigra pars reticulata: segregated patterns of striatal afferents and relationship to the topography of corticostriatal projections. *Neuroscience* 1996; 73: 761-81.
- Depaulis A, Marescaux C, Liu Z, Vergnes M. The GABAergic nigro-collicular pathway is not involved in the inhibitory control of audiogenic seizures in the rat. *Neurosci Lett* 1990a; 111: 269-74.
- Depaulis A, Vergnes M, Liu Z, Kempf E, Marescaux C. Involvement of the nigral output pathways in the inhibitory control of the substantia nigra over generalized non-convulsive seizures in the rat. *Neuroscience* 1990b; 39: 339-49.
- Depaulis A, Vergnes M, Marescaux C. Endogenous control of epilepsy: the nigral inhibitory system. *Prog Neurobiol* 1994; 42: 33-52.
- Depaulis A, Vergnes M, Marescaux C, Lannes B, Warter JM. Evidence that activation of GABA receptors in the substantia nigra suppresses spontaneous spike-and-wave discharges in the rat. *Brain Res* 1988; 448: 20-9.
- Deransart C, Depaulis A. The control of seizures by the basal ganglia? A review of experimental data. *Epileptic Disord* 2002; 4 Suppl 3: S61-72.
- Deransart C, Hellwig B, Heupel-Reuter M, Leger JF, Heck D, Lucking CH. Single-unit analysis of substantia nigra pars reticulata neurons in freely behaving rats with genetic absence epilepsy. *Epilepsia* 2003; 44: 1513-20.
- Deransart C, Le BT, Marescaux C, Depaulis A. Role of the subthalamo-nigral input in the control of amygdala-kindled seizures in the rat. *Brain Res* 1998a; 807: 78-83.
- Deransart C, Marescaux C, Depaulis A. Involvement of nigral glutamatergic inputs in the control of seizures in a genetic model of absence epilepsy in the rat. *Neuroscience* 1996; 71: 721-8.
- Deransart C, Riban V, Le B, Marescaux C, Depaulis A. Dopamine in the striatum modulates seizures in a genetic model of absence epilepsy in the rat. *Neuroscience* 2000; 100: 335-44.
- Deransart C, Vercueil L, Marescaux C, Depaulis A. The role of basal ganglia in the control of generalized absence seizures. *Epilepsy Res* 1998b; 32: 213-23.
- Deransart CD, A. Le concept de contrôle nigral des épilepsies s'applique-t-il aux épilepsies partielles pharmacorésistantes? *Epilepsies* 2004; 16 75-82.
- Di Chiara G, Porceddu ML, Morelli M, Mulas ML, Gessa GL. Substantia nigra as an out-put station for striatal dopaminergic responses: role of a GABA-mediated inhibition of pars reticulata neurons. *Naunyn Schmiedeberg's Arch Pharmacol* 1979; 306: 153-9.
- Dinner DS, Neme S, Nair D, Montgomery EB, Jr., Baker KB, Rezai A, et al. EEG and evoked potential recording from the subthalamic nucleus for deep brain stimulation of intractable epilepsy. *Clin Neurophysiol* 2002; 113: 1391-402.
- Dlugos DJ. The early identification of candidates for epilepsy surgery. *Arch Neurol* 2001; 58: 1543-6.

- Dupont S, Semah F, Baulac M, Samson Y. The underlying pathophysiology of ictal dystonia in temporal lobe epilepsy: an FDG-PET study. *Neurology* 1998; 51: 1289-92.
- Duprez TP, Serieh BA, Raftopoulos C. Absence of memory dysfunction after bilateral mammillary body and mammillothalamic tract electrode implantation: preliminary experience in three patients. *AJNR Am J Neuroradiol* 2005; 26: 195-7; author reply 197-8.
- Dybdal D, Gale K. Postural and anticonvulsant effects of inhibition of the rat subthalamic nucleus. *J Neurosci* 2000; 20: 6728-33.
- Ebner A. Lateral (neocortical) temporal lobe epilepsy. In: Wolf P, editor. *Epileptic seizures and syndromes*. London: John Libbey, 1994: 375-382.
- Ebner A, Dinner DS, Noachtar S, Luders H. Automatisms with preserved responsiveness: a lateralizing sign in psychomotor seizures. *Neurology* 1995; 45: 61-4.
- Ellis TL, Stevens A. Deep brain stimulation for medically refractory epilepsy. *Neurosurg Focus* 2008; 25: E11.
- Engel J, Jr. The goal of epilepsy therapy: no seizures, no side effects, as soon as possible. *CNS Spectr* 2004; 9: 95-7.
- Engel J, Jr., Wolfson L, Brown L. Anatomical correlates of electrical and behavioral events related to amygdaloid kindling. *Ann Neurol* 1978; 3: 538-44.
- Esteller R, Echauz J, D'Alessandro M, Worrell G, Cranstoun S, Vachtsevanos G, et al. Continuous energy variation during the seizure cycle: towards an on-line accumulated energy. *Clin Neurophysiol* 2005; 116: 517-26.
- Feddersen B, Vercueil L, Noachtar S, David O, Depaulis A, Deransart C. Controlling seizures is not controlling epilepsy: a parametric study of deep brain stimulation for epilepsy. *Neurobiol Dis* 2007; 27: 292-300.
- Fedi M, Berkovic SF, Scheffer IE, O'Keefe G, Marini C, Mulligan R, et al. Reduced striatal D1 receptor binding in autosomal dominant nocturnal frontal lobe epilepsy. *Neurology* 2008; 71: 795-8.
- Feger J, Bevan M, Crossman AR. The projections from the parafascicular thalamic nucleus to the subthalamic nucleus and the striatum arise from separate neuronal populations: a comparison with the corticostriatal and corticosubthalamic efferents in a retrograde fluorescent double-labelling study. *Neuroscience* 1994; 60: 125-32.
- Fernandes MJ, Dube C, Boyet S, Marescaux C, Nehlig A. Correlation between hypermetabolism and neuronal damage during status epilepticus induced by lithium and pilocarpine in immature and adult rats. *J Cereb Blood Flow Metab* 1999; 19: 195-209.
- Fish D, Andermann F, Olivier A. Complex partial seizures and small posterior temporal or extratemporal structural lesions: surgical management. *Neurology* 1991; 41: 1781-4.
- Fisher RS, Uematsu S, Krauss GL, Cysyk BJ, McPherson R, Lesser RP, et al. Placebo-controlled pilot study of centromedian thalamic stimulation in treatment of intractable seizures. *Epilepsia* 1992; 33: 841-851.
- Fogarasi A, Jokeit H, Faveret E, Janszky J, Tuxhorn I. The effect of age on seizure semiology in childhood temporal lobe epilepsy. *Epilepsia* 2002; 43: 638-43.
- Fountas KN, Smith JR. A novel closed-loop stimulation system in the control of focal, medically refractory epilepsy. *Acta Neurochir Suppl* 2007; 97: 357-62.
- Fuentes R, Petersson P, Siesser WB, Caron MG, Nicoletis MA. Spinal cord stimulation restores locomotion in animal models of Parkinson's disease. *Science* 2009; 323: 1578-82.

- Gabr M, Luders H, Dinner D, Morris H, Wyllie E. Speech manifestations in lateralization of temporal lobe seizures. *Ann Neurol* 1989; 25: 82-87.
- Garcia L, D'Alessandro G, Fernagut PO, Bioulac B, Hammond C. Impact of high-frequency stimulation parameters on the pattern of discharge of subthalamic neurons. *J Neurophysiol* 2005; 94: 3662-9.
- Gates JR, Leppik IE, Yap J, Gumnit RJ. Corpus callosotomy: clinical and electroencephalographic effects. *Epilepsia* 1984; 25: 308-316.
- Gelbard HA, Applegate CD. Persistent increases in dopamine D2 receptor mRNA expression in basal ganglia following kindling. *Epilepsy Res* 1994; 17: 23-9.
- Glenn LL, Steriade M. Discharge rate and excitability of cortically projecting intralaminar thalamic neurons during waking and sleep states. *J Neurosci* 1982; 2: 1387-404.
- Godoy J, Luders H, Dinner DS, Morris HH, Wyllie E. Versive eye movements elicited by cortical stimulation of the human brain. *Neurology* 1990; 40: 296-299.
- Gotman J. Seizure recognition and analysis. *Electroencephalogr Clin Neurophysiol Suppl* 1985; 37: 133-45.
- Gotman J. Automatic detection of seizures and spikes. *J Clin Neurophysiol* 1999; 16: 130-40.
- Gradinaru V, Mogri M, Thompson KR, Henderson JM, Deisseroth K. Optical deconstruction of parkinsonian neural circuitry. *Science* 2009; 324: 354-9.
- Groenewegen HJ, Berendse HW. Connections of the subthalamic nucleus with ventral striatopallidal parts of the basal ganglia in the rat. *J Comp Neurol* 1990; 294: 607-22.
- Groenewegen HJ, Berendse HW, Wolters JG, Lohman AH. The anatomical relationship of the prefrontal cortex with the striatopallidal system, the thalamus and the amygdala: evidence for a parallel organization. *Prog Brain Res* 1990; 85: 95-116; discussion 116-8.
- Groenewegen HJ, Wright CI, Beijer AV, Voorn P. Convergence and segregation of ventral striatal inputs and outputs. *Ann N Y Acad Sci* 1999; 877: 49-63.
- Groenewegen HJ, Wright CI, Uylings HB. The anatomical relationships of the prefrontal cortex with limbic structures and the basal ganglia. *J Psychopharmacol* 1997; 11: 99-106.
- Hammond C, Ammari R, Bioulac B, Garcia L. Latest view on the mechanism of action of deep brain stimulation. *Mov Disord* 2008; 23: 2111-21.
- Hauser WA, Annegers JF, Kurland LT. Prevalence of epilepsy in Rochester, Minnesota: 1940-1980. *Epilepsia* 1991; 32: 429-45.
- Hauser WA, Rich SS, Annegers JF, Anderson VE. Seizure recurrence after a 1st unprovoked seizure: an extended follow-up. *Neurology* 1990; 40: 1163-1170.
- Heinrich C, Nitta N, Flubacher A, Muller M, Fahrner A, Kirsch M, et al. Reelin deficiency and displacement of mature neurons, but not neurogenesis, underlie the formation of granule cell dispersion in the epileptic hippocampus. *J Neurosci* 2006; 26: 4701-13.
- Henkel A, Noachtar S, Pfander M, Luders HO. The localizing value of the abdominal aura and its evolution: a study in focal epilepsies. *Neurology* 2002; 58: 271-6.
- Henkel A, Winkler PA, Noachtar S. Ipsilateral blinking: a rare lateralizing seizure phenomenon in temporal lobe epilepsy. *Epileptic Disord* 1999; 1: 195-7.
- Henry TR. Therapeutic mechanisms of vagus nerve stimulation. *Neurology* 2002; 59: S3-14.
- Hilker R, Portman AT, Voges J, Staal MJ, Burghaus L, van Laar T, et al. Disease progression continues in patients with advanced Parkinson's disease and

- effective subthalamic nucleus stimulation. *J Neurol Neurosurg Psychiatry* 2005; 76: 1217-21.
- Hodaie M, Wennberg RA, Dostrovsky JO, Lozano AM. Chronic anterior thalamus stimulation for intractable epilepsy. *Epilepsia* 2002; 43: 603-8.
- Hoshi E, Tremblay L, Feger J, Carras PL, Strick PL. The cerebellum communicates with the basal ganglia. *Nat Neurosci* 2005; 8: 1491-3.
- Huang M, Li Z, Ichikawa J, Dai J, Meltzer HY. Effects of divalproex and atypical antipsychotic drugs on dopamine and acetylcholine efflux in rat hippocampus and prefrontal cortex. *Brain Res* 2006; 1099: 44-55.
- Huff RM. Signal transduction pathways modulated by the D2 subfamily of dopamine receptors. *Cell Signal* 1996; 8: 453-9.
- Hufnagel A, Noachtar S. Epilepsien und ihre medikamentöse Behandlung. In: Brandt T, Dichgans J and Diener J, editors. *Therapie neurologischer Erkrankungen*. München: Kohlhammer, 2003: 212-235.
- Iadarola MJ, Gale K. Substantia nigra: site of anticonvulsant activity mediated by gamma-aminobutyric acid. *Science* 1982; 218: 1237-40.
- Iasemidis LD, Sackellares JC, Zaveri HP, Williams WJ. Phase space topography and the Lyapunov exponent of electrocorticograms in partial seizures. *Brain Topogr* 1990; 2: 187-201.
- Ichikawa J, Chung YC, Dai J, Meltzer HY. Valproic acid potentiates both typical and atypical antipsychotic-induced prefrontal cortical dopamine release. *Brain Res* 2005; 1052: 56-62.
- Jackson JH. The Lumleian lectures on convulsive seizures. *Br Med J* 1890; 1: 821-827.
- Jadhav JH, Balsara JJ, Jeurkar AJ, Chandorkar AG. Effect of ethosuximide on dopaminergically mediated behaviours. *Indian J Physiol Pharmacol* 1981; 25: 274-8.
- Janz D, Christian W. Impulsiv-Petit mal. *Dtsch Z Nervenheilk* 1957; 176: 346-386.
- Jasper HH. Current evaluation of the concepts of centrencephalic and cortico-reticular seizures. *Electroencephalogr Clin Neurophysiol* 1991; 78: 2-11.
- Jensen AA, Pedersen UB, Din N, Andersen PH. The dopamine D1 receptor family: structural and functional aspects. *Biochem Soc Trans* 1996; 24: 163-9.
- Jokeit H. [Neuropsychological diagnosis in patients with epilepsy]. *Ther Umsch* 2001; 58: 650-5.
- Jokeit H, Daamen M, Zang H, Janszky J, Ebner A. Seizures accelerate forgetting in patients with left-sided temporal lobe epilepsy. *Neurology* 2001; 57: 125-6.
- Joo EY, Hong SB, Han HJ, Tae WS, Kim JH, Han SJ, et al. Postoperative alteration of cerebral glucose metabolism in mesial temporal lobe epilepsy. *Brain* 2005; 128: 1802-10.
- Joo EY, Hong SB, Lee EK, Tae WS, Kim JH, Seo DW, et al. Regional cerebral hyperperfusion with ictal dystonic posturing: ictal-interictal SPECT subtraction. *Epilepsia* 2004; 45: 686-9.
- Kaniff TE, Chuman CM, Neafsey EJ. Substantia nigra single unit activity during penicillin-induced focal cortical epileptiform discharge in the rat. *Brain Res Bull* 1983; 11: 11-3.
- Kaufmann WE, Krauss GL, Uematsu S, Lesser RL. Treatment of epilepsy with multiple subpial transections: an acute histologic analysis in human subjects. *Epilepsia* 1996; 37: 342-352.
- Kerrigan JF, Litt B, Fisher RS, Cranstoun S, French JA, Blum DE, et al. Electrical stimulation of the anterior nucleus of the thalamus for the treatment of intractable epilepsy. *Epilepsia* 2004; 45: 346-54.

- Kita H, Kitai ST. Amygdaloid projections to the frontal cortex and the striatum in the rat. *J Comp Neurol* 1990; 298: 40-9.
- Klee MR, Lux HD. [Intracellular studies on the influence of inhibiting potentials in the motor cortex. II. The effect of electric stimulation of the nucleus caudatus.]. *Arch Psychiatr Nervenkr Z Gesamte Neurol Psychiatr* 1962; 203: 667-89.
- Klepper J, Willemsen M, Verrips A, Guertsen E, Herrmann R, Kutzick C, et al. Autosomal dominant transmission of GLUT1 deficiency. *Hum Mol Genet* 2001; 10: 63-8.
- Kostopoulos GK. Involvement of the thalamocortical system in epileptic loss of consciousness. *Epilepsia* 2001; 42, Suppl. 3: 13-19.
- Kotagal P, Bleasel A, Geller E, Kankirawatana P, Moorjani BI, Rybicki L. Lateralizing value of asymmetric tonic limb posturing observed in secondarily generalized tonic-clonic seizures. *Epilepsia* 2000; 41: 457-462.
- Kotagal P, Lüders H, Morris HH, Dinner DS, Wyllie E, Godoy J, et al. Dystonic posturing in complex partial seizures of temporal lobe onset: a new lateralizing sign. *Neurology* 1989; 39: 196-201.
- Krämer G. persönliche Mitteilung, 1997.
- Kramer RE, Luders H, Goldstick LP, Dinner DS, Morris HH, Lesser RP, et al. Ictus emeticus: an electroclinical analysis. *Neurology* 1988; 38: 1048-1052.
- Kuba R, Rektor I, Brazdil M. Ictal limb dystonia in temporal lobe epilepsy. an invasive video-EEG finding. *Eur J Neurol* 2003; 10: 641-9.
- Kunzle H. An autoradiographic analysis of the efferent connections from premotor and adjacent prefrontal regions (areas 6 and 9) in macaca fascicularis. *Brain Behav Evol* 1978; 15: 185-234.
- Kwan P, Brodie MJ. Early identification of refractory epilepsy. *N Engl J Med* 2000; 342: 314-319.
- Kwan P, Brodie MJ. Effectiveness of first antiepileptic drug. *Epilepsia* 2001; 42: 1255-60.
- La Grutta V, Amato G, Zagami MT. The control of amygdaloid and temporal paroxysmal activity by the caudate nucleus. *Experientia* 1971; 27: 278-9.
- La Grutta V, Sabatino M. Focal hippocampal epilepsy: effect of caudate stimulation. *Exp Neurol* 1988; 99: 38-49.
- Lado FA. Chronic bilateral stimulation of the anterior thalamus of kainate-treated rats increases seizure frequency. *Epilepsia* 2006; 47: 27-32.
- Lado FA, Moshe SL. How do seizures stop? *Epilepsia* 2008; 49: 1651-64.
- Lado FA, Velisek L, Moshe SL. The effect of electrical stimulation of the subthalamic nucleus on seizures is frequency dependent. *Epilepsia* 2003; 44: 157-64.
- Lai YY, Siegel JM. Medullary regions mediating atonia. *J Neurosci* 1988; 8: 4790-4796.
- Langlois M, Sallet S, Feddersen B, Minotti L, Vercueil L, Chabardès S, et al. Deep brain stimulation in epilepsy: experimental and clinical data. In: *Deep Brain Stimulation*. Editors: Mark H. Rogers and Paul B. Anderson. Nova Science Publishers, Inc. 2009.
- Le Van Quyen M, Adam C, Martinerie J, Baulac M, Clemenceau S, Varela F. Spatio-temporal characterizations of non-linear changes in intracranial activities prior to human temporal lobe seizures. *Eur J Neurosci* 2000; 12: 2124-34.
- Le Van Quyen M, Martinerie J, Navarro V, Boon P, D'Have M, Adam C, et al. Anticipation of epileptic seizures from standard EEG recordings. *Lancet* 2001; 357: 183-8.

- Lee KH, Meador KJ, Park YD, King DW, Murro AM, Pillai JJ, et al. Pathophysiology of altered consciousness during seizures: Subtraction SPECT study. *Neurology* 2002; 59: 841-6.
- Lehnertz K, Mormann F, Osterhage H, Muller A, Prusseit J, Chernihovskyi A, et al. State-of-the-art of seizure prediction. *J Clin Neurophysiol* 2007; 24: 147-53.
- Lesser RP, Kim SH, Beyderman L, Miglioretti DL, Webber WR, Bare M, et al. Brief bursts of pulse stimulation terminate afterdischarges caused by cortical stimulation. *Neurology* 1999; 53: 2073-81.
- Leutmezer F, Baumgartner C. Postictal signs of lateralizing and localizing significance. *Epileptic Disord* 2002; 4: 43-8.
- Li SC, Schoenberg BS, Wang CC, Cheng XM, Zhou SS, Bolis CL. Epidemiology of epilepsy in urban areas of the People's Republic of China. *Epilepsia* 1985; 26: 391-4.
- Lim SN, Lee ST, Tsai YT, Chen IA, Tu PH, Chen JL, et al. Electrical stimulation of the anterior nucleus of the thalamus for intractable epilepsy: a long-term follow-up study. *Epilepsia* 2007; 48: 342-7.
- Lindsay J, Glaser G, Richards P, Ounsted C. Developmental aspects of focal epilepsies of childhood treated by neurosurgery. *Dev Med Child Neurol* 1984; 26: 574-87.
- Loddenkemper T, Pan A, Neme S, Baker KB, Rezai AR, Dinner DS, et al. Deep brain stimulation in epilepsy. *J Clin Neurophysiol* 2001; 18: 514-32.
- Loscher W, Czuczwar SJ, Jackel R, Schwarz M. Effect of microinjections of gamma-vinyl GABA or isoniazid into substantia nigra on the development of amygdala kindling in rats. *Exp Neurol* 1987; 95: 622-38.
- Loscher W, Schmidt D. Which animal models should be used in the search for new antiepileptic drugs? A proposal based on experimental and clinical considerations. *Epilepsy Res* 1988; 2: 145-81.
- Lozano AM, Hamani C. The future of deep brain stimulation. *J Clin Neurophysiol* 2004; 21: 68-9.
- Luders H. Depth electrode studies in mesial temporal epilepsy. *Epilepsy surgery* 1991: 371-384.
- Lüders H, Acharya J, Baumgartner C, Benbadis S, Bleasel A, Burgess R, et al. Semiological seizure classification. *Epilepsia* 1998; 39: 1006-13.
- Lüders H, Hahn J, Lesser RP, Dinner DS, Morris HH, 3d, Wyllie E, et al. Basal temporal subdural electrodes in the evaluation of patients with intractable epilepsy. *Epilepsia* 1989; 30: 131-142.
- Lüders HO, Awad IA. Conceptual considerations. In: Lüders HO, editor. *Epilepsy surgery*. New York: Raven Press, 1992: 51-62.
- Lüders HO, Dinner DS, Morris HH, Wyllie E, Comair YG. Cortical electrical stimulation in humans. The negative motor areas. *Adv Neurol* 1995; 67: 115-129.
- Manford M, Fish DR, Shorvon SD. An analysis of clinical seizure patterns and their localizing value in frontal and temporal lobe epilepsies. *Brain* 1996; 119: 17-40.
- Marescaux C, Vergnes M, Depaulis A. Genetic absence epilepsy in rats from Strasbourg--a review. *J Neural Transm Suppl* 1992; 35: 37-69.
- Maurice N, Deniau JM, Glowinski J, Thierry AM. Relationships between the prefrontal cortex and the basal ganglia in the rat: physiology of the corticosubthalamic circuits. *J Neurosci* 1998a; 18: 9539-46.

- Maurice N, Deniau JM, Glowinski J, Thierry AM. Relationships between the prefrontal cortex and the basal ganglia in the rat: physiology of the cortico-nigral circuits. *J Neurosci* 1999; 19: 4674-81.
- Maurice N, Deniau JM, Menetrey A, Glowinski J, Thierry AM. Position of the ventral pallidum in the rat prefrontal cortex-basal ganglia circuit. *Neuroscience* 1997; 80: 523-34.
- Maurice N, Deniau JM, Menetrey A, Glowinski J, Thierry AM. Prefrontal cortex-basal ganglia circuits in the rat: involvement of ventral pallidum and subthalamic nucleus. *Synapse* 1998b; 29: 363-70.
- McNamara JO. Cellular and molecular basis of epilepsy. *J Neurosci* 1994; 14: 3413-25.
- Meeren H, van Luijckelaar G, Lopes da Silva F, Coenen A. Evolving concepts on the pathophysiology of absence seizures: the cortical focus theory. *Arch Neurol* 2005; 62: 371-6.
- Meeren HK, Pijn JP, Van Luijckelaar EL, Coenen AM, Lopes da Silva FH. Cortical focus drives widespread corticothalamic networks during spontaneous absence seizures in rats. *J Neurosci* 2002; 22: 1480-95.
- Meldrum BS. Metabolic factors during prolonged seizures and their relation to nerve cell death. *Adv Neurol* 1983; 34: 261-75.
- Mervaala E, Andermann F, Quesney LF, Krelina M. Common dopaminergic mechanism for epileptic photosensitivity in progressive myoclonus epilepsies. *Neurology* 1990; 40: 53-6.
- Mink JW. The basal ganglia: focused selection and inhibition of competing motor programs. *Prog Neurobiol* 1996; 50: 381-425.
- Mink JW, Thach WT. Basal ganglia intrinsic circuits and their role in behavior. *Curr Opin Neurobiol* 1993; 3: 950-7.
- Mizobuchi M, Matsuda K, Inoue Y, Sako K, Sumi Y, Chitoku S, et al. Dystonic posturing associated with putaminal hyperperfusion depicted on subtraction SPECT. *Epilepsia* 2004; 45: 948-53.
- Monakow KH, Akert K, Kunzle H. Projections of the precentral motor cortex and other cortical areas of the frontal lobe to the subthalamic nucleus in the monkey. *Exp Brain Res* 1978; 33: 395-403.
- Montgomery EB, Jr., Baker KB. Mechanisms of deep brain stimulation and future technical developments. *Neurol Res* 2000; 22: 259-66.
- Mormann F, Andrzejak RG, Elger CE, Lehnertz K. Seizure prediction: the long and winding road. *Brain* 2007; 130: 314-33.
- Mormann F, Kreuz T, Rieke C, Andrzejak RG, Kraskov A, David P, et al. On the predictability of epileptic seizures. *Clin Neurophysiol* 2005; 116: 569-87.
- Morrell F, Whisler WW, Bleck TP. Multiple subpial transection: a new approach to the surgical treatment of focal epilepsy. *J Neurosurg* 1989; 70: 231-9.
- Morrell HL, Bergey G, Barkley G, Wharen R, Murro AB, Fisch, Marvin Rossi, D. Labar, R. Duckrow, Joseph Sirven, J. Drazkowski, Gregory Worrell and Ryder Gwinn. Long-term safety and efficacy of the RNS™ system in adults with medically intractable partial onset seizures. *Epilepsia* 2008; 47.
- Morris HH, Dinner DS, Luders H, Wyllie E, Kramer R. Supplementary motor seizures: clinical and electroencephalographic findings. *Neurology* 1988; 38: 1075-1082.
- Mouroux M, Hassani OK, Feger J. Electrophysiological and Fos immunohistochemical evidence for the excitatory nature of the parafascicular projection to the globus pallidus. *Neuroscience* 1997; 81: 387-97.
- Nauta WJ, Domesick VB. Afferent and efferent relationships of the basal ganglia. *Ciba Found Symp* 1984; 107: 3-29.

- Newton MR, Berkovic SF, Austin MC, Reutens DC, McKay WJ, Bladin PF. Dystonia, clinical lateralization, and regional blood flow changes in temporal lobe seizures. *Neurology* 1992; 42: 371-377.
- Noachtar S, Arnold S. Clonic seizures. In: Lüders HO and Noachtar S, editors. *Epileptic seizures: pathophysiology and clinical semiology*. New York: Churchill Livingstone, 2000: 412-424.
- Noachtar S, Desudchit T, Lüders HO. Dialectic seizures. In: Lüders HO and Noachtar S, editors. *Epileptic seizures: pathophysiology and clinical semiology*. New York: Churchill Livingstone, 2000: 361-376.
- Noachtar S, Ebner A, Dinner DS. Das Auftreten von Automatismen bei erhaltenem Bewusstsein. Zur Frage der Bewusstseinsstörung bei komplex-fokalen Anfällen. In: Scheffner D, editor. *Epilepsie 91*. Reinbek: Einhorn-Press Verlag, 1992: 82-87.
- Noachtar S, Rosenow F, Arnold S, Baumgartner C, Ebner A, Hamer H, et al. Semiologic classification of epileptic seizures. *Nervenarzt* 1998; 69: 117-26.
- Noachtar S, Winkler PA, Lüders HO. Surgical therapy of epilepsy. In: Brandt T, Caplan C, Dichgans J, Diener J and Kennard C, editors. *Neurological disorders: course and treatment*. San Diego: Academic Press, 2003: 235-244.
- O'Dwyer R, Silva Cunha JP, Vollmar C, Mauerer C, Feddersen B, Burgess RC, et al. Lateralizing significance of quantitative analysis of head movements before secondary generalization of seizures of patients with temporal lobe epilepsy. *Epilepsia* 2007; 48: 524-30.
- Oakley JC, Ojemann GA. Effects of chronic stimulation of the caudate nucleus on a preexisting alumina seizure focus. *Exp Neurol* 1982; 75: 360-7.
- Ochs R, Gloor P, Quesney F, Ives J, Olivier A. Does head-turning during a seizure have lateralizing or localizing significance? *Neurology* 1984; 34: 884-890.
- Okada R, Moshe SL, Wong BY, Sperber EF, Zhao DY. Age-related substantia nigra-mediated seizure facilitation. *Exp Neurol* 1986; 93: 180-7.
- Ono K, Wada JA. Facilitation of premotor cortical seizure development by intranigral muscimol. *Brain Res* 1987; 405: 183-6.
- Osorio I, Overman J, Giftakis J, Wilkinson SB. High frequency thalamic stimulation for inoperable mesial temporal epilepsy. *Epilepsia* 2007; 48: 1561-71.
- Packard MG, Cahill L. Affective modulation of multiple memory systems. *Curr Opin Neurobiol* 2001; 11: 752-6.
- Palmini A, Gloor P. The localizing value of auras in partial epilepsies. *Neurology* 1992; 42: 801-808.
- Paxinos G, Watson C. *The rat brain in stereotaxic coordinates*. 2005; fifth edition.
- Paz JT, Chavez M, Saillet S, Deniau JM, Charpier S. Activity of ventral medial thalamic neurons during absence seizures and modulation of cortical paroxysms by the nigrothalamic pathway. *J Neurosci* 2007; 27: 929-41.
- Paz JT, Deniau JM, Charpier S. Rhythmic bursting in the cortico-subthalamo-pallidal network during spontaneous genetically determined spike and wave discharges. *J Neurosci* 2005; 25: 2092-101.
- Penfield W, Jasper H. *Epilepsy and the functional anatomy of the human brain*. Boston: Brown Little & Co, 1954.
- Pfander M, Arnold S, Henkel A, Weil S, Werhahn KJ, Eisensehr I, et al. Clinical features and EEG findings differentiating mesial from neocortical temporal lobe epilepsy. *Epileptic Disord* 2002; 4: 189-95.
- Polack PO, Guillemain I, Hu E, Deransart C, Depaulis A, Charpier S. Deep layer somatosensory cortical neurons initiate spike-and-wave discharges in a genetic model of absence seizures. *J Neurosci* 2007; 27: 6590-9.

- Polkey CE. Alternative surgical procedures to help drug-resistant epilepsy - a review. *Epileptic Disord* 2003; 5: 63-75.
- Popovych S, Gail A, Schropp J. Complex dynamics of a single neuron model. *Phys Rev E Stat Nonlin Soft Matter Phys* 2006; 74: 041914.
- Psatta DM. Control of chronic experimental focal epilepsy by feedback caudatum stimulations. *Epilepsia* 1983; 24: 444-54.
- Quesney LF, Andermann F, Gloor P. Dopaminergic mechanism in generalized photosensitive epilepsy. *Neurology* 1981; 31: 1542-4.
- Rada P, Hernandez L. Opposite changes of dopamine turnover in prefrontal cortex and nucleus accumbens after amygdaloid kindling. *Neurosci Lett* 1990; 117: 144-8.
- Ramsay RE, Uthman BM, Augustinsson LE, Upton AR, Naritoku D, Willis J, et al. Vagus nerve stimulation for treatment of partial seizures: 2. Safety, side effects, and tolerability. First International Vagus Nerve Stimulation Study Group. *Epilepsia* 1994; 35: 627-36.
- Rasmussen T. Localizational aspects of epileptic seizure phenomena. In: Thompson RA and Green JR, editors. *New perspectives in cerebral localization*. New York: Raven Press, 1982: 177-203.
- Rektor I, Kuba R, Brazdil M. Interictal and ictal EEG activity in the basal ganglia: an SEEG study in patients with temporal lobe epilepsy. *Epilepsia* 2002; 43: 253-62.
- Rizzone M, Lanotte M, Bergamasco B, Tavella A, Torre E, Facani G, et al. Deep brain stimulation of the subthalamic nucleus in Parkinson's disease: effects of variation in stimulation parameters. *J Neurol Neurosurg Psychiatry* 2001; 71: 215-9.
- Robillard A, Saint-Hilaire JM, Mercier M, Bouvier G. The lateralizing and localizing value of aversion in epileptic seizures. *Neurology* 1983; 33: 1241-1242.
- Rodrigues MC, Beleboni Rde O, Coutinho-Netto J, dos Santos WF, Garcia-Cairasco N. Behavioral effects of bicuculline microinjection in the dorsal versus ventral hippocampal formation of rats, and control of seizures by nigral muscimol. *Epilepsy Res* 2004; 58: 155-65.
- Rosenow F, Luders H. Presurgical evaluation of epilepsy. *Brain* 2001; 124: 1683-1700.
- Rosenow J, Das K, Rovit RL, Couldwell WT, Irving S, Cooper and his role in intracranial stimulation for movement disorders and epilepsy. *Stereotact Funct Neurosurg* 2002; 78: 95-112.
- Ryan LJ, Clark KB. Alteration of neuronal responses in the subthalamic nucleus following globus pallidus and neostriatal lesions in rats. *Brain Res Bull* 1992; 29: 319-27.
- Ryan LJ, Sanders DJ, Clark KB. Auto- and cross-correlation analysis of subthalamic nucleus neuronal activity in neostriatal- and globus pallidal-lesioned rats. *Brain Res* 1992; 583: 253-61.
- Saillet S, Langlois M, Feddersen B, Minotti L, Vercueil L, Chabardès S, et al. Manipulating the epileptic brain using stimulation: a review of experimental and clinical studies. *Epileptic Disorders* 2009; in press.
- Schelter B, Winterhalder M, Dahlhaus R, Kurths J, Timmer J. Partial phase synchronization for multivariate synchronizing systems. *Phys Rev Lett* 2006; 96: 208103.
- Schlaepfer TE, Frick C, Zobel A, Maier W, Heuser I, Bajbouj M, et al. Vagus nerve stimulation for depression: efficacy and safety in a European study. *Psychol Med* 2008; 38: 651-61.

- Schmidt D. Two antiepileptic drugs for intractable epilepsy with complex- partial seizures. 1982; 45: 1119-1124.
- Semah F, Picot MC, Adam C, Broglin D, Arzimanoglou A, Bazin B, et al. Is the underlying cause of epilepsy a major prognostic factor for recurrence? Neurology 1998; 51: 1256-1262.
- Shi LH, Luo F, Woodward D, Chang JY. Deep brain stimulation of the substantia nigra pars reticulata exerts long lasting suppression of amygdala-kindled seizures. Brain Res 2006; 1090: 202-7.
- Shin C, Silver JM, Bonhaus DW, McNamara JO. The role of substantia nigra in the development of kindling: pharmacologic and lesion studies. Brain Res 1987; 412: 311-7.
- Shin WC, Hong SB, Tae WS, Kim SE. Ictal hyperperfusion patterns according to the progression of temporal lobe seizures. Neurology 2002; 58: 373-80.
- Slaght SJ, Leresche N, Deniau JM, Crunelli V, Charpier S. Activity of thalamic reticular neurons during spontaneous genetically determined spike and wave discharges. J Neurosci 2002a; 22: 2323-34.
- Slaght SJ, Paz T, Chavez M, Deniau JM, Mahon S, Charpier S. On the activity of the corticostriatal networks during spike-and-wave discharges in a genetic model of absence epilepsy. J Neurosci 2004; 24: 6816-25.
- Slaght SJ, Paz T, Mahon S, Maurice N, Charpier S, Deniau JM. Functional organization of the circuits connecting the cerebral cortex and the basal ganglia: implications for the role of the basal ganglia in epilepsy. Epileptic Disord 2002b; 4 Suppl 3: S9-22.
- Snead OC, 3rd. An investigation of the relationship between the dopaminergic and electroencephalographic effects of gamma-butyrolactone. Neuropharmacology 1982; 21: 539-43.
- Spencer SS, Schramm J, Wyler A, O'Connor M, Orbach D, Krauss G, et al. Multiple subpial transection for intractable partial epilepsy: an international meta-analysis. Epilepsia 2002; 43: 141-5.
- Sramka M, Fritz G, Gajdosova D, Nadvornik P. Central stimulation treatment of epilepsy. Acta Neurochir Suppl (Wien) 1980; 30: 183-7.
- Sramka M, Fritz G, Galanda M, Nadvornik P. Some observations in treatment stimulation of epilepsy. Acta Neurochir (Wien) 1976: 257-62.
- Steinhoff BJ, Schindler M, Herrendorf G, Kurth C, Bittermann HJ, Paulus W. The lateralizing value of ictal clinical symptoms in uniregional temporal lobe epilepsy. 1998; 39: 72-79.
- Sugimoto T, Hattori T. Confirmation of thalamosubthalamic projections by electron microscopic autoradiography. Brain Res 1983; 267: 335-9.
- Sugimoto T, Hattori T, Mizuno N, Itoh K, Sato M. Direct projections from the centre median-parafascicular complex to the subthalamic nucleus in the cat and rat. J Comp Neurol 1983; 214: 209-16.
- Sun FT, Morrell MJ, Wharen RE, Jr. Responsive cortical stimulation for the treatment of epilepsy. Neurotherapeutics 2008; 5: 68-74.
- Sussman NMG, H.W.; Jackel R.A. et al. Anterior thalamic stimulation in medically intractable epilepsy. Part II: Preliminary clinical results (abstract):. Epilepsia 1988; 29: 677.
- Suzuki F, Junier MP, Guilhem D, Sorensen JC, Onteniente B. Morphogenetic effect of kainate on adult hippocampal neurons associated with a prolonged expression of brain-derived neurotrophic factor. Neuroscience 1995; 64: 665-74.

- Talairach J, Bancaud J, Geier S, Bordas-Ferrer M, Bonis A, Szikla G, et al. The cingulate gyrus and human behavior. *Electroenceph Clin Neurophysiol* 1973; 34: 45-52.
- Tellez-Zenteno JF, McLachlan RS, Parrent A, Kubu CS, Wiebe S. Hippocampal electrical stimulation in mesial temporal lobe epilepsy. *Neurology* 2006; 66: 1490-4.
- Tellez Zenteno JF. Can we consider thymectomy before pregnancy in female patients with myasthenia gravis? *Eur J Cardiothorac Surg* 2006; 30: 411-2; author reply 412.
- Theodore WH, Fisher RS. Brain stimulation for epilepsy. *Lancet Neurol* 2004; 3: 111-8.
- Theodore WH, Porter RJ, Albert P, Kelley K, Bromfield E, Devinsky O, et al. The secondarily generalized tonic-clonic seizure: a videotape analysis. *Neurology* 1994; 44: 1403-7.
- Thurley K, Senn W, Luscher HR. Dopamine increases the gain of the input-output response of rat prefrontal pyramidal neurons. *J Neurophysiol* 2008; 99: 2985-97.
- Trinka E, Walser G, Unterberger I, Luef G, Benke T, Bartha L, et al. Asymmetric termination of secondarily generalized tonic-clonic seizures in temporal lobe epilepsy. *Neurology* 2002; 59: 1254-6.
- Turski L, Cavalheiro EA, Bortolotto ZA, Ikonomidou-Turski C, Kleinrok Z, Turski WA. Dopamine-sensitive anticonvulsant site in the rat striatum. *J Neurosci* 1988; 8: 4027-37.
- Turski L, Cavalheiro EA, Turski WA, Meldrum BS. Excitatory neurotransmission within substantia nigra pars reticulata regulates threshold for seizures produced by pilocarpine in rats: effects of intranigral 2-amino-7-phosphonoheptanoate and N-methyl-D-aspartate. *Neuroscience* 1986; 18: 61-77.
- Turski L, Ikonomidou C, Turski WA, Bortolotto ZA, Cavalheiro EA. Review: cholinergic mechanisms and epileptogenesis. The seizures induced by pilocarpine: a novel experimental model of intractable epilepsy. *Synapse* 1989; 3: 154-71.
- Urrestarazu E, Iriarte J, Alegre M, Guridi J, Rodriguez-Oroz MC, Obeso J, et al. Subthalamic role on the generation of spikes in temporal epilepsy. *Epilepsy Res* 2009; 83: 257-60.
- Usui N, Maesawa S, Kajita Y, Endo O, Takebayashi S, Yoshida J. Suppression of secondary generalization of limbic seizures by stimulation of subthalamic nucleus in rats. *J Neurosurg* 2005; 102: 1122-9.
- Van Hese P, Martens JP, Waterschoot L, Boon P, Lemahieu I. Automatic detection of spike and wave discharges in the EEG of genetic absence epilepsy rats from Strasbourg. *IEEE Trans Biomed Eng* 2009; 56: 706-17.
- van Rijckevorsel K, Abu Serieh B, de Tourtchaninoff M, Raftopoulos C. Deep EEG recordings of the mammillary body in epilepsy patients. *Epilepsia* 2005; 46: 781-5.
- Velasco AL, Velasco F, Velasco M, Trejo D, Castro G, Carrillo-Ruiz JD. Electrical stimulation of the hippocampal epileptic foci for seizure control: a double-blind, long-term follow-up study. *Epilepsia* 2007a; 48: 1895-903.
- Velasco AL, Velasco M, Velasco F, Menes D, Gordon F, Rocha L, et al. Subacute and chronic electrical stimulation of the hippocampus on intractable temporal lobe seizures: preliminary report. *Arch Med Res* 2000a; 31: 316-28.

- Velasco F, Velasco AL, Velasco M, Jimenez F, Carrillo-Ruiz JD, Castro G. Deep brain stimulation for treatment of the epilepsies: the centromedian thalamic target. *Acta Neurochir Suppl* 2007b; 97: 337-42.
- Velasco F, Velasco M, Cepeda C, Munoz H. Wakefulness-sleep modulation of thalamic multiple unit activity and EEG in man. *Electroencephalogr Clin Neurophysiol* 1979; 47: 597-606.
- Velasco F, Velasco M, Jimenez F, Velasco AL, Brito F, Rise M, et al. Predictors in the treatment of difficult-to-control seizures by electrical stimulation of the centromedian thalamic nucleus. *Neurosurgery* 2000b; 47: 295-304; discussion 304-5.
- Velasco F, Velasco M, Jimenez F, Velasco AL, Marquez I. Stimulation of the central median thalamic nucleus for epilepsy. *Stereotact Funct Neurosurg* 2001a; 77: 228-32.
- Velasco F, Velasco M, Ogarrio C, Fanghanel G. Electrical stimulation of the centromedian thalamic nucleus in the treatment of convulsive seizures: a preliminary report. *Epilepsia* 1987; 28: 421-30.
- Velasco F, Velasco M, Velasco AL, Jimenez F, Marquez I, Rise M. Electrical stimulation of the centromedian thalamic nucleus in control of seizures: long-term studies. *Epilepsia* 1995; 36: 63-71.
- Velasco F, Velasco M, Velasco AL, Menez D, Rocha L. Electrical stimulation for epilepsy: stimulation of hippocampal foci. *Stereotact Funct Neurosurg* 2001b; 77: 223-7.
- Velisek L, Veliskova J, Moshe SL. Electrical stimulation of substantia nigra pars reticulata is anticonvulsant in adult and young male rats. *Exp Neurol* 2002; 173: 145-52.
- Veliskova J, Velisek L, Moshe SL. Subthalamic nucleus: a new anticonvulsant site in the brain. *Neuroreport* 1996; 7: 1786-8.
- Vercueil L. Parkinsonism and Epilepsy: Case Report and Reappraisal of an Old Question. *Epilepsy Behav* 2000; 1: 128-130.
- Vercueil L, Benazzouz A, Deransart C, Bressand K, Marescaux C, Depaulis A, et al. High-frequency stimulation of the subthalamic nucleus suppresses absence seizures in the rat: comparison with neurotoxic lesions. *Epilepsy Res* 1998; 31: 39-46.
- Vesper J, Steinhoff B, Rona S, Wille C, Bilic S, Nikkhah G, et al. Chronic high-frequency deep brain stimulation of the STN/SNr for progressive myoclonic epilepsy. *Epilepsia* 2007; 48: 1984-9.
- Vonck K, Boon P, Achten E, De Reuck J, Caemaert J. Long-term amygdalohippocampal stimulation for refractory temporal lobe epilepsy. *Ann Neurol* 2002; 52: 556-65.
- Vonck K, Van Laere K, Dedeurwaerdere S, Caemaert J, De Reuck J, Boon P. The mechanism of action of vagus nerve stimulation for refractory epilepsy: the current status. *J Clin Neurophysiol* 2001; 18: 394-401.
- Voss NF, Davies KG, Boop FA, Montouris GD, Hermann BP. Spitting automatism in complex partial seizures: a nondominant temporal localizing sign? *Epilepsia* 1999; 40: 114-6.
- Wada JA. Unilateral blinking as a lateralizing sign of partial complex seizure of temporal lobe origin. In: Wada JA and Penry JK, editors. *Advances in Epileptology, Xth Epilepsy International Symposium*. New York: Raven Press, 1980: 533.

- Wallace RH, Marini C, Petrou S, Harkin LA, Bowser DN, Panchal RG, et al. Mutant GABA(A) receptor gamma2-subunit in childhood absence epilepsy and febrile seizures. *Nat Genet* 2001; 28: 49-52.
- Weil S, Arnold S, Eisensehr I, Noachtar S. Heart rate increase in otherwise subclinical seizures is different in temporal versus extratemporal seizure onset: support for temporal lobe autonomic influence. *Epileptic Disord* 2005; 7: 199-204.
- Wennberg R. Postictal coughing and noserubbing coexist in temporal lobe epilepsy. *Neurology* 2001; 56: 133-134.
- Werhahn KJ, Landvogt C, Klimpe S, Buchholz HG, Yakushev I, Siessmeier T, et al. Decreased dopamine D2/D3-receptor binding in temporal lobe epilepsy: an [¹⁸F]fallypride PET study. *Epilepsia* 2006; 47: 1392-6.
- Werhahn KJ, Noachtar S, Arnold S, Pfander M, Henkel A, Winkler PA, et al. Tonic seizures: their significance for lateralization and frequency in different focal epileptic syndromes. *Epilepsia* 2000; 41: 1153-61.
- Westerink BH, Korf J. Comparison of effects of drugs on dopamine metabolism in the substantia nigra and the corpus striatum of rat brain. *Eur J Pharmacol* 1976; 40: 131-6.
- Wiebe S, Blume WT, Girvin JP, Eliasziw M. A randomized, controlled trial of surgery for temporal-lobe epilepsy. *N Engl J Med* 2001; 345: 311-318.
- Williamson PD, Spencer DD, Spencer SS, Novelly RA, Mattson RH. Complex partial seizures of frontal lobe origin. *Ann Neurol* 1985; 18: 497-504.
- Wilson DH, Reeves AG, Gazzaniga MS. "Central" commissurotomy for intractable generalized epilepsy: series two. *Neurology* 1982; 32: 687-97.
- Windels F, Bruet N, Poupard A, Feuerstein C, Bertrand A, Savasta M. Influence of the frequency parameter on extracellular glutamate and gamma-aminobutyric acid in substantia nigra and globus pallidus during electrical stimulation of subthalamic nucleus in rats. *J Neurosci Res* 2003; 72: 259-67.
- Windels F, Bruet N, Poupard A, Urbain N, Chouvet G, Feuerstein C, et al. Effects of high frequency stimulation of subthalamic nucleus on extracellular glutamate and GABA in substantia nigra and globus pallidus in the normal rat. *Eur J Neurosci* 2000; 12: 4141-6.
- Wyler AR. Modern management of epilepsy. Recommended medical and surgical options. *Postgrad Med* 1993; 94: 97-8, 103-8.
- Wyllie E, Luders H, Morris HH, 3d, Lesser RP, Dinner DS, Hahn J, et al. Clinical outcome after complete or partial cortical resection for intractable epilepsy. *Neurology* 1987; 37: 1634-1641.
- Wyllie E, Lüders H, Morris HH, Lesser RP, Dinner DS. The lateralizing significance of versive head and eye movements during epileptic seizures. *Neurology* 1986a; 36: 606-611.
- Wyllie E, Luders H, Morris HH, Lesser RP, Dinner DS, Goldstick L. Ipsilateral forced head and eye turning at the end of the generalized tonic-clonic phase of versive seizures. *Neurology* 1986b; 36: 1212-1217.
- Zhang B, Chu J, Zhang J, Ma Y. Change of extracellular glutamate and gamma-aminobutyric acid in substantia nigra and globus pallidus during electrical stimulation of subthalamic nucleus in epileptic rats. *Stereotact Funct Neurosurg* 2008; 86: 208-15.
- Ziemann AE, Schnitzler MK, Albert GW, Severson MA, Howard MA, 3rd, Welsh MJ, et al. Seizure termination by acidosis depends on ASIC1a. *Nat Neurosci* 2008; 11: 816-22.

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SCIENTIFIC PRODUCTION

Article 1

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Does ictal dystonia have an inhibitory effect on seizure propagation in focal epilepsies?

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Abstract

Background: Several experimental studies have suggested that the basal ganglia are involved in the control of epileptic seizures. Clinical evidence is, however, sparse. In focal epilepsy, ictal version and ictal dystonia are thought to reflect seizure spread into the frontal eye field and the basal ganglia, respectively. Here we investigated whether the occurrence of dystonia during seizure evolution reflects mechanisms preventing secondary generalization. To this aim, the evolution of seizures in patients with focal epilepsies was compared as to whether concomitant (1) dystonia, (2) dystonia *and* version, or (3) version occurred.

Methods: Seizure evolutions of 79 patients characterized by either dystonia (n=29; 232 seizures), dystonia *and* head version in the same seizure evolution (n=9; 83 seizures) or head version (n=41; 330 seizures), were included in the study.

Results: Seizures with version generalized more often (95%, 82 of 86 seizures) than seizures without version (10%, 25 of 244 seizures, $p<0.0001$). The rate of secondary generalization was significantly lower in seizure evolutions in which ictal dystonia *and* version (62%, 13 of 21 seizures) occurred than in seizures with isolated version (95%, 82 of 86 seizures, $p<0.001$). The rate of secondary generalization was similar in seizures with (8%, 6 of 72 seizures) and seizures without ictal dystonia (3%, 5 of 160 seizures; $p>0.05$).

Conclusion: This study shows that unilateral ictal dystonia is associated with a lack of secondary generalization. This effect is likely to reflect the involvement of inhibitory mechanisms related to the basal ganglia, which exert an inhibiting effect on secondary seizure generalization if epileptic activity spreads into the frontal eye field.

Introduction

Experimental data accumulated over the past few years suggest that the basal ganglia system is involved in the propagation or control of epileptic seizures (Depaulis et al., 1994; Deransart and Depaulis, 2002). Indeed, since the pioneering work of Iadarola and Gale (1982), several animal studies have shown that most pharmacological manipulations to decrease the activity of neurons in the substantia nigra pars reticulata (SNr), one of the main output stations of the basal ganglia in rodents, suppress epileptic seizures in different animal models (Deransart and Depaulis, 2002; Iadarola and Gale 1982). Similarly, pharmacological manipulations of either the striatum, globus pallidus, or subthalamic nucleus, which result in a decrease of SNr neuron activity, have antiepileptic effects. Conversely, manipulations of the basal ganglia structures to increase their activity exacerbate the seizures (Turski et al., 1988; Deransart et al., 1988). Concomitant changes in the neural activity of basal ganglia structures during seizures have provided further insight into the cellular mechanisms (Deransart et al., 2001; Slaght et al., 2004; Paz et al., 2005). Furthermore, high-frequency stimulations of the subthalamic nucleus, as well as the SNr, interrupt epileptic seizures in different animal models (Vercueil et al., 1998; Velisek et al., 2002; Feddersen et al., 2007).

Only discrete changes have been reported in basal ganglia recordings during seizures in patients with epilepsy (Rektor et al., 2002). [18F]-Fluorodeoxyglucose positron emission tomography (FDG-PET) in patients with mesial temporal lobe epilepsy and contralateral ictal dystonia of the limbs has shown interictal hypometabolism in the striatum ipsilateral to the seizure focus (Dupont et al., 1988). A decrease of [18F] fluoro-L-DOPA uptake was observed in the putamen and the caudate nucleus of patients with ring chromosome 20 epilepsy (Biraben et al., 2004) or with refractory temporal lobe epilepsy (TLE) (Bouilleret et al., 2008). A reduction of dopamine transporter binding was also reported in patients with juvenile myoclonic epilepsy (Ciumas et al., 2008), and a reduction of D2/D3-receptor binding in the temporal lobe of TLE patients (Werhahn et al., 2006). Finally, clinical studies have reported that high-frequency stimulation of the subthalamic nucleus has antiepileptic effects in drug-resistant patients (Chabardes et al., 2002; Kahane et al., 2008). The analysis of seizure semiology is a clinically well established method for localizing the epileptogenic zone in patients being considered for resective epilepsy surgery (Rosenow and Lüders, 2001). Changes in seizure semiology reflect the propagation

of epileptic activity. This has been validated by electrical stimulation and imaging studies (Dupont et al., 1988; Godoy et al., 1990; Newton et al., 1992). In particular, contralateral head versions were shown to typically occur prior to secondary generalization in patients with focal epilepsy (Wyllie et al., 1986; O'Dwyer et al., 2007). This appears to be due to the propagation of the seizure to the frontal eye field, since electrical stimulation of this structure also elicits versive movements of the eyes and head to the opposite side (Godoy et al., 1990). On the other hand, ictal limb dystonia is one of the best lateralizing signs. It occurs contralateral to the seizure focus in TLE (Kotagal et al., 1989), and appears to reflect the involvement of the basal ganglia. A short-term increase in the perfusion of the basal ganglia was reported contralateral to the dystonic limb (Newton et al., 1992; Shin et al., 2002; Mizobuchi et al., 2004). In patients with ictal dystonia, interictal hypometabolism was observed in the striatal region with [18F] fluorodeoxyglucose positron emission tomography (FDG–PET) (Dupont et al., 1988). Recently, a negative correlation between ictal dystonia and the rate of secondary generalization of focal seizures was shown in patients with temporal lobe epilepsy (Cleto Dal-Col et al., 2008). Altogether, these data suggest that epileptic patients with dystonia exhibit less generalization than patients with version and that this difference is due to the involvement of the basal ganglia.

The present study was designed to explore the hypothesis that propagation of seizure activity to the basal ganglia could interfere with secondary generalization. To this aim, we compared the rate of secondary generalization in patients with focal epilepsies, in whom (1) dystonia, (2) version, or (3) dystonia *and* version occurred during their seizure evolution.

Methods

A database search was performed in the video archive of the University of Munich Epilepsy Monitoring Unit (EMU) using the terms version and dystonia. All digital videos were then reviewed; nine were excluded from further evaluation because of low technical quality. Six hundred forty-five seizures of 79 patients were included in the final analysis on the basis of the seizure video criteria described below.

Patients

All patients had medically refractory focal epilepsies and underwent a standardized presurgical evaluation including multichannel EEG-video monitoring, high resolution magnetic resonance imaging (MRI) specified for chronic epilepsy, and neuropsychological testing. Additional imaging studies in selected patients included interictal FDG-PET and subtraction of ictal and interictal 99mTc-ethyl-cysteinate-dimer single photon emission computerized tomography (ECD-SPECT). These procedures were performed according to protocols published in detail previously (Noachtar et al., 1998; Arnold et al., 2000). The localization of the epileptogenic zone was defined in a patient management meeting attended by epileptologists, neuroradiologists, neurosurgeons, and neuropsychologists. Localization to one lobe required concordance of at least two of the following methods: interictal EEG, ictal EEG, MRI, PET, SPECT, seizure semiology, and no contradictory results of other methods.

EEG-video monitoring

All patients underwent at least 3 days of continuous non-invasive EEG-video monitoring with closely spaced surface electrodes (10-10 system) and sphenoidal electrodes using 32-128 channel EEG machines (Vanguard, Cleveland/Ohio, and XLTEK, London, Ontario/Canada). The interictal and ictal EEG data were classified according to a system described in detail previously (Lüders and Noachtar, 2000; Pfänder et al., 2002).

Seizure semiology

The seizures were first analyzed visually by at least two senior epileptologists and classified according to a semiological seizure classification (Lüders et al., 1998). Ictal dystonia and ictal version were assessed by two observers which were blinded to the EEG. Seizures of patients were only included when concordance of semiologic findings was obtained from both observers, independently. Secondary generalization was defined by loss of consciousness and generalized increase in the muscular tone evolving into bilateral clonic movements with a decrease in frequency and gain in amplitude. Seizures were divided into the following three groups:

Ictal Dystonia Group

In this group were patients who had at least one seizure with ictal dystonia recorded in the EMU. Seizures with ictal dystonia were defined as sustained unnatural posturing with a tonic and a rotatory component of one upper or lower extremity (Kotagal et al., 1989). Unilateral tonic seizures without the rotatory component were excluded. No patient showed independent ictal dystonia bilaterally.

Ictal Dystonia and Version Group

Patients in whom head version and dystonia appeared during at least one seizure evolution were included in this group. Seizures with solely dystonia or version were excluded from the final analysis.

Ictal Version Group

These patients had at least one seizure with version during EEG-video recording. Seizures with version were defined as late contralateral forced and involuntary head movement resulting in unnatural positioning (Wyllie et al., 1986) also initially ipsilateral movements followed by contralateral head movements were included (O'Dwyer et al., 2007).

Statistical analysis

χ^2 analysis or Fisher's exact test was used to evaluate the significance of the relationship of seizures with dystonia and/or version and the rate of secondary generalization. Significance was assumed at $p < 0.05$.

Results

The data of the patients whose ictal videos were included in the study are summarized in Table 1. Thirty-six of the 79 included patients were females; the average age of the group was 36 ± 11 years (range 13-67 years), the mean age of onset was 16 ± 12 years (range 1-55 years), and the average duration of epilepsy was 22 ± 12 years (range 2-49). Epilepsy syndromes included temporal lobe epilepsy (n=58), frontal lobe epilepsy (n=9), parieto-occipital epilepsy (n=1), and focal epilepsies that could not be further localized (n=10). Of the 58 patients with TLE, 52 had unilateral TLE and 6 patients had bilateral TLE (ictal lateralization of head movement direction or dystonia in each seizure was defined by the localization of the

ictal EEG). As we included patients whose seizures started in different cortical zones, we tested if the site of seizures origin could influence the occurrence of secondary generalization. This was not the case in our study population. We included 678 seizures of 79 patients in this study (mean 8,6 seizures; median 7 seizures; range 1 to 24 seizures per patient). However, we couldn't rule out that the likelihood of secondary generalization was, at least in part, correlated to the extent of the epileptogenic zone.

The ictal dystonia group contained 29 patients with 232 seizures. Of the 232 seizures, ictal dystonia occurred in 72 seizures evolutions (mean 2,5; median 2; min 1; max 7 seizures per patient) and in 160 seizures of these patients ictal dystonia was absent. In the ictal dystonia *and* ictal version group, 9 patients with 83 seizures were evaluated. Dystonia *and* version was recorded in 21 seizures (mean 3; median 3; min 1; max 4 seizures per patient) of all 83 seizures. Neither ictal dystonia nor ictal version occurred in 62 seizures of these patients occurred. Ictal version occurred prior to ictal dystonia in only one seizure evolution with ictal dystonia *and* ictal version. The ictal version group included 41 patients with 330 seizures. Eighty-six seizures of these patients included version (mean 2,2; median 2; min 1; max 9 seizures per patient) in their seizure evolution but in 244 seizures of these patients no ictal version occurred. The comparison of the above mentioned groups regarding the rate of secondary generalization of the seizures revealed the following results:

1. Among the three different groups, patients showed in some seizure evolutions ictal dystonia, ictal dystonia *and* version and ictal version which were absent in other seizure evolutions. Seizures without dystonia, without dystonia *and* version, and without version did not show any difference in the rate of secondary generalization (5 of 160 (3%) vs 5 of 62 (8%) vs 25 of 244 (10%), respectively; $p > 0.05$) (Fig. 1).
2. Secondary generalization significantly correlated with version:
 - a) Seizures with version generalized more often (95%, 82 of 86 seizures) than seizures without version (10%, 25 of 244 seizures, $p < 0.0001$) (Fig. 2 C).
 - b) Secondary generalization occurred more frequently when dystonia *and* version occurred (62%, 13 of 21 seizures), as compared to seizures without dystonia *and* without version (8%, 5 of 62 seizures, $p < 0.0001$) (Fig. 2 B).
 - c) Secondary generalization also occurred more frequently when seizures with dystonia *and* version (62%, 13 of 21 seizures) were compared to seizures with solely dystonia (8%, 6 of 72 seizures, $p < 0.0001$) (Fig. 2).

- d) Seizures with version generalized more often (95%, 82 of 86 seizures) than seizures with dystonia (8%, 6 of 72 seizures, $p < 0.0001$) (Fig. 2).
3. The rate of secondary generalization was significantly lower in seizure evolutions, in which ictal dystonia *and* version (62%, 13 of 21 seizures) occurred, compared with seizures with isolated version (95%, 82 of 86 seizures, $p < 0.001$) (Fig. 2).
4. The rate of secondary generalization was similar in seizures with ictal dystonia (8%, 6 of 72 seizures) and in seizures without ictal dystonia (3%, 5 of 160 seizures; $p > 0.05$) (Fig. 1 A).

Discussion

We investigated the rate of secondary generalization in three settings of seizure evolutions, i.e. seizures with (1) ictal version, (2) ictal version *and* dystonia in the same seizure evolution, and (3) ictal dystonia. Secondary generalization was more frequently observed in seizures with versions, which reflects seizure activity in the frontal eye field. Furthermore, our study revealed that secondary generalization followed significantly more often after seizures with ictal version, than after seizures with ictal dystonia or the combination of ictal dystonia and version (Fig. 1). This is in agreement with previous findings, indicating the probability of secondary generalization after ictal version is high (Wyllie et al., 1986). Version occurs with epileptic activation or spread of epileptic seizure activity into the frontal eye field (Godoy et al., 1990). It has been speculated that the high rate of secondary generalization following version in focal seizures is related to the high cortical connectivity of the frontal eye field (Croxson et al. 2005). This high connectivity would only lead to a high rate of secondary generalization if facilitatory mechanisms dominate and inhibitory mechanisms are absent. Our results show that the rate of secondary generalization is reduced when unilateral ictal limb dystonia occurred in addition to ictal head version. This finding suggests that ictal dystonia is associated with an inhibitory effect on seizure evolution, i.e. reduces the rate of secondary generalization only if concomitant activation of the frontal eye field occurs as reflected by head version. In clinical practice, the concomitant occurrence of version and dystonia is rare, and may occur staggered in time. In our study population, only nine patients exhibited both symptoms. Thus, it was not possible to further explore the interactions between version and dystonia in more detail.

The synchronization of EEG activity during sleep has been suggested to facilitate the initiation and propagation of partial seizures and that effects of sleep depend, at least in part, on the location of the epileptic focus (Herman et al., 2001). The effects of sleep on secondary generalization were reported to be significant between frontal versus parietal-occipital localization but not versus temporal localizations (with a high rate of sleep related secondary generalization in occipital lobe epilepsy). Although the effects of sleep on seizure evolution were not investigated in our patients and taking into account that most of them had temporal origin (58 out of 79 patients) with only one patient with parietal seizure the effects of sleep on secondary generalization depending on the seizure focus were assumed to have minor impact in our investigations.

The rate of secondary generalization was equal in all three groups studied, when either ictal dystonia and/or ictal version did not occur. This reflects the homogeneity of these groups and shows that the probability of secondary generalization is associated with the different semiological features reflecting different spread patterns of epileptic activity. In the present study, the group of patients with only ictal dystonia had the lowest probability of secondary generalization compared to seizure evolutions with ictal dystonia *and* version and compared to seizure evolutions with ictal version (Fig. 2). A recent study reported also a negative correlation between the occurrence of dystonia and bilateral tonic or clonic behaviors in patients with TLE (Cleto Dal-Col et al., 2008). It was suggested that the lower rate of generalization in patients with dystonia could be due to the involvement of the basal ganglia (Cleto Dal-Col et al., 2008). However, the rate of secondary generalization in our study was similar in the patients who exhibited ictal dystonia in a given seizure or not.

Therefore, based on our data, ictal dystonia itself is not sufficient to explain the low rate of secondary generalization. Our results show that ictal dystonia only in the presence of version is associated with reduced rate of secondary generalization (Fig.2). However, the authors do not mention the occurrence of version in their patients (Cleto Dal-Col et al., 2008). It is tempting to speculate that ictal dystonia reflects seizure inhibiting mechanisms, which are related to the high interconnections between the basal ganglia and the frontal lobes (Leh et al., 2007).

SPECT studies showed that ictal dystonia is associated with hyperperfusion in the striatum

(Newton et al., 1992); Mizobuchi et al., 2004; Joo et al., 2004). It remains unclear, however, if such hyperperfusion reflects a physiological activation or an inhibition of these structures. Patients with ictal dystonia have widespread temporal and extratemporal hypometabolism, also in the putamen, suggesting that dystonic posturing may result from the involvement of both putaminal and extratemporal cortical areas (Rusu et al., 2005). In the latter study, however, a higher rate of generalization was seen in patients with ictal dystonia. This may be explained by their higher rate of ictal version.

A study using invasive EEG recordings of the putamen contralateral to the dystonic limb and temporal and/or frontal lobe suggested that ictal dystonia is a “late symptom” in temporal lobe epilepsy (Kuba et al., 2003). According to the authors, widespread activation of the contralateral temporal and frontal lobes is required for the occurrence of ictal dystonia. However, the critical region involved in the genesis of ictal dystonia was not discussed. Although non-specific changes were reported in the putamen contralateral to ictal dystonia, they were not epileptic as such, and it is very unlikely that the putamen participates in the genesis of the epileptic discharge during its course (Kuba et al., 2003; Vercueil and Hirsch, 2002).

Animal studies have demonstrated that pharmacological manipulations or electrical stimulations of the basal ganglia suppress epileptic seizures (Deransart et al., 2002). It remains debatable whether dystonia in human patients reflects an activation or an inhibition of basal ganglia circuits due to seizure spread. However, electrophysiological recordings in animal models (Paz et al., 2005; Deransart et al., 2003) strongly suggest that when epileptic activity spreads to the basal ganglia, it may suppress the physiological firing rate of some circuits, which results in the termination of epileptic seizures. Further clinical studies are necessary to address this hypothesis.

Conclusions

Our data suggest that the basal ganglia play a role in controlling the propagation of epileptic seizures. Epileptic activation of the frontal eye field facilitates an inhibitory effect of the basal ganglia. A better understanding of such control mechanisms in epilepsy may open new vistas for therapeutic strategies such as deep brain stimulations or pharmacological approaches using dopaminergic compounds.

References

- Arnold S, Berthele A, Drzezga A, Tölle TR, Weis S, Werhahn KJ, Henkel A, Yousry TA, Winkler PA, Bartenstein P, Noachtar S. (2000) Reduction of benzodiazepine receptor binding is related to the seizure onset zone in extratemporal focal cortical dysplasia. *Epilepsia* 41:818-824.
- Biraben A, Semah F, Ribeiro MJ, Douaud G, Remy P, Depaulis A. (2004) PET evidence for a role of the basal ganglia in patients with ring chromosome 20 epilepsy. *Neurology* 63:73-77.
- Bouilleret V, Semah F, Chassoux F, Mantzarides M, Biraben A, Trebossen R, Ribeiro MJ. (2008) Basal ganglia involvement in temporal lobe epilepsy: a functional and morphologic study. *Neurology* 70:177-184.
- Chabardès S, Kahane P, Minotti L, Koudsie A, Hirsch E, Benabid AL. (2002) Deep brain stimulation in epilepsy with particular reference to the subthalamic nucleus. *Epileptic Disord* 4(Suppl 3):S83-93.
- Ciomas C, Wahlin TB, Jucaite A, Lindstrom P, Halldin C, Savic I. (2008) Reduced dopamine transporter binding in patients with juvenile myoclonic epilepsy. *Neurology* 71:788-794.
- Cleto Dal-Cól ML, Bertti P, Terra-Bustamante VC, Velasco TR, Araujo Rodrigues MC, Wichert-Ana L, Sakamoto AC, Garcia-Cairasco N. (2008) Is dystonic posturing during temporal lobe epileptic seizures the expression of an endogenous anticonvulsant system? *Epilepsy Behav* 12:39-48.
- Croxson PL, Johansen-Berg H, Behrens TE, Robson MD, Pinski MA, Gross CG, Richter W, Richter MC, Kastner S, Rushworth MF. (2005) Quantitative investigation of connections of the prefrontal cortex in the human and macaque using probabilistic diffusion tractography. *J Neurosci* 25:8854-8866.
- Depaulis A., M. Vergnes, Marescaux C. (1994) Endogenous control of epilepsy: the nigral inhibitory system. *Prog Neurobiol* 42:33-52.
- Deransart C, Vercueil L, Marescaux C, Depaulis A. (1988) The role of basal ganglia in the control of generalized absence seizures. *Epilepsy Res* 32:213-223.
- Deransart C, Lê-Pham BT, Hirsch E, Marescaux C, Depaulis A. (2001) Inhibition of the substantia nigra suppresses absences and clonic seizures in audiogenic rats, but not tonic seizures: evidence for seizure specificity of the nigral control. *Neuroscience* 105:203-211.
- Deransart C, Depaulis A. (2002) The control of seizures by the basal ganglia? A review of experimental data. *Epileptic Disord* 4 (Suppl 3):61-72.
- Deransart C, Hellwig B, Heupel-Reuter M, Léger JF, Heck D, Lücking CH. (2003) Single-unit analysis of substantia nigra pars reticulata neurons in freely behaving rats with genetic absence epilepsy. *Epilepsia* 44:1513-1520.
- Dupont S, Semah F, Baulac M, Samson Y. (1988) The underlying pathophysiology of ictal dystonia in temporal lobe epilepsy: an FDG-PET study. *Neurology* 51:1289-1292.
- Feddersen B, Vercueil L, Noachtar S, David O, Depaulis A, Deransart C. (2007) Controlling seizures is not controlling epilepsy: a parametric study of deep brain stimulation for epilepsy. *Neurobiol Dis* 27:292-300.

Godoy J, Lüders H, Dinner DS, Morris HH, Wyllie E. (1990) Versive eye movements elicited by cortical stimulation of the human brain. *Neurology* 40:296-299.

Herman ST, Walczak TS, Bazil CW. (2001) Distribution of partial seizures during the sleep--wake cycle: differences by seizure onset site. *Neurology* 56:1453-1459.

Iadorala MJ, Gale K. (1982) Substantia nigra: site of anticonvulsant activity mediated by gamma-aminobutyric acid. *Science* 218:1237-40.

Joo EY, Hong SB, Lee EK, Tae WS, Kim JH, Seo DW, Hong SC, Kim S, Kim MH. (2004) Regional cerebral hyperperfusion with ictal dystonic posturing: ictal-interictal SPECT subtraction. *Epilepsia* 45:686-689.

Kahane P, Saillet S, Minotti L, Vercueil L, Chabardès S, Depaulis A. (2008) Neurostimulation for epilepsy: myth or reality? In Kahane P, Berg A, Löscher W, Nordli D, Perucca E, (eds). *Drug-resistant epilepsies. Progress in epileptic disorders Vol. 7*. Montrouge:John Libbey Eurotext:153-169.

Kotagal P, Lüders H, Morris HH, Dinner DS, Wyllie E, Godoy J, Rothner AD. (1989) Dystonic posturing in complex partial seizures of temporal lobe onset: a new lateralizing sign. *Neurology* 39:196-201.

Kuba R, Rektor I, Brázdil M. (2003) Ictal limb dystonia in temporal lobe epilepsy. an invasive video-EEG finding. *Eur J Neurol* 10:641-649.

Leh SE, Ptito A, Chakravarty MM, Strafella AP. (2007) Fronto-striatal connections in the human brain: a probabilistic diffusion tractography study. *Neurosci Lett* 419:113-118.

Lüders H, Acharya J, Baumgartner C, Benbadis S, Bleasel A, Burgess R, Dinner DS, Ebner A, Foldvary N, Geller E, Hamer H, Holthausen H, Kotagal P, Morris H, Meencke HJ, Noachtar S, Rosenow F, Sakamoto A, Steinhoff BJ, Tuxhorn I, Wyllie E. (1998) Semiological seizure classification. *Epilepsia* 39:1006-1013.

Lüders HO, Noachtar S. (2000) Atlas and Classification of Electroencephalography. Philadelphia: Saunders.

Mizobuchi M, Matsuda K, Inoue Y, Sako K, Sumi Y, Chitoku S, Tsumaki K, Takahashi M. (2004) Dystonic posturing associated with putaminal hyperperfusion depicted on subtraction SPECT. *Epilepsia* 45:948-953.

Newton MR, Berkovic SF, Austin MC, Reutens DC, McKay WJ, Bladin PF. (1992) Dystonia, clinical lateralization, and regional blood flow changes in temporal lobe seizures. *Neurology* 42:371-377.

Noachtar S, Arnold S, Yousry TA, Bartenstein P, Werhahn KJ, Tatsch K. (1998) Ictal technetium-99m ethyl cysteinate dimer single-photon emission tomographic findings and propagation of epileptic seizure activity in patients with extratemporal epilepsies. *Eur J Nucl Med* 25:166-172.

O'Dwyer R, Silva Cunha JP, Vollmar C, Mauerer C, Feddersen B, Burgess RC, Ebner A, Noachtar S. (2007) Lateralizing significance of quantitative analysis of head movements before secondary generalization of seizures of patients with temporal lobe epilepsy. *Epilepsia* 48:524-530.

- Paz JT, Deniau JM, Charpier S. (2005) Rhythmic bursting in the cortico-subthalamo-pallidal network during spontaneous genetically determined spike and wave discharges. *J Neurosci* 25:2092-2101.
- Pfänder M, Arnold S, Henkel A, Weil S, Werhahn KJ, Eisensehr I, Winkler PA, Noachtar S. (2002) Clinical features and EEG findings differentiating mesial from neocortical temporal lobe epilepsy. *Epileptic Disord* 4:189-195.
- Rektor I, Kuba R, Brázdil M. (2002) Interictal and ictal EEG activity in the basal ganglia: an SEEG study in patients with temporal lobe epilepsy. *Epilepsia* 43:253-262.
- Rosenow F, Lüders H. (2001) Presurgical evaluation of epilepsy. *Brain* 124:1683-1700.
- Rusu V, Chassoux F, Landré E, Bouilleret V, Nataf F, Devaux BC, Turak B, Semah F. (2005) Dystonic posturing in seizures of mesial temporal origin: electroclinical and metabolic patterns. *Neurology* 65:1612-1619.
- Shin WC, Hong SB, Tae WS, Kim SE. (2002) Ictal hyperperfusion patterns according to the progression of temporal lobe seizures. *Neurology* 58:373-380.
- Slaght SJ, Paz T, Chavez M, Deniau JM, Mahon S, Charpier S. (2004) On the activity of the corticostriatal networks during spike-and-wave discharges in a genetic model of absence epilepsy. *J Neurosci* 24:6816-6825.
- Turski L, Cavalheiro EA, Bortolotto ZA, Ikonomidou-Turski C, Kleinrok Z, Turski WA. (1988) Dopamine-sensitive anticonvulsant site in the rat striatum. *J Neurosci* 8:4027-4037.
- Velíšek L, Velísková J, Moshé SL. (2002) Electrical stimulation of substantia nigra pars reticulata is anticonvulsant in adult and young male rats. *Exp Neurol* 173:145-152.
- Vercueil L, Benazzouz A, Deransart C, Bressand K, Marescaux C, Depaulis A, Benabid AL. (1998) High-frequency stimulation of the subthalamic nucleus suppresses absence seizures in the rat: comparison with neurotoxic lesions. *Epilepsy Res* 31:39-46.
- Vercueil L, Hirsch E. (2002) Seizures and the basal ganglia: a review of the clinical data. *Epileptic Disord* 4(Suppl 3):S47-54.
- Werhahn KJ, Landvogt C, Klimpe S, Buchholz HG, Yakushev I, Siessmeier T, Müller-Forell W, Piel M, Rösch F, Glaser M, Schreckenberger M, Bartenstein P. (2006) Decreased dopamine D2/D3-receptor binding in temporal lobe epilepsy: an [18F]fallypride PET study. *Epilepsia* 47:1392-1396.
- Wyllie E, Lüders H, Morris HH, Lesser RP, Dinner DS, Goldstick L. (1986) Ipsilateral forced head and eye turning at the end of the generalized tonic-clonic phase of versive seizures. *Neurology* 36:1212-1217.

Table 1: Patient data

	All	Patients with seizures with dystonia	Patients with seizures with dystonia & version	Patients with seizures with version
Patients	79	29	9	41
Female/male	36/43	13/16	5/4	18/23
Age (years)	36 ± 11	36 ± 11	37 ± 12	36 ± 11
Age at onset (years)	16 ± 12	14 ± 11	10 ± 11	18 ± 13
Duration of epilepsy (years)	22 ± 12	22 ± 12	26 ± 11	18 ± 11
Temporal lobe epilepsy (TLE)	58	22	7	29
<i>mesial TLE</i>	23	10	3	10
<i>neocortical TLE</i>	29	10	2	17
<i>Bitemporal</i>	6	2	2	2
Frontal lobe epilepsy	10	1	0	9
Parietal lobe epilepsy	1	1	0	0
Focal Epilepsy (not further localized)	10	5	2	3

Patient data including gender, age, age at onset, duration of epilepsy, and epilepsy syndrome.

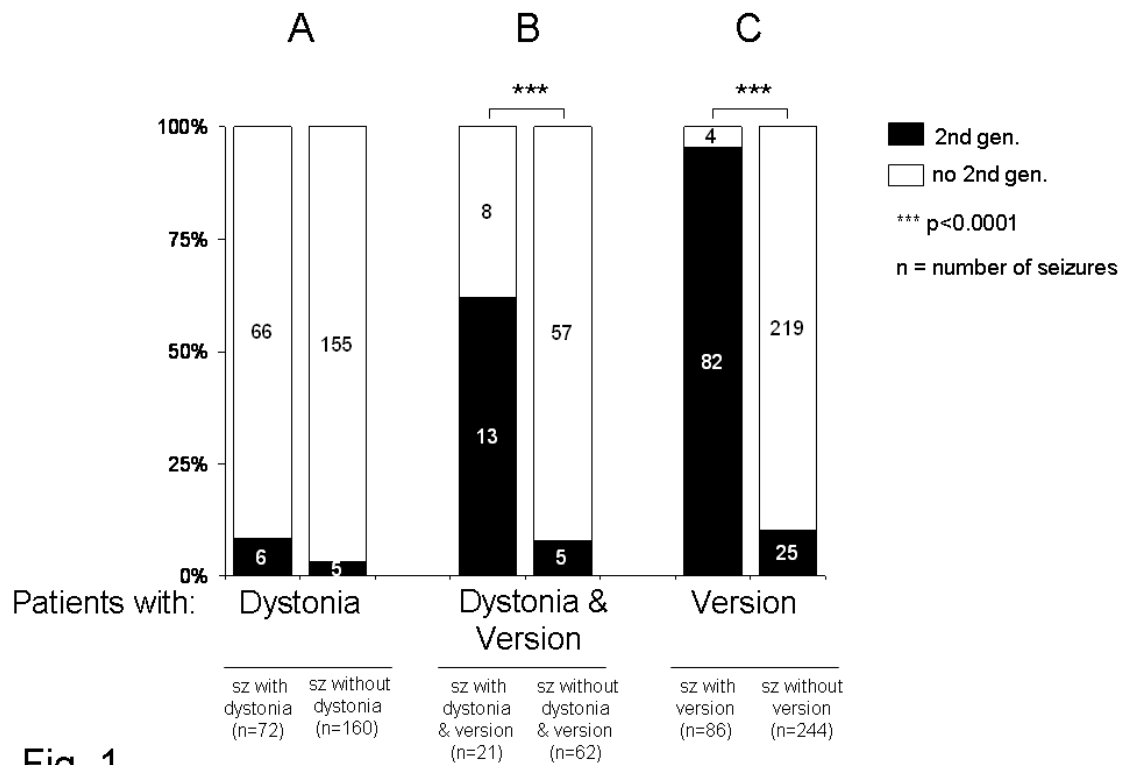


Figure 1 shows the rate of secondary generalization in seizures of each group with and without dystonia, dystonia *and* version, or version.

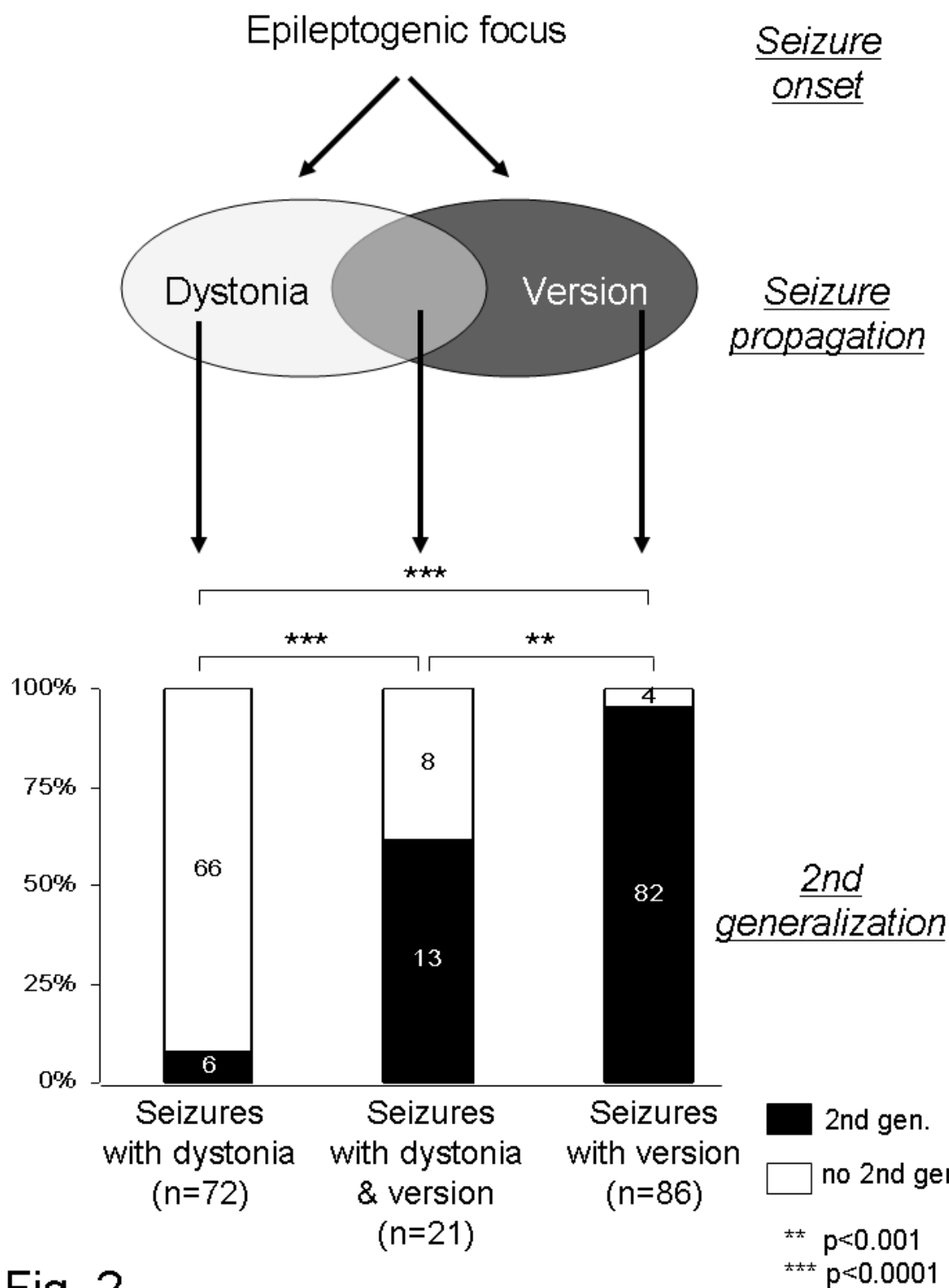


Figure 2 indicates the rate of secondary generalization in seizures with dystonia compared to seizures with dystonia *and* version, and seizures with version.

Article 2

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Controlling seizures is not controlling epilepsies: a
parametric study of deep brain stimulation for epilepsy.

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Controlling seizures is not controlling epilepsy: A parametric study of deep brain stimulation for epilepsy

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Pharmacological inhibition and high-frequency stimulation (HFS) of the substantia nigra pars reticulata (SNr) suppress seizures in different animal models of epilepsy. The aim of the present study was to determine the optimal parameters of HFS to control spontaneous seizures in a genetic model of absence epilepsy in the rat. Single SNr stimulation that was bilateral, bipolar and monophasic at 60 Hz frequency and with 60- μ s pulse width was optimal. However, when used for repeated stimulations, long-term suppression did not occur and even the number of seizures increased. A delay of at least 60 s between stimulations was necessary to be fully effective. Although single HFS of the SNr can be used to suppress ongoing seizures, repeated HFS is ineffective and could even aggravate seizures in our model. Thus investigations of accurate stimulation procedures are still needed.
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Keywords: High-frequency stimulation; Deep brain stimulation; Parameters; Epilepsy; Substantia nigra; Animal model

Introduction

About one third of epileptic patients are resistant to antiepileptic drugs (AED), and only 30% are candidates for resective surgery (Hauser and Hesdorffer, 1990; Semah et al., 1998; Wiebe et al., 2001). Deep brain stimulation (DBS) has been considered as an alternative therapy since subcortical networks are assumed to control cortical excitability. Several structures have been targeted for the neuromodulation of seizures (Theodore and Fisher, 2004; Chabardes et al., 2002; Deransart et al., 2006). Recently, the subthalamic nucleus (STN) has attracted attention because of neurological expertise developed in the treatment of movement disorders (Benabid, 2003; Perlmutter and Mink, 2006), as well as

experimental studies suggesting that the basal ganglia control several types of seizures (Deransart and Depaulis, 2002; Gale, 1985; Depaulis et al., 1994). In particular, it was shown that pharmacological inhibition of the STN has an antiepileptic effect in different animal models (Deransart et al., 1996; Veliskova et al., 1996; Dybdal and Gale, 2000) and that high-frequency stimulations (HFS) of the STN interrupt seizures (Vercueil et al., 1998; Lado et al., 2003). Therefore, a few clinical studies have explored the effects of STN-HFS in patients with drug-resistant epilepsy (Chabardes et al., 2002; Benabid et al., 2002; Loddenkemper et al., 2001; Handforth et al., 2006) with encouraging results. However, seizures were suppressed in only some patients, but not in others. This difference may be due to the heterogeneity of the population studied but also to the non-optimal nature of the conditions. Indeed, so far there are no data supporting the view that the STN is the optimal target for DBS in epilepsy or that the HFS protocols used for movement disorders should be applied. The need to determine optimal target, stimulation modes and parameters for DBS in epilepsy is further motivated by the fact that, unlike Parkinsonian symptoms which can be investigated in the surgery room (Limousin et al., 1995, 1998; Rizzone et al., 2001; Moro et al., 2002), epileptic seizures are less frequent and the impact of optimal and safe stimulation parameters is critical (Theodore and Fisher, 2004; Deransart et al., 2006).

The substantia nigra pars reticulata (SNr) is an interesting alternative target for DBS in epilepsy. As the main output of the basal ganglia, it was shown to be a key structure for the control of seizures in different models (Deransart and Depaulis, 2002; Gale, 1985; Depaulis et al., 1994; Velisek et al., 2002). Moreover, electrode contacts close to the SNr were reported to be the most effective at suppressing seizures in epileptic patients (Chabardes et al., 2002). Therefore, the aim of the present study was to examine the SNr as a potential target for DBS in epilepsy and to determine the optimal modes and parameters of stimulation to suppress generalized seizures in an animal model of chronic epilepsy with spontaneous recurrent seizures, the Generalized

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Absence Epilepsy Rat from Strasbourg (GAERS) (Danover et al., 1998; Depaulis and van Luitjelaar, 2005). Although AED normally controls typical absence seizures in humans, this validated model offers three advantages: (i) the high recurrence of spontaneous seizure provides the possibility of investigating most of the stimulation parameters; (ii) it is responsive to inhibition of the SNr (Deransart et al., 1996; Depaulis et al., 1988) and was used for the first proof of concept of STN-DBS in epilepsy (Vercueil et al., 1998); (iii) a thalamo-cortical circuit is known to generate spike-and-wave discharges (SWD), a circuit involved in different forms of generalized seizures (Danover et al., 1998; Depaulis and van Luitjelaar, 2005). Using this model, we first determined the modes and parameters of stimulation for obtaining optimal antiepileptic effects after single 5-s stimulations. In the second part of this study, different protocols of repeated stimulations were tested.

Materials and methods

Animals

Adult male GAERS (250–350 g) bred in our laboratory were used in this study. This strain has absence seizures during quiet wakefulness (Danover et al., 1998). They are characterized by behavioral arrest associated with cortical and thalamic bilateral spike-and-wave discharges (SWD) (frequency, 7–9 C/s; amplitude, 400–600 μ V; mean duration 20 s). Rats were kept in individual cages under a 12/12 h normal light/dark cycle, with food and water *ad libitum*. All experiments were carried out in accordance with the European Community Council Directive of November 24, 1986 (86/609/EEC) and all procedures were approved by the local department of the veterinarian services for the use and care of animals (DSV).

Surgery

Four single contact epidural stainless-steel electrodes, placed bilaterally over the frontal and parietal cortex, were implanted in 46 rats under general anesthesia (diazepam 4 mg/kg *i.p.*, ketamine 100 mg/kg *i.p.*). An additional single contact electrode was positioned over the left cerebellum and served as the reference. Two bipolar electrodes formed of two enamel-insulated twisted wires (175 μ m) separated by 400–600 μ m at the tip were placed stereotactically in the right and left SNr (AP: +2.7 mm; ML: \pm 2.2 mm; DV: -8.2 mm from the interaural line according to Paxinos and Watson (1998). All electrodes were connected to a female microconnector that was fixed to the skull by acrylic cement. Animals were allowed 1 week for recovery, during which they were handled daily for habituation. After the implantations, the rats were kept a maximum of 2 months (46 ± 5 days) before being killed.

Electroencephalographic recordings

Electroencephalograms (EEGs) were recorded in awake freely moving animals using a digital acquisition system (Coherence 3NT, Deltamed, France). Sampling rate: 256 Hz, high pass filter 1 Hz/low pass filter 97 Hz). During the recording and stimulation sessions, the rats were continuously watched to detect changes in their posture and behavior. All sessions did not exceed 3 h and were performed between 9:00 a.m. and 5:00 p.m. No significant difference was observed in the number (27 ± 3.5 vs 26 ± 2.0) and mean duration of SWD (18 ± 1.7 vs 20 ± 1.8 s, $n=8$) between the first reference period and the last one (21 ± 0.7 days in between).

Intracerebral stimulation

Single stimulations

All stimulations were performed with a Grass S88 stimulator delivering square current pulses of constant current. After the animals were habituated to the test cage for 10–15 min, the experimenter detected seizures by online continuous visual inspection of the EEG. Five-second single-shock electrical stimulations were applied within 2 s after the beginning of an SWD, as previously reported in the same model (Vercueil et al., 1998). The intensity was progressively increased in steps of 5 μ A, with at least 2 min between two stimulations, until (i) an interruption of the SWD (=antiepileptic threshold); (ii) head orientation or oral automatisms (=behavioral threshold) or (iii) clonic movements of the limbs or contralateral whole body turning around the axis (=motor threshold) was observed. The maximal intensity cut-off was set at 300 μ A. Effective interruption of the SWD was defined as a return to baseline activity in the cortex within 2 s following the start of the stimulation and was validated by time–frequency analysis of the EEG signal (see below). Such thresholds were determined for different modes of stimulation (referential vs bipolar; monophasic vs biphasic; unilateral vs bilateral) and different parameters (pulse width=10, 30, 60, 120, 200 μ s and frequency=5, 30, 60, 130, 350, 500 Hz) to obtain optimal stimulation parameters, defined by the lowest possible antiepileptic threshold and maximal discrimination to thresholds inducing side effects (behavioral and motor threshold).

For the localization study, stimulations had the following parameters: referential, monophasic, unilateral, pulse width=60 μ s, frequency=130 Hz and intensity=0–300 μ A. With two bipolar electrodes per rat, a maximum of four different referential recordings site were obtained per animal. For this reason, “*n*” indicates the number of animals used and “*c*” the number of electrodes contacts.

A time–frequency analysis of six interrupted SWDs obtained in six rat was performed using an in-house developed toolbox of Statistical Parametric Mapping 5 software (www.fil.ion.ucl.ac.uk/spm, Wellcome Department of Imaging Neuroscience, University College London, UK) for dynamical analysis of intracerebral EEG. For each interrupted SWD, the amplitude (square-root of power) of oscillatory activity between 2 and 128 Hz, from 10 s before the stimulation onset and up to 15 s thereafter, was obtained using standard time–frequency analysis based on the Morlet wavelet transform (Le Van Quyen et al., 2001). For each frequency, the amplitude was computed on 7 periods length sliding time-window, providing an effective frequency specific time resolution. Time–frequency sampling of the time–frequency plane was 19.5 ms/4 Hz. Time–frequency data were normalized using the standard procedure (for each frequency, the mean of the baseline was subtracted and then data were divided by the standard deviation of the baseline, here defined as the 5 s preceding the stimulation onset). Finally, the time–frequency plane was averaged over the SWDs to obtain the common pattern between the SWDs.

Repeated stimulations

Repeated stimulations were performed in the same animals using the optimal modes and parameters determined in the preceding experiment. After the animals were habituated to the test cage, EEG was recorded for a 20-min reference period followed by 40 min of EEG with repeated stimulations and then by another 20 min period without stimulation. First, three different ON and OFF sequences were tested (continuously ON; 5 s ON 5 s OFF; 5 s ON 15 s OFF). In

a second experiment, two seizure-dependent stimulation modes were used in which the experimenter triggered the stimulation (i) upon onset of every seizure and (ii) upon onset of a seizure but with a minimum delay of 1 min after the preceding stimulation. For each 20 min period, (i) the number of SWD, (ii) their cumulated duration and (iii) their mean durations were measured.

Histology

Upon completion of the study, the animals were killed by an overdose of pentobarbital and the brains were removed and cut in 20 μ m coronal sections. These sections were stained with cresyl violet and each stimulation site was localized with reference to the atlas of Paxinos and Watson (1998).

Data analysis

All data (thresholds or SWD) were expressed as mean \pm S.E.M. and were compared using the non-parametric Kruskal–Wallis and Mann–Whitney tests when independent groups were concerned (localization study, comparisons between modes of stimulation, mean duration of the SWD) or using the non-parametric Friedman test and Wilcoxon tests for related samples (comparisons between parameters of stimulations, comparison between periods). The significance level for all statistical analyses was set at $p < 0.05$.

Results

Single stimulations

Suppressive effect of high-frequency stimulation of SNr

The effects of a unilateral 5-s stimulation of the SNr in a monophasic and bipolar modes and with “classical” parameters

(frequency: 130 Hz, pulse width: 60 μ s) were tested in a first experiment in 14 GAERS at both electrode locations within the SNr. In all animals, such stimulations interrupted the SWDs at a mean threshold of 32.9 ± 7.1 μ A. This threshold was significantly lower than either behavioral or motor thresholds (42.0 ± 6.8 and 50.5 ± 7.2 μ A, $p < 0.05$, respectively) (Fig. 1). Averaged ($n=6$) time–frequency analysis of EEG recordings 10 s before, during and 10 s after stimulation at the antiepileptic threshold (zoom of the time–frequency plane shown in Fig. 1C) revealed that the interruption of SWDs by electrical stimulation of the SNr was rapid (less than 1 s) and was not accompanied by any reproducible (surviving averaging) cortical pattern of facilitation or suppression of power, in comparison to baseline power, whatever the frequency (from 2 Hz up to 128 Hz) and the latency (from the onset of stimulation up to 15 s thereafter).

SNr anatomical specificity

In order to determine SNr anatomical specificity, the thresholds were compared between sites located in the SNr and adjacent regions (substantia nigra pars compacta, zona incerta, cerebral peduncle). Since no significant differences were observed between right ($c=17$; $n=11$) and left sides ($c=39$; $n=24$) for antiepileptic thresholds (66.7 ± 3.6 and 73.8 ± 9.1 μ A, respectively, $p > 0.05$) stimulation sites were compared irrespective of their side. The lowest values were obtained in the SNr for each type of threshold. The differences versus SNr were significant for sites located in the zona incerta (+30%) and cerebral peduncles (+312%), whereas non-significant values were obtained at sites located in the SNC (Figs. 2A and B).

Comparison of antiepileptic thresholds between sites located in the dorsomedial ($c=22$) vs ventrolateral SNr parts ($c=34$) revealed no significant difference (data not shown). Similarly, threshold values at sites located in the anterior part of the SNr (i.e.,

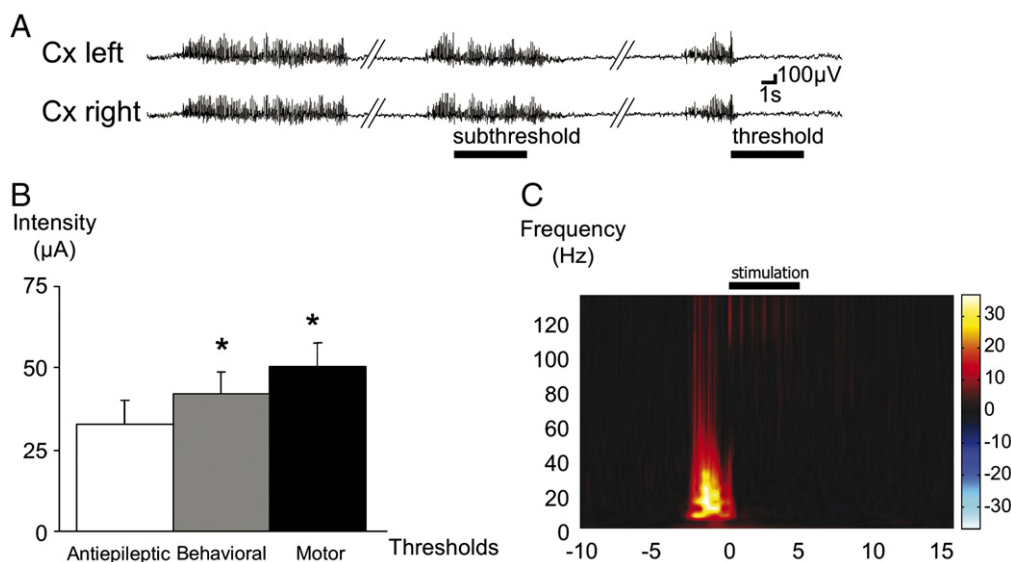


Fig. 1. Seizure interruption with single unilateral bipolar SNr stimulation in GAERS (stimulation mode: bipolar, monophasic, unilateral, 60 μ s, 130 Hz). (A) Epidural cortical EEG recordings (frontal and parietal referential derivations, upper and lower traces respectively) with subthreshold and antiepileptic threshold stimulations. (B) Antiepileptic, behavioral and motor thresholds as determined by 5 μ A incremental steps ($*p < 0.05$, Wilcoxon test, compared to antiepileptic thresholds). (C) Time–frequency chart of power averaged over derivations and over six SWDs suppressed by 130 Hz stimulation. Before averaging the power was frequency-normalized according to interictal activity. The color scale indicates the increase (reddish) or decrease (bluish) of power expressed in standard deviations of the interictal activity.

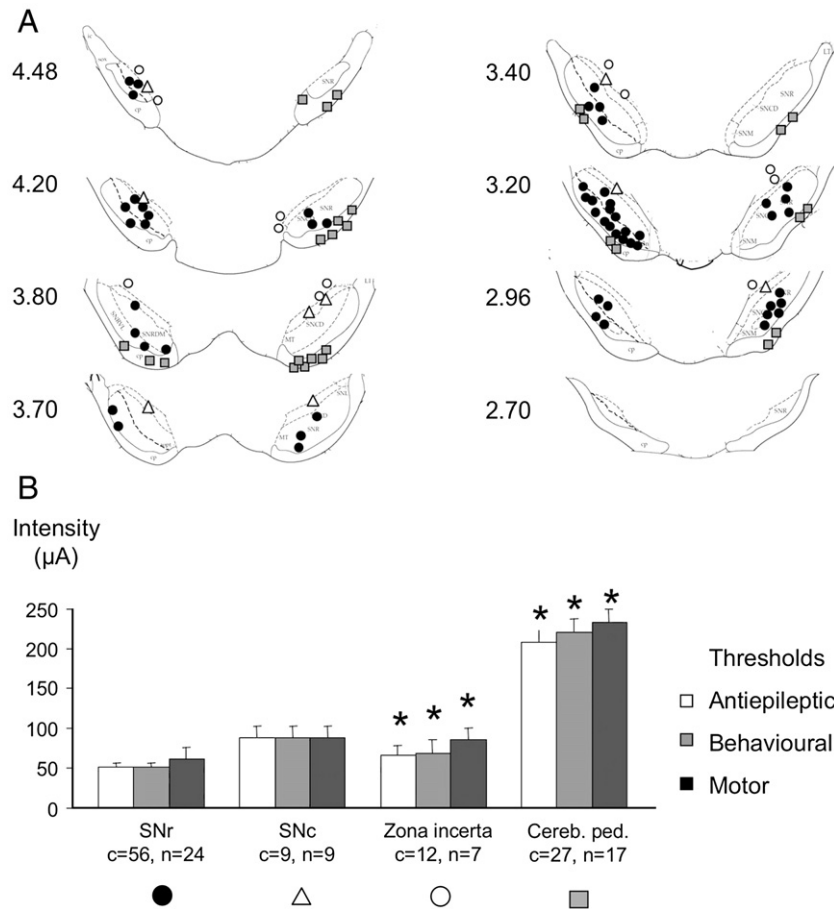


Fig. 2. Optimal localization of single unilateral referential stimulation (stimulation mode: referential, monophasic, unilateral, 60 µs, 130 Hz). (A) Distribution of electrode tips (numbers on the left refer to the antero-posterior coordinates; adapted from Paxinos and Watson). (B) Intensity thresholds according to electrode tips (Cereb. ped.: cerebral peduncles; * $p < 0.05$, Mann–Whitney U -test, compared with SNr values).

4.48–3.70 mm to interaural; $c=21$) were not significantly different from those obtained at sites located in the posterior part of the SNr (3.40–2.70 mm to interaural; $c=35$; data not shown).

Effects of modes of stimulation

Referential versus bipolar. In 14 animals in which both tips of electrodes were located inside the boundaries of the SNr, at least on one side, the monophasic, unilateral, 60-µs pulse width, 130 Hz frequency stimulation was compared with either a referential mode (one SNr tip as the cathode, reference electrode as the anode) or a bipolar mode (one SNr tip as the cathode, the other tip as the anode). Bipolar antiepileptic and behavioural thresholds were significantly lower (−26 and −11%, respectively) than referential ones whereas no differences were observed for motor thresholds (Fig. 3A).

Monophasic versus biphasic. In 10 animals with electrodes located in the SNr, bipolar, unilateral stimulations at a frequency of 130 Hz were compared whether they were monophasic (pulse width 60 µs) or biphasic (pulse width 30/30 µs or 60/60 µs up and down). All three thresholds obtained with either kind of biphasic stimulations were significantly 3-fold higher than with monophasic stimulations (+273, +239 and +215%, respectively) (Fig. 3B).

Bilateral versus unilateral. In eight animals with all four electrode tips in the SNr, the mean thresholds of bipolar, monophasic (pulse width=60 µs; frequency=130 Hz) stimulations were compared whether they were applied unilaterally or bilaterally. All three thresholds were significantly lower when bilateral stimulations were applied, as compared to the unilateral stimulation mode (−13, −17 and −17%, respectively) (Fig. 3C).

Influence of the stimulation parameters

Pulse width. The effects of bipolar, monophasic and unilateral SNr stimulations (frequency=130 Hz) were compared in seven animals (eight contacts) at different pulse width durations (10, 30, 60, 120, 200 µs). All three threshold values decreased in a hyperbolically way with the increase of the pulse width duration (Fig. 4A, upper panel). In addition, the difference between the antiepileptic and the motor thresholds was reduced when pulse width was increased; it was no longer significant at 200 µs (Fig. 4A, lower panel).

Frequency. The effects of bipolar, monophasic and unilateral SNr stimulations (pulse width=60 µs) were compared in the same seven animals (eight contacts) at different frequencies (5, 30, 60, 130, 350 and 500 Hz). No thresholds could be deter-

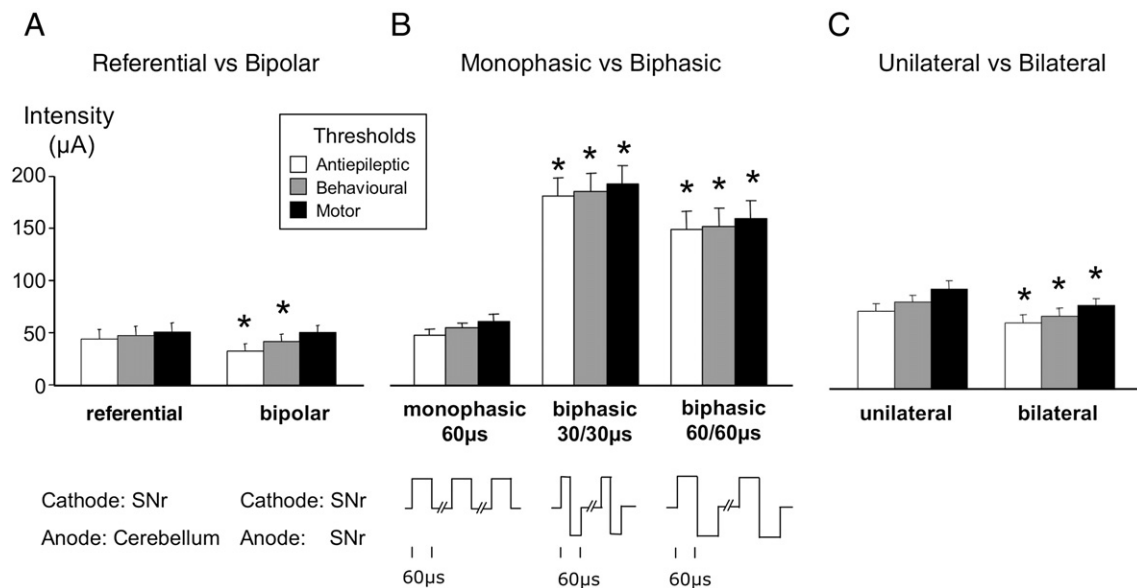


Fig. 3. Single high-frequency stimulation (60 µs, 130 Hz) changing stimulation mode: polarity, phase or laterality. Configurations of parameter changes are summarized under each corresponding graph. (A) Effect of polarity on intensity thresholds using monophasic unilateral stimulations ($p < 0.05$, Wilcoxon test, compared with referential values). (B) Effect of phase on intensity thresholds using bipolar unilateral stimulations ($p < 0.05$, Wilcoxon test, compared with monophasic values). (C) Effect of laterality on intensity thresholds using bipolar monophasic stimulations ($p < 0.05$, Wilcoxon test, compared with unilateral values).

mined below 300 µA at 5 Hz. Interruption of SWD was already observed at 30 Hz and the thresholds decreased at 60 Hz and higher frequencies (Fig. 4B, upper panel). Although no main

differences in antiepileptic threshold were observed at frequencies higher than 60 Hz, the difference in motor threshold was reduced (Fig. 4B, lower panel).

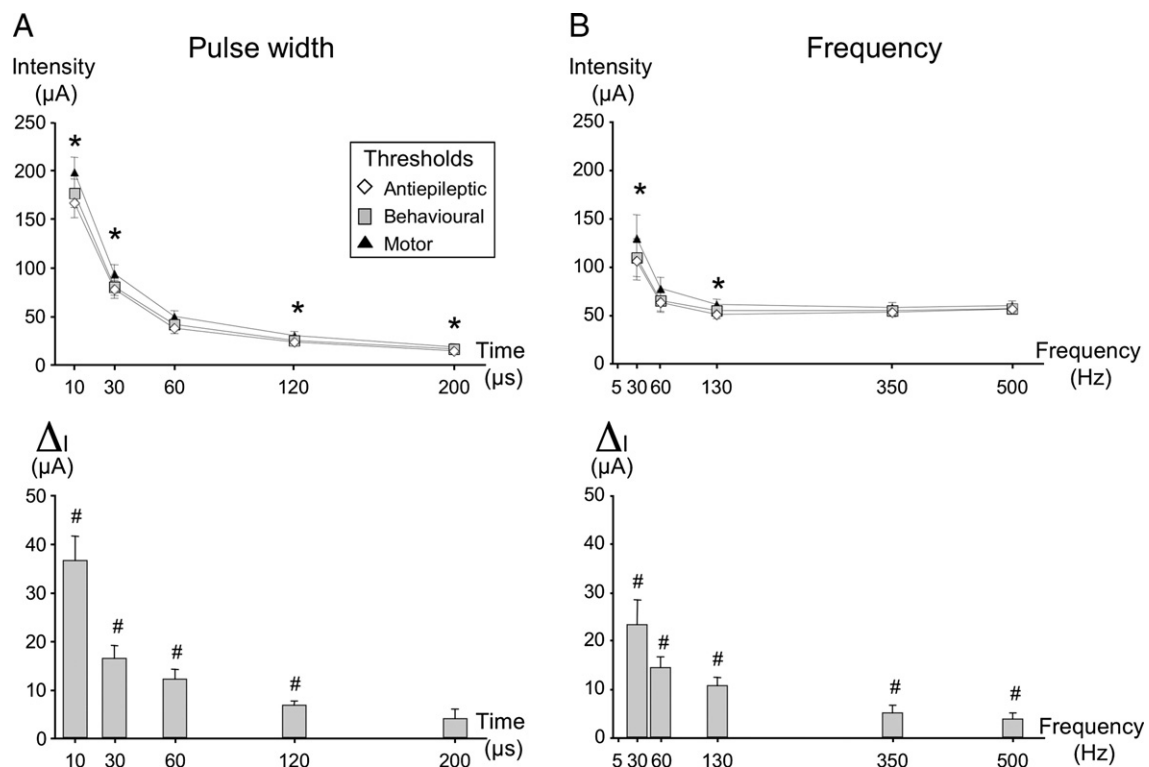


Fig. 4. Single bipolar monophasic unilateral stimulation changes stimulation parameters: pulse width (left panels) or frequency (right panels). (A) Effect of pulse width on intensity thresholds (upper panel, $p < 0.05$, Wilcoxon test, compared to antiepileptic threshold at 60 µs) and on differences between antiepileptic and motor thresholds (lower panel, $p < 0.05$, Wilcoxon test) using 130 Hz stimulation. (B) Effect of frequency on intensity thresholds (upper panel, $p < 0.05$, Wilcoxon test, compared to antiepileptic threshold at 60 Hz) and on differences between antiepileptic and motor thresholds (lower panel, $p < 0.05$, Wilcoxon test) using 60-µs pulse width.

This first series of experiments showed that it is possible to interrupt ongoing SWD in GAERS by a 5-s HFS of the SNr. This structure appeared to be the most sensitive one in the ventral part of the midbrain and there was no regional difference within the SNr. In addition, the lowest antiepileptic thresholds were obtained for bipolar, monophasic and bilateral stimulations of the SNr. Finally, an increasing of the duration of the pulse width or the frequency reduced the dissociation between antiepileptic and motor thresholds.

Repeated stimulations

In the second part of this study, the effects of repeated stimulations of the SNr were compared between different protocols. In order to use the lowest intensity that was dissociated from behavioral or motor effects, bipolar, monophasic and bilateral stimulations were used with a pulse width of 60 μ s and a frequency of 60 Hz. These modes and parameters appeared to be the optimal compromise to suppress the SWDs.

Effects of ON/OFF alternation

In this experiment performed in six GAERS, after a 20 min reference period either (i) continuous (ON), (ii) 5 s ON/5 s OFF or (iii) 5 s ON/15 s OFF stimulations were applied for 2 \times 20 min, in a randomized order with at least one day between two sessions. No significant changes of either the number of seizures, their cumulated duration or their mean duration were observed during these three different protocols, or as compared to the reference period (data not shown). In addition, due to the great variance of the data, no significant changes were observed in the latency for the first SWD to occur in these three different protocols (63.0 ± 10.8 s; 39.0 ± 23.3 s and 94.5 ± 14.8 s, respectively; $p = 0.67$; Kruskal–Wallis test). Data of this experiment suggest that repeated stimulation of the SNr using classical protocols does not result in a lasting antiepileptic effect.

Effects of seizure-triggered stimulations

The effectiveness of repeated bipolar, monophasic, bilateral (60 μ s, 60 Hz) stimulations triggered with each SWD was first tested in six GAERS for 2 \times 20 min. The experimenter continuously watched the EEG, applying the stimulation each time an SWD occurred. This protocol led to a 50% significant decrease in the number of seizures during the first 20 min period as compared to the pre-stimulation period, whereas no significant difference was observed during the second 20 min period (Fig. 5A).

Fifty percent of the seizures that were not interrupted in this protocol generally occurred shortly after a former interrupted seizure (within 19.2 ± 7.2 s). This was confirmed by a significantly higher time interval between two effective stimulations as compared to the time interval between an effective and a non-effective stimulation (Fig. 5B). This suggests the existence of a refractory period of about 50–60 s during which a seizure cannot be stopped. To test this hypothesis, we investigated the effect of repeated seizure-triggered dependent stimulations with a minimal interval of 60 s between two stimulations, in the same series of animals. Over the 40 min of cumulated stimulation period, this protocol allowed more than 90% of the stimulations to block ongoing SWD (Fig. 5C). The ratio of efficacy was significantly higher than in the previous protocol.

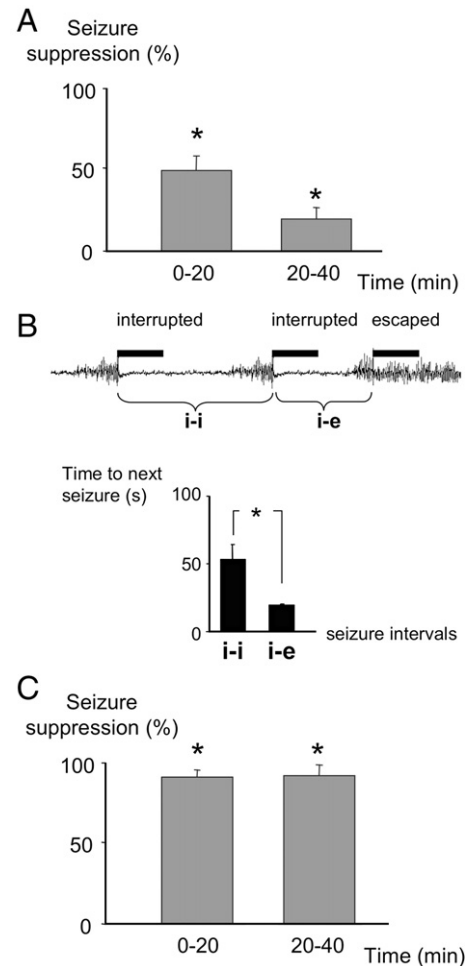


Fig. 5. Seizure-triggered stimulations (mode: bipolar, monophasic, bilateral; parameters: 60 μ s, 60 Hz). Effect of seizure-triggered stimulations on the percentage of seizure suppression when stimulations were (A) applied each time a seizure occurred or (C) when stimulations were applied with a 1-min interval (data obtained from six animals, $*p < 0.05$, Wilcoxon test, compared to the 20 min reference period before stimulation). (B) Time differences between two consecutive interrupted ("i-i", 51 events) and escaped ("i-e", 80 events) seizures ($*p < 0.05$ Mann–Whitney *U*-test).

Unexpectedly, examination of the occurrence of seizure onsets—irrespective of whether they were stimulated or not—during these seizure-triggered protocols revealed an *increase* in the number of seizure occurrence during the 40 min stimulation periods (Figs. 6A, B). The mean duration of non-stimulated seizure in the 1-min interval also increased during the first 20 min period of stimulation, as compared to the pre-stimulation period (Fig. 6C). Hence, no difference in the time until the first seizure was observed once running the different repeated stimulation protocols (results not shown).

This second set of data shows that repeated stimulations must be applied each time a seizure occurs—instead of using ON/OFF alternation cycles—in order to suppress the seizures with efficacy. Allowing for a 1-min time interval between two consecutive seizure-triggered stimulations allows a more efficient suppression of ongoing ictal activity. However, under such

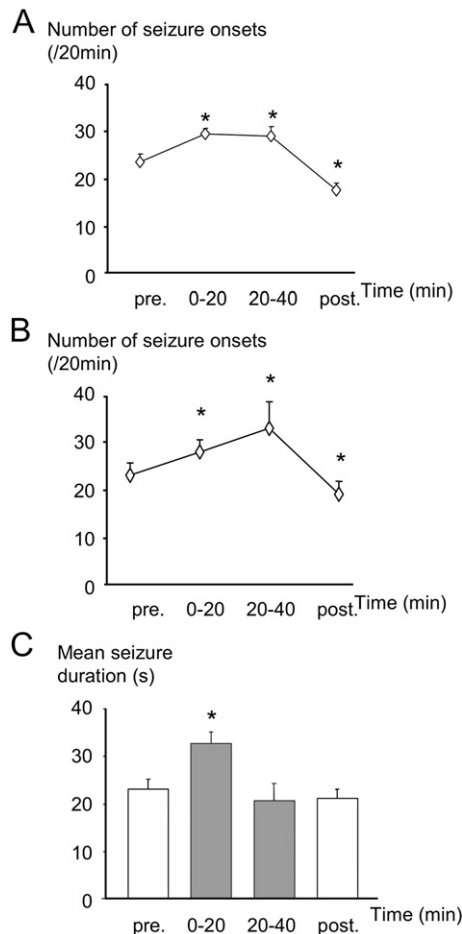


Fig. 6. Seizure-triggered stimulations (mode: bipolar, monophasic, bilateral; parameters: 60 μ s, 60 Hz). Effect of seizure-triggered stimulations on the occurrence of seizure onsets when stimulations were (A) applied each time a seizure occurred or (B) when stimulations were applied with a 1-min interval. (C) Effect of seizure-triggered stimulations with a 1-min interval on the mean seizure duration in the non-stimulated interval (data were obtained from six animals, * $p < 0.05$, Wilcoxon test, compared to the 20 min reference period before stimulation).

conditions, seizures tend to re-appear more frequently and to last longer.

Discussion

Using a genetic model of absence epilepsy (GAERS) we showed that a single 5-s HFS of the SNr interrupts ongoing epileptic discharges. Moreover this effect is specific to the SNr. Our data also show that bilateral, bipolar, monophasic stimulations at a frequency of 60 Hz and with a pulse width of 60 μ s are the optimal conditions to suppress these seizures. More importantly, the present study shows that repeated HFS of the SNr, whether they are continuous or on onset of a seizure, is not antiepileptic because of a refractory period of about 60 s after the stimulation. Furthermore, when a 1-min delay is applied between stimulation, aggravation may occur. These data are critical for the further clinical application of DBS for epilepsy.

SNr as a target for DBS in epilepsy

Lower antiepileptic thresholds were obtained in this study when stimulations were applied within the boundaries of the SNr in contrast to stimulations within the SNc, zona incerta and white matter surrounding the SNc, and cerebral peduncle. When compared to antiepileptic threshold obtained for STN stimulation ($100 \pm 26 \mu$ A) in our initial study using the same modes and parameters (monophasic, bipolar, bilateral, 60 μ s and 130 Hz) (Vercueil et al., 1998), the antiepileptic threshold for SNr stimulation appears to be significantly lower ($32.9 \pm 7.1 \mu$ A). This site specificity and greater efficacy for SNr modulation are in agreement with previous pharmacological studies on the same model (Deransart et al., 1996; Depaulis et al., 1988) and with clinical data (Chabardes et al., 2002).

Optimal modes and parameters of stimulation for DBS in epilepsy

Single stimulation of the SNr at an intensity significantly lower than thresholds that induce behavioral and motor side effects interrupted ongoing seizures in GAERS. This discrimination of motor side effects (e.g., contralateral circling) is very important in clinical practice because it is not possible in epileptic patients to adjust the threshold during or immediately after surgery by controlling motor symptoms as it is in Parkinson patients. A compromise between safety and efficacy is thus mandatory in the use of DBS in epilepsy. A difference of up to 30% could be observed between the antiepileptic thresholds and the intensity necessary to obtain the very first behavioral changes.

Bipolar stimulation better prevented SWD, compared to referential stimulation and allowed a better discrimination between antiepileptic and behavioral thresholds. Bipolar stimulation involves a more limited and specific neuronal population. This is in line with the site specificity for SNr described above and in agreement with previous studies (Temel et al., 2004). Our data thus suggest that bipolar stimulation might be more effective than referential stimulation in epilepsy as it is not delivered continuously to prevent lesional side effects.

Monophasic stimulations also required a significantly lower intensity to interrupt seizures, as compared to biphasic ones, whatever the pulse durations. Unlike the polarity, monophasic stimulations did not really improve the discrimination between antiepileptic and behavioral effects. This difference is in full agreement with both theoretical and experimental reports showing that biphasic stimulations require more current to achieve the same efficacy (Merrill et al., 2005). Indeed, monophasic pulsing causes the greatest shift of the electrode potential. Because such stimulations may result in more tissue damage, they are only recommended when using a phase reversal at the end of the stimulation period to avoid tissue polarization. This is good clinical practice in DBS in other pathologies.

Finally, bilateral stimulations also proved more effective to stop seizures than unilateral stimulations. This is in agreement with our previous study on HFS of the STN in GAERS (Vercueil et al., 1998). It is also in full agreement with pharmacological studies performed in GAERS or other models showing that bilateral manipulations in the SNr, STN, striatum and superior colliculus were always found to be more efficient (Depaulis et al., 1994).

Experiments performed at different pulse width and frequencies also allowed us to determine optimal parameters for DBS in epilepsy. The best compromise between a low intensity and

discrimination between antiepileptic and behavioral side effects was provided by a 60- μ s pulse. This pulse width is also sufficiently short to avoid tissue damage, especially if monophasic stimulations are to be used (Merrill et al., 2005). Finally, a 60- μ s pulse is generally used for DBS in PD patients, in whom it appears to be the optimal value (Rizzone et al., 2001; Moro et al., 2002). On the contrary, our data do not support the use of a 130-Hz frequency to interrupt epileptic seizures. Seizure suppression was already observed at 30 Hz, and 60 Hz was found to offer a close to maximal suppression with still a good discrimination between antiepileptic and behavioral side effects. Increasing the frequency up to 500 Hz did not further reduce the antiepileptic threshold and rather decrease the difference between therapeutic and side effects, in agreement with another study (Lado, 2006). The 60-Hz frequency is in full agreement with previous experimental studies showing that either electrophysiological or neurochemical effects could be obtained at this frequency (Windels et al., 2003). Lowering the frequency of stimulation for a similar effect may be interesting to increase the lifetime of the battery for implantable set-up in human patients.

Repeated stimulations do not allow long-lasting suppression of seizures

Although optimal modes and parameters as defined from single stimulation were used in our study, we clearly showed that repeated stimulations of the SNr did not result in a long-term suppression of seizures, whichever protocol was used. At most the SWDs were suppressed for up to 2 min. This lack of lasting effect is in agreement with our previous study on the STN (Vercueil et al., 1998). However, this “escape” phenomenon is in contrast to the lasting effects observed upon continuous stimulation of the STN in both experimental and clinical studies of Parkinson’s disease (PD) (Temel et al., 2006; Salin et al., 2002; Krack et al., 2002; Visser-Vandewalle et al., 2005). The fact that basal ganglia circuits remain intact in epileptic individuals, as opposed to PD patients and models, may explain the difference in duration of DBS efficacy between the two pathologies. More puzzling is the difference in clinical studies in which chronic HFS stimulations were effective throughout time (Chabardes et al., 2002; Loddenkemper et al., 2001). However, success of stimulation also accounts for the stimulation site and the underlying epileptogenic circuit. Our results in a genetic absence model require further confirmations to be transferred to clinical trials aimed at stimulating patients with pharmacoresistant focal epilepsies. It is also possible that HFS stimulation of the STN or SNr becomes effective on epileptic seizures only after several days/weeks of chronic stimulations or upon repeated session, as suggested recently (Shi et al., 2006). The protocol used in our study did not allow us to examine this point, although no significant reduction of SWD was observed before the first SNr stimulation and upon completion of the experiment, about 3 weeks later. The possibility that HFS-SNr has buildup effects is an interesting point that deserves further investigations.

This investigation of the effect of seizure-triggered stimulations allowed us to confirm that the antiepileptic effects of HFS-SNr disappear when repeated. In addition, our data show that a minimum delay of about 60 s between two stimulations is necessary for HFS-SNr to be effective. Because of the high occurrence of SWD in the GAERS model, seizure-triggered stimulations were found to be ineffective when applied to each

seizure. When a 60 s delay was used, then each stimulation became effective. These data suggest the existence of a refractory period after each stimulation, during which the “control network” cannot be reactivated. No refractory period was observed in *in vitro* slice preparation of the STN and related structures (Garcia et al., 2005) suggesting that the “control network” involves further downstream structures (Deransart and Depaulis, 2002). This supports the view that HFS, instead of providing long-lasting inhibition of the SNr acutely disrupts synchronization of the thalamo-cortical loop. Thus, for such stimulation to be efficient it has to be delivered through pulsatile stimulation protocols which take into account the refractory period of the control system to be triggered (Popovych et al., 2006).

Does DBS aggravate seizures?

When seizure-triggered stimulations were used, with a minimum delay of 60 s, SWDs occurred between two stimulations. In fact, an aggravation in the occurrence of seizures was even observed when both the interrupted and “escaped” seizures were taken into consideration. Aggravating effects were also evident in the increase in seizure duration that occurs during the 1-min interval without stimulation. Aggravating effects were also recently reported in a rat model of generalized seizures during bilateral chronic DBS of the anterior thalamic nucleus (Lado, 2006). Aggravating effects of repeated stimulations are probably specific to the high recurrence of seizures in our model (about 1/min in GAERS) and this may be taken into account in epileptic syndromes with highly recurrent seizures, whatever the protocol of stimulation. Such unexpected adverse effects warrant further investigations since non-responding patients have also been reported during DBS, irrespective of the stimulated target area (Chabardes et al., 2002; Loddenkemper et al., 2001).

A need for further investigation in protocols for DBS for epilepsy

Our data stress the importance of clearly delineated preclinical parametrical studies for DBS in epilepsy. Stimulation parameters that are optimal within the SNr in a genetic model of absence epilepsy were established for single seizure interruptions. These parameters differ somewhat from those established in STN stimulation for PD. Thus, the therapeutic effect of DBS in both pathologies differs, mainly because the state of the circuit is completely different in PD and epileptic individuals. We have shown in the present study that a bipolar, bilateral and monophasic stimulations of the SNr allow the use of lower intensities, and a better discrimination is possible between antiepileptic and motor side effects. Because repeated HFS of the SNr does not support marked suppression of seizures and even suggests that transient aggravation of seizure occurrence could occur, further investigations of chronic protocols using either open- or closed-loop stimulation procedures need to be investigated (Li and Mogul, 2007).

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References

- Benabid, A.L., 2003. Deep brain stimulation for Parkinson's disease. *Curr. Opin. Neurobiol.* 13, 696–706.
- Benabid, A.L., Minotti, L., Koudsie, A., et al., 2002. Antiepileptic effect of high-frequency stimulation of the subthalamic nucleus (corpus Luysi) in a case of medically intractable epilepsy caused by focal dysplasia: a 30 month follow-up: technical case report. *Neurosurgery* 50, 1385–1391.
- Chabardes, S., Kahane, P., Minotti, L., et al., 2002. Deep brain stimulation in epilepsy with particular reference to the subthalamic nucleus. *Epileptic Disord.* 4, S83–S93.
- Danober, L., Deransart, C., Depaulis, A., et al., 1998. Pathophysiological mechanisms of genetic absence epilepsy in the rat. *Prog. Neurobiol.* 55, 27–57.
- Depaulis, A., van Luitelaar, G., 2005. Genetic models of absence epilepsy. In: Pitkanen, A., Schwartzkroin, P., Moshe, S. (Eds.), *The Rat Models of Seizures and Epilepsy*. Elsevier, San Diego, pp. 233–248.
- Depaulis, A., Bourguignon, J.J., Marescaux, C., et al., 1988. Effects of gamma-hydroxybutyrate and gamma-butyrolactone derivatives on spontaneous generalized non-convulsive seizures in the rat. *Neuropharmacology* 27, 683–689.
- Depaulis, A., Vergnes, M., Marescaux, C., 1994. Endogenous control of epilepsy: the nigral inhibitory system. *Prog. Neurobiol.* 42, 33–52.
- Deransart, C., Depaulis, A., 2002. The control of seizures by the basal ganglia? A review of experimental data. *Epileptic Disord.* 4, S61–S72.
- Deransart, C., Marescaux, C., Depaulis, A., 1996. Involvement of nigral glutamatergic inputs in the control of seizures in a genetic model of absence epilepsy in the rat. *Neuroscience* 71, 721–728.
- Deransart, C., Bressand, K., Kahane, P., et al., 2006. Deep brain stimulation in epilepsy. In: Bezdard, E. (Ed.), *Recent Breakthroughs in Basal Ganglia Research*. NOVA Science Publisher, New York, pp. 403–411.
- Dybdal, D., Gale, K., 2000. Postural and anticonvulsant effects of inhibition of the rat subthalamic nucleus. *J. Neurosci.* 20, 6728–6733.
- Gale, K., 1985. Mechanisms of seizure control mediated by gamma aminobutyric acid: role of the substantia nigra. *Fed. Proc.* 44, 2414–2424.
- Garcia, L., D'Alessandro, G., Bioulac, B., et al., 2005. High-frequency stimulation in Parkinson's disease: more or less? *Trends Neurosci.* 28, 209–216.
- Handforth, A., DeSalles, A.A.F., Kahl, S.E., 2006. Deep brain stimulation of the subthalamic nucleus as adjunct treatment for refractory epilepsy. *Epilepsia* 47, 1233–1241.
- Hauser, W.A., Hesdorffer, D.C., 1990. Incidence and prevalence. In: Hauser, W.A., Hesdorffer, D.C. (Eds.), *Epilepsy Frequency Causes and Consequences*. Demos, New York, pp. 1–51.
- Krack, P., Fraix, V., Mendes, A., et al., 2002. Postoperative management of subthalamic nucleus stimulation for Parkinson's disease. *Mov. Disord.* 17, S188–S197.
- Lado, F.A., 2006. Chronic bilateral stimulation of anterior thalamus of kainate-treated rats increases seizure frequency. *Epilepsia* 47, 27–32.
- Lado, F.A., Velisek, L., Moshe, S.L., 2003. The effect of electrical stimulation of the subthalamic nucleus on seizures is frequency dependent. *Epilepsia* 44, 157–164.
- Le Van Quyen, M., Foucher, J., Lachaux, J.P., et al., 2001. Comparison of Hilbert transform and wavelet methods for the analysis of neuronal synchrony. *J. Neurosci. Methods* 111, 83–98.
- Li, Y., Mogul, D.J., 2007. Electrical control of epileptic seizures. *J. Clin. Neurophysiol.* 24, 197–204.
- Limousin, P., Pllak, P., Benazzouz, A., et al., 1995. Bilateral subthalamic nucleus stimulation for severe Parkinson's disease. *Mov. Disord.* 10, 672–674.
- Limousin, P., Krack, P., Pollak, P., et al., 1998. Electrical stimulation of the subthalamic nucleus in advanced Parkinson's disease. *N. Engl. J. Med.* 339, 1105–1111.
- Loddenkemper, T., Pam, A., Neme, S., et al., 2001. Deep brain stimulation in epilepsy. *J. Clin. Neurophysiol.* 18, 514–532.
- Merrill, D.R., Bikson, M., Jefferys, J.G., 2005. Electrical stimulation of excitable tissue: design of efficacious and safe protocols. *J. Neurosci. Methods* 141, 171–198.
- Moro, E., Esselink, R.J.A., Xie, J., et al., 2002. The impact on Parkinson's disease of electrical parameter settings in STN stimulation. *Neurology* 59, 706–713.
- Paxinos, G., Watson, C., 1998. *The Rat Brain in Stereotaxic Coordinates* 4th ed. Academic Press, San Diego.
- Perlmutter, J.S., Mink, J.W., 2006. Deep brain stimulation. *Annu. Rev. Neurosci.* 29, 229–257.
- Popovych, O.V., Hauptmann, C., Tass, P.A., 2006. Control of neuronal synchrony by nonlinear delayed feedback. *Biol. Cybern.* 95, 69–85.
- Rizzone, M., Lanotte, M., Bergamasco, B., et al., 2001. Deep brain stimulation of the subthalamic nucleus in Parkinson's disease: effects of variation in stimulation parameters. *J. Neurol. Neurosurg. Psychiatry* 71, 215–219.
- Salin, P., Manrique, C., Forni, C., et al., 2002. High-frequency stimulation of the subthalamic nucleus selectively reverses dopamine denervation-induced cellular defects in the output structures of the basal ganglia in the rat. *J. Neurosci.* 22, 5137–5148.
- Semah, F., Picot, M.C., Adam, C., et al., 1998. Is the underlying cause of epilepsy a major prognostic factor for recurrence? *Neurology* 51, 1256–1262.
- Shi, L.-H., Luo, F., Woodward, D., et al., 2006. Deep brain stimulation of the substantia nigra pars reticulata exerts long lasting suppression of amygdala-kindled seizures. *Brain Res.* 1090, 202–207.
- Temel, Y., Visser-Vandewalle, V., van der Wolf, M., et al., 2004. Monopolar versus bipolar high frequency stimulation in the rat subthalamic nucleus: differences in histological damage. *Neurosci. Lett.* 367, 92–96.
- Temel, Y., Visser-Vandewalle, V., Kaplan, S., et al., 2006. Protection of nigral cell death by bilateral subthalamic nucleus stimulation. *Brain Res.* 1120, 100–105.
- Theodore, W.H., Fisher, R.S., 2004. Brain stimulation for epilepsy. *Lancet Neurol.* 3, 111–118.
- Velisek, L., Veliskova, J., Moshe, S.L., 2002. Electrical stimulation of substantia nigra pars reticulata is anticonvulsant in adult and young male rats. *Exp. Neurol.* 173, 145–152.
- Veliskova, J., Velisek, L., Moshe, S.L., 1996. Subthalamic nucleus: a new anticonvulsant site in the brain. *NeuroReport* 7, 1786–1788.
- Vercueil, L., Benazzouz, A., Deransart, C., et al., 1998. High frequency stimulation of the subthalamic nucleus suppresses absence seizures in the rat: comparison with neurotoxic lesions. *Epilepsy Res.* 31, 39–46.
- Visser-Vandewalle, V., van der Linden, C., Temel, Y., et al., 2005. Long-term effects of bilateral subthalamic nucleus stimulation in advanced Parkinson disease: a four year follow-up study. *Parkinsonism Relat. Disord.* 11, 157–165.
- Wiebe, S., Blume, W.T., Girvin, J.P., et al., 2001. Effectiveness and efficiency of surgery for temporal lobe epilepsy study group. A randomized, controlled trial of surgery for temporal-lobe epilepsy. *N. Engl. J. Med.* 345, 311–318.
- Windels, F., Bruet, N., Poupard, A., et al., 2003. Influence of the frequency parameter on extracellular glutamate and gamma-aminobutyric acid in substantia nigra and globus pallidus during electrical stimulation of subthalamic nucleus in rats. *J. Neurosci. Res.* 72, 259–267.

Article 3

B. Feddersen, R. Meier, A. Depaulis, C. Deransart. EEG Changes Between Left and Right Substantia Nigra Heralds the Occurrence of Generalized Seizures in a model of GAERS.

In preparation, to be submitted to Epilepsia as a short communication

Changes in Coherence Between Left and Right Substantia Nigra Heralds the Occurrence of Generalized Seizures in Genetic Absence Epilepsy Rats from Strasbourg (GAERS)

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Abstract

Changes in neuronal synchronization that may occur between the Substantia nigra pars reticulata (SNr) in GAERS before the occurrence of spike and wave discharges (SWDs) may help to develop a close-loop device allowing detection and stimulation through the same electrode. Coherence analysis was performed between bipolar SNr derivations before SWDs and were compared to episodes of wakefulness or sleep. without SWD in order to verify whether the differences were specific to SWDs or rather reflect a change of vigilance state. Our data show that the coherence between the two bipolar SNr electrodes increased 12 to 8 s before the onset of SWD at frequencies between 10 – 40 Hz (35 Hz, -10 sec, > 5 SD, $p < 0.001$). Such changes were not observed during wake or sleep periods or between the left and right cortex before SWDs. This early coupling of the two SNr suggests that changes in the dynamics of the basal ganglia may “predispose” the cortex to seize.

Key words: Basal ganglia; Anticipation; Seizure; Closed Loop Stimulation

Introduction

Experimental data have accumulated over the past few years to suggest that the basal ganglia system is involved in the propagation or control of epileptic seizures (Deransart and Depaulis, 2002). Indeed, several animal studies have shown that most pharmacological manipulations aimed at decreasing the activity of neurons in the substantia nigra pars reticulata (SNr), one of the main output station of the basal ganglia in rodents, suppress epileptic seizures in different animal models (Deransart and Depaulis, 2002). More recently, concomitant changes in neuronal activity of basal ganglia structures during seizures have been recorded (Slaght et al., 2004). Finally, high-frequency stimulations of the subthalamic nucleus, as well as the SNr, interrupt epileptic seizures in different animal models (Feddersen et al., 2007; Velisek et al., 2002; Vercueil et al., 1998).

Deep brain stimulation (DBS) is considered as an alternative therapy for epileptic patients who are pharmacoresistant and not candidate for resective neurosurgery. Several pilot studies in humans have targeted different subcortical structures, including the thalamus and the subthalamic nuclei (STN) obtaining heterogenous results (for review see (Saillet et al., 2009)) and further evaluation in animal models are necessary. We have previously determined the optimal stimulation parameters

for seizure interruption (Feddersen et al., 2007). However, when repeated stimulation protocols are used, these did not result in long-term suppression of seizures. These findings point-out to the need of a closed-loop stimulation system with seizure detection and stimulation by the same electrodes.

Here, we have addressed the possibility to detect seizure occurrence by electroencephalographic recordings at the stimulation site. Using GAERS with bipolar electrodes implanted within the SNr, we analyze the coherence between the two structures before the occurrence of spike and wave discharges (SWD) and compared them with episodes at the end of SWD and with episodes during sleep and wakefulness without SWD, since vigilance states have been shown to influence seizure occurrence in this model (Danober et al., 1998; Pinault et al., 2001). As a control, changes in coherence before SWDs were also investigated at the cortical level between left and right fronto-parietal electrodes.

Material and Methods

Animals

Adult male GAERS (250–350 g) were used in this study. These rats are characterized by behavioral arrest associated with cortical and thalamic bilateral spike-and-wave discharges (SWD) (frequency, 7–9 C/s; amplitude, 400–600 μ V; mean duration 20 s) (Danober et al., 1998). They were kept in individual cages under a 12/12 h normal light/dark cycle, with food and water ad libitum. All experiments were carried out in accordance with the European Community Council Directive of November 24, 1986 (86/609/EEC) and all procedures were approved by the local department of the veterinarian services for the use and care of animals (DSV).

Surgery

Eight GAERS were implanted with both epidural stainless-steel electrodes, placed bilaterally over the frontal and parietal cortex, and two bipolar electrodes formed of enamel-insulated twisted wires (175 μ m) in the right and left SNr, proven by histology, as described before (Feddersen et al., 2007). Electroencephalograms (EEGs) were recorded in awake freely moving animals using a digital acquisition system (Coherence 3NT, Deltamed, France) as described previously (Feddersen et al., 2007).

Seizures were detected manually, the first spike appearing in the SNr (left or right) were used as seizure onset (time point 0), the last one at seizure end. SWDs were defined when spikes exceeded the baseline amplitude at least threefold. In the analysis, we included 15 s before seizure onset and 15 s after seizure end. The 10 s periods of “wake” and “sleep” were only included in the analysis when they were not overlapping with a time period before or after a seizure. During wakefulness in GAERS rats, most of the spontaneous SWD (SW complexes at about 6-8 Hz) emerged from short episodes (0.5-3 s) of medium-voltage 5-9-Hz oscillations on a background of low-voltage desynchronize (Pinault et al., 2001). Sleeping rats were characterized by an immobile, curled, ball-like position with closed eyes, and by a concomitant high-voltage slow wave synchronized activity in the EEG (Pinault et al., 2001).

Coherence analysis

The coherence analysis was performed using field potential signals recorded from two bipolar derivations between both electrodes within left and right SNr. The mean coefficient of correlation ± 1 standard deviation (SD) for sliding windows of 2 s width (shifted by one data sample (50 μ s) each) was calculated. We analyzed 152 SWD onsets (n=8 animals), 152 SWD offsets (n=8), 77 wake periods (n=8) and 46 sleep periods. To obtain time-resolved values, spectral and coherence analyses were calculated (using Matlab) for sliding time windows of 1 s, shifted by 0.2 s at a time. The average power spectral density in the frequency range between 1 Hz and 80 Hz was calculated for each SNr recording electrode and each window. Additionally, the coherence was analyzed using the Matlab function ‘mscohere’ (Signal Processing Toolbox). The number of bins for the fast Fourier transform (FFT) was set to 215 points and we used periodic Hamming windowing with a window length of 0.125 s and 50% overlap. We thus obtained a phase synchronization measure as a function of frequency aligned to SWD onset.

The coherence for four frequency bands: (i) 1-4Hz; (ii) 4–13 Hz; (iii) 13-40Hz and (iv) 40–80 Hz was assessed. The average coherence in a window between 20 s and 18 s before SWD onset was taken as baseline and this value was subtracted from the coherence in each window, negative values indicate coherence smaller than baseline, whereas positive values correspond to increased coherence. Time-resolved

coherence averaged across all rats illustrates the temporal development of phase-synchronization relative to the onset of SWD.

Results

Local field potentials (LFP) were recorded in animals with histological proven location of both bipolar electrodes within the SNr. Coherence between SNr showed a transient (2-4 s) significant increase in the theta (4-13 Hz) and alpha (13-40 Hz) bands, 10 ± 2 seconds before SWD onset and were followed by a decrease back to baseline before the SWD onset (Fig. 1, $p < 0.001$, student t-test). In the delta and gamma range no significant changes could be observed before SWD onset (Fig. 1). Such changes were not observed on the cortical level prior to the SWDs, neither after SWD (Fig. 1C). No significant changes in coherence were observed in the transition windows in the states of wakefulness and sleep (Fig. 2).

Discussion

The present study shows significant changes in the coupling between SNr within the 10 s that precedes SWD in GAERS. This was observed in the 4-13 Hz and 13-40 Hz bands and appears specific to SWD as no such changes were observed during wake or during sleep. In addition, such changes were not observed between cortical electrodes, suggesting that the transient coupling was specific to SNr. Although the cortical electrodes were not placed over the exact focus of SWD as demonstrated recently (Polack et al., 2007), a possible delay cannot account for the changes observed up to 10 sec before SWD onset. Indeed, the maximal delay that was observed within different regions of the cortex and subcortical structure was never superior to 2 sec (Polack et al., 2007).

Several studies have reported changes in the signal dynamic that precedes seizures in a variety of animal models as well as in epileptic patients (for review see (Le Van Quyen, 2005)). Factors predicting seizures can only rarely be seen on the EEG and signal analysis is necessary to detect early changes in the dynamics of brain activity leading to a seizure. Changes were mostly observed at the region of onset of the seizures and have been proposed as a tool to anticipate seizures (Le Van Quyen, 2005). In some studies, bilateral changes in the coupling between the seizure focus and the homologous regions were suggested to participate in the seizure generation

or maintenance (Meier et al., 2007). The investigation of interhippocampal synchronization preceding spontaneous epileptiform events in a model of unilateral hippocampal sclerosis has shown that coherence between the ipsilateral sclerotic hippocampus and the contralateral intact hippocampus decreased consistently and reliably for all epileptiform events at 8 to 12 s before their onset at high frequencies (>100 Hz) (Meier et al., 2007).

In absence seizures, a recent signal analysis study of the activity recorded at the focus site failed to detect any change of anticipation before the occurrence of SWD (Sitnikova and van Luijckelaar, 2009).

Our study is therefore the first to show anticipatory changes in absence epilepsy. In addition, to our knowledge, no changes have ever been reported so far between structures involved in the *control* rather than the *generation* of seizures, whatever the type of seizures. This finding is of great technical importance as it could allow to use the same electrode for both detection and stimulation in a closed-loop DBS device targeted at control structures. However, this remains to be validated as the changes reported here are the results of analysis of several seizures. At this stage, we cannot assess if online coherence analysis will allow to detect seizure with a sufficient specificity and sensitivity. Further experiments and developments are necessary to use our findings as a detection tool.

In addition to the technical aspects, our findings raise an important conceptual issue concerning the role of the control subcortical circuits in the generation of seizures. Our data suggest that a change in activity of these circuits may condition the possibility for the cortex to develop seizure and/or oscillatory activities in a given frequency band. However, this hypothesis remains to be further explored.

In conclusion, using a well recognized model of spontaneous seizures in the rat, our study shows a significant coupling in two specific frequency bands in the SNr. This structure is known to play a critical role in the control of epileptic seizures and our data suggest the possibility that such coupling “predispose” the cortex to seize. On a more practical aspect, our finding may be used to develop a close-loop device allowing detection and stimulation through the same electrode.

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References

- Danober, L, Deransart, C, Depaulis, A, Vergnes, M, Marescaux, C (1998) Pathophysiological mechanisms of genetic absence epilepsy in the rat. *Prog Neurobiol* 55: 27-57.
- Deransart, C, Depaulis, A (2002) The control of seizures by the basal ganglia? A review of experimental data. *Epileptic Disord* 4 Suppl 3: S61-72.
- Feddersen, B, Vercueil, L, Noachtar, S, David, O, Depaulis, A, Deransart, C (2007) Controlling seizures is not controlling epilepsy: a parametric study of deep brain stimulation for epilepsy. *Neurobiol Dis* 27: 292-300.
- Le Van Quyen, M (2005) Anticipating epileptic seizures: from mathematics to clinical applications. *C R Biol* 328: 187-198.
- Meier, R, Haussler, U, Aertsen, A, Deransart, C, Depaulis, A, Egert, U (2007) Short-term changes in bilateral hippocampal coherence precede epileptiform events. *Neuroimage* 38: 138-149.
- Pinault, D, Vergnes, M, Marescaux, C (2001) Medium-voltage 5-9-Hz oscillations give rise to spike-and-wave discharges in a genetic model of absence epilepsy: in vivo dual extracellular recording of thalamic relay and reticular neurons. *Neuroscience* 105: 181-201.
- Polack, PO, Guillemain, I, Hu, E, Deransart, C, Depaulis, A, Charpier, S (2007) Deep layer somatosensory cortical neurons initiate spike-and-wave discharges in a genetic model of absence seizures. *J Neurosci* 27: 6590-6599.
- Saillet, S, Langlois, M, Feddersen, B, Minotti, L, Vercueil, L, Chabardès, S, David, O, Deransart, C, Depaulis, A, Kahane, P (2009) Manipulating the epileptic brain using stimulation: a review of experimental and clinical studies. *Epileptic Disorders* in press.
- Sitnikova, E, van Luijckelaar, G (2009) Electroencephalographic precursors of spike-wave discharges in a genetic rat model of absence epilepsy: Power spectrum and coherence EEG analyses. *Epilepsy Res* 84: 159-171.
- Slaght, SJ, Paz, T, Chavez, M, Deniau, JM, Mahon, S, Charpier, S (2004) On the activity of the corticostriatal networks during spike-and-wave discharges in a genetic model of absence epilepsy. *J Neurosci* 24: 6816-6825.
- Velisek, L, Veliskova, J, Moshe, SL (2002) Electrical stimulation of substantia nigra pars reticulata is anticonvulsant in adult and young male rats. *Exp Neurol* 173: 145-152.
- Vercueil, L, Benazzouz, A, Deransart, C, Bressand, K, Marescaux, C, Depaulis, A, Benabid, AL (1998) High-frequency stimulation of the subthalamic nucleus suppresses absence seizures in the rat: comparison with neurotoxic lesions. *Epilepsy Res* 31: 39-46.

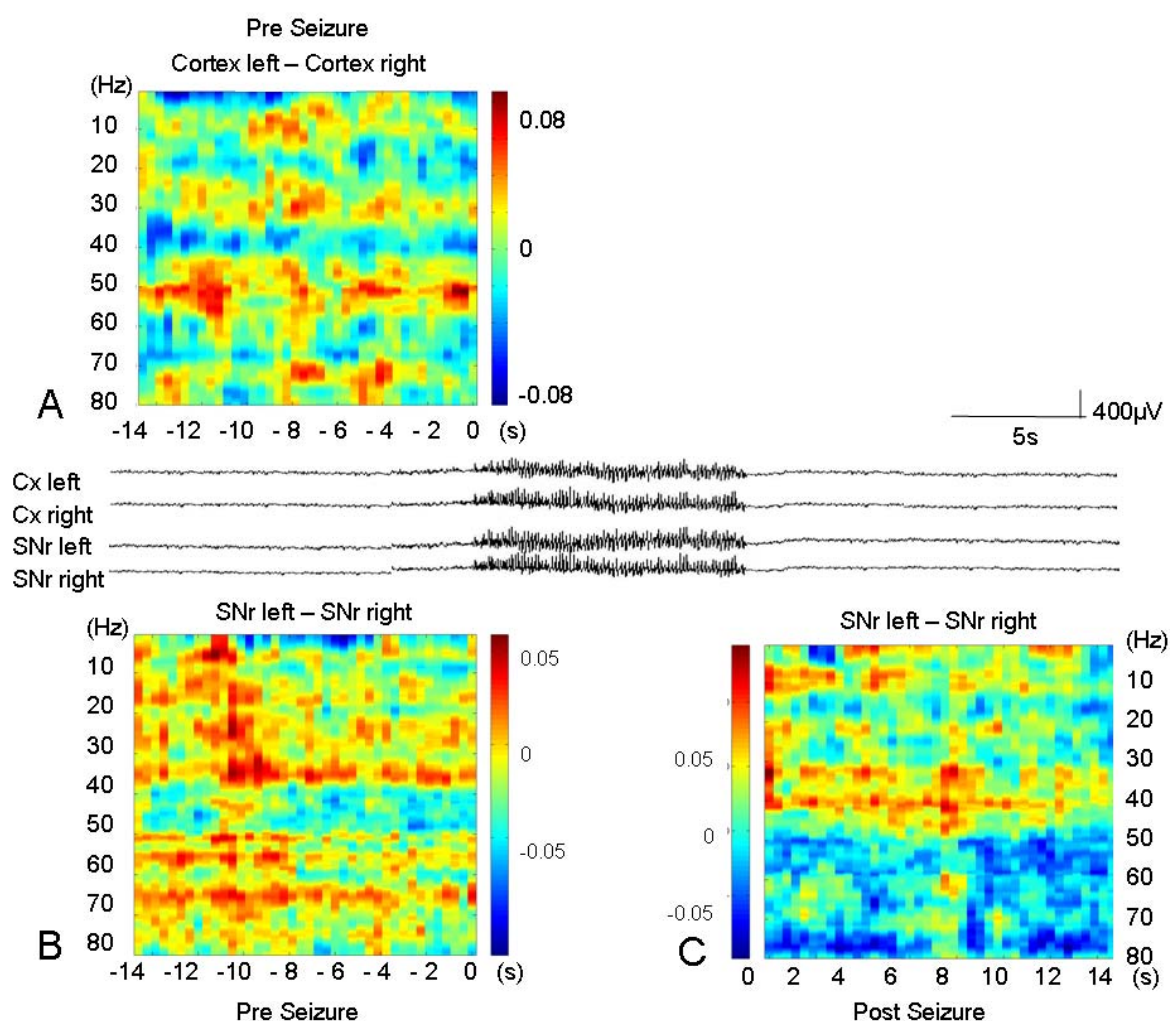


Fig. 1

Figure 1:

The coherence analysis between the left and right SNr in the range of 0-80 Hz is shown in figure 1 B. Red colour indicates an increase of coherence, which is seen between -12 to -8 s before the onset of SWDs in the range of 10-30 Hz. Such changes are inapparent between left and right cortical derivations in figure 1 A and after the occurrence of SWD in between both SNr in the postictal period.

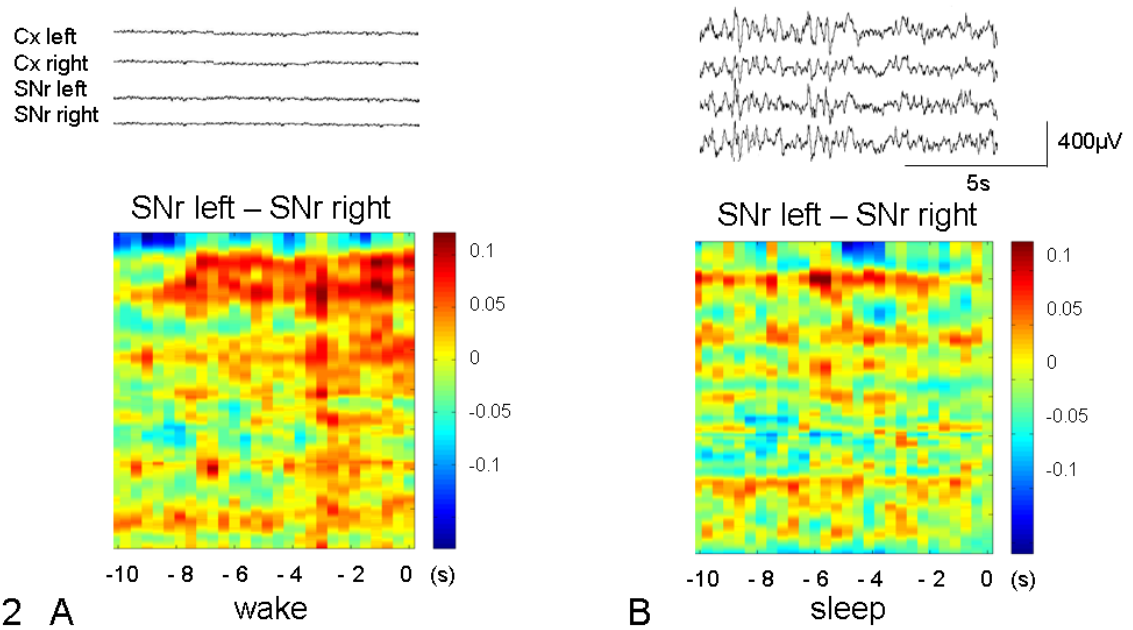


Figure 2:

Coherence analysis between left and right SNr during different vigilance states are shown in figure 2 A wake and 2 B sleep. No changes in coherence were observed.

Article 4

M. Langlois, S. Saillet, B. Feddersen, L Minotti, L Vercueil,
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Deep brain stimulation in epilepsy: experimental and clinical data.
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Deep brain stimulation in epilepsy: experimental and clinical data.

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1 - Introduction

About 30% of epileptic patients do not respond to antiepileptic drugs (Kwan & Brodie, 2000), of whom only a minority can benefit from resective surgery. Such a therapeutic option is considered only in patients who suffer from focal seizures with an epileptogenic zone clearly identified and safely removable. Therefore, patients with seizures arising from eloquent cortices, or which are multifocal, bilateral, or generalized, represent a particular challenge to « new » or « alternative » therapies. For these patients, neurostimulation appears with a great potential (Polkey et al., 2003; Theodore and Fisher, 2004). Different approaches to neurostimulation in epileptic patients now exist and depend on (i) the brain region which is targeted and (ii) the way the stimulation is applied (Oommen et al., 2005 ; Morrell, 2006 ; Theodore and Fisher, 2004 ; Vonck et al., 2007). The aim of neurostimulation in epilepsy is to reduce the probability of seizure occurrence and/or propagation, either by manipulating remote control systems (vagus nerve stimulation, deep brain stimulation), or by interfering with the epileptogenic zone itself (repetitive transcranial magnetic stimulation, cortical stimulation). In most cases, stimulation is delivered continuously or intermittently according to a scheduled protocol. In particular, new progress in biotechnology and EEG signal analysis now allows stimulation in response to detection of electrographic seizures (e.g., closed-loop stimulation). Here, we review the various experimental and clinical attempts that have been made to control epileptic seizures by the means of deep brain electrical stimulation.

2 - Deep brain stimulation (DBS)

For more than two decades, stimulation of a number of deep brain targets has been shown to be feasible, safe, and effective in humans suffering from different forms of movement disorders. This has led to the development of deep brain stimulation (DBS) in an increasing number of neurological and non-neurological diseases, including epilepsy (Benabid et al., 2001). Although the cortex plays a crucial role in seizure generation, accumulating evidence has pointed to the role of subcortical structures in the clinical expression, propagation and control of epileptic seizures in humans (Semah, 2002 ; Vercueil and Hirsch, 2002). Based on experimental findings, DBS has been applied to a number of targets, including the cerebellum, different

nuclei of the thalamus, and several structures of the basal ganglia system. Although encouraging, published results do not reach a definite conclusion and require further studies using animal models. Indeed, the study of the mechanisms of actions of such DBS on epileptic seizures is critical to understand the transitions between normal and paroxysmal activities of the epileptic networks.

2.1 - Cerebellum

During the 1950s and 1960s, cortical cerebellar stimulation was shown to have antiepileptic properties on different animal models of seizures, mostly penicillin and cobalt foci in cats (Cooke and Snider, 1955 ; Dow et al., 1962 ; Mutani et al., 1969). Following this, and assuming cerebellar outflow is inhibitory in nearly all patients, Cooper and colleagues showed that seizures were modified or inhibited in 10 out of their 15 epileptic patients, without adverse effects (Cooper et al., 1973; 1976; 1978). These data raised the issue of distant modulation of cortical epileptogenicity by electrical currents. More especially, this study showed for the first time the feasibility and safety of a therapeutic stimulation technique in epileptic patients. Later, a large open study on 115 patients reported that 31 became seizure-free and 56 were significantly improved by stimulation of the cerebellum (Davis and Emmonds, 1992). Such promising results, however, were not confirmed in 3 controlled clinical trials involving 14 patients, of whom only 2 were improved (Krauss and Fisher, 1993 ; Van Buren et al., 1978 ; Wright et al., 1984). Additional animal studies conducted in monkeys with cortical focal seizures induced by alumina cream, or in kindled cats, did not confirm previous experimental findings (Ebner et al., 1980 ; Lockard et al., 1979 ; Majkowski et al., 1980) and the interest for cerebellar stimulation in epilepsy disappeared for many years. Recently, however, a double-blind, randomized controlled pilot study conducted in 5 patients suffering from intractable motor seizures has renewed the interest in such stimulation (Velasco et al., 2005). In this study, 10-Hz stimulations were applied to the upper medial surface of each cerebellar hemisphere, and parameters were adjusted to deliver a constant charge density of 2.0 microC/cm²/phase. During the initial 3-month double-blind phase, seizures were significantly reduced when the patients were stimulated. Over the following 6-month open-label phase, where all the patients were stimulated, seizures were reduced by 41% (14-75%) and the difference was significant for tonic and tonic-clonic seizures.

Effectiveness was maintained over 2 years and few complications occurred. Altogether, although cerebellar stimulation appears to possess antiepileptic effects in some patients and/or some forms of epilepsy, the rationale of such suppressive effects remains to be determined. No clinical studies targeting this structure are currently under progress.

2.2 - Thalamus

Since the 1980s, different nuclei of the thalamus have been studied to understand the physiopathology of epilepsy because many interaction pathways exist between these nuclei and the cortex. Several thalamic targets have been stimulated to suppress seizures, mainly the anterior nucleus and the centromedian nucleus. There is limited proof from animal studies that stimulation of these structures can influence seizure threshold. However, there is clinical evidence that continuous stimulation of these targets in epileptic patients reduces seizure frequency and severity.

2.2.a - Anterior thalamus (AN)

The anterior nucleus (AN) of the thalamus receives projections from the hippocampus via the fornix, the mamillary bodies and the mamillo-thalamic fascicle of Vicq d'Azir and has outputs to the cingulate cortex and, via the cingulum, to the entorhinal cortex and back to the hippocampus. It appears to be in close interaction with the circuit of Papez which is often involved in some forms of epilepsies (e.g. temporal lobe epilepsies). AN therefore is central in the network which underlies limbic seizures and, as such, represents an attractive target for DBS in epileptic patients. Cooper and his group, encouraged by their experience on cerebellar stimulation, were the first to direct their interest to this nucleus, based on the hypothesis that AN could act as a "pacemaker" for the cortex. They showed that bilateral chronic stimulation of AN in 6 epileptic patients resulted in 60% reduction of seizure frequency in 5 of them, as well as a decrease in EEG spikes (Cooper and Upton, 1985). Using an experimental approach, it was later shown that AN and mamillary bodies were involved in the genesis of pentylentetrazol-induced seizures and were activated during ethosuximide-induced suppression of these seizures (Mirski and Ferrendelli, 1986a ; 1986b). In addition, the section of the mamillo-

thalamic bundle prevented pentylenetetrazol-induced seizures in guinea pigs (Mirsky and Ferrendelli, 1984). Furthermore, it was reported that 100-Hz electrical stimulation of the mammillary nuclei and AN increased the seizure threshold of pentylenetetrazol in rats (Mirski and Fisher, 1994; Mirski et al., 1997). These anticonvulsant effects were dependent on the intensity of the stimulation rather than on its frequency. On the contrary, low-frequency AN stimulation tended to be proconvulsive (Mirski et al., 1997). More recently, high-frequency AN stimulation suppressed focal cortical and limbic seizures induced by intra-cortical or intra-amygdaloid kainic acid injections, respectively (Takebayashi et al., 2007a and 2007b) and delayed both status epilepticus and seizures induced by pilocarpine although without complete suppression (Hamani et al., 2004, 2008). Finally, 100-Hz AN stimulation was found to *aggravate* recurrent seizures observed following status epilepticus produced by systemic kainic acid (Lado, 2006).

These experimental data gave weight to the need of re-assessing the effect of AN stimulation in epileptic patients. Four open-label trials were reported showing that seizure frequency was reduced from 20 to 92% and being statistically significant in 12 of the 18 patients (Hodaie et al., 2002 ; Kerrigan et al., 2004 ; Lim et al., 2007 ; Osorio et al., 2007). Two patients presented a complication (small frontal hemorrhage and extension erosion over the scalp), which did not result in major or permanent neurological deficit. A study showed that insertion of AN electrodes by itself could reduce seizures (Lim et al., 2007) and another one that the observed benefits did not differ between stimulation-on and stimulation-off periods (Hodaie et al., 2002), thus raising the issue of a lesional, placebo or carry-over effect. To address this question, a large multicenter prospective randomized trial of AN stimulation for partial and secondarily generalized seizures (Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy or SANTE) is currently under investigation in North America. Whether AN stimulation could be more effective in temporal lobe epilepsy (Zumsteg et al., 2006) and whether other components of the circuit of Papez, namely the mamillary bodies and mamillo-thalamic tract (Duprez et al., 2005 ; van Rijckevorsel et al., 2005) are possible targets for DBS are important issues for clinical trials.

2.2.b - Centromedian thalamus (CM)

In addition to the AN, attention was also directed towards one of the intralaminar nuclei of the thalamus, the centromedian nucleus (CM). This nucleus is part of the reticulothalamocortical system mediating cerebral cortex excitability (Jasper, 1991), and has been suggested to participate in the modulation of vigilance states (Velasco et al., 1979). Although experimental findings remain rare (Arduini and Lary Bounes, 1952), a first open-label study was conducted in 5 patients with bilateral CM stimulation at the end of the 1980s (Velasco et al., 1987). Initial results indicated an improvement of seizure frequency and EEG spiking over 3 months of chronic stimulation. Later, Velasco's group accumulated data in a cohort of 49 patients suffering from different forms of seizures and epilepsies (Velasco et al., 2001a ; 2002). Among these patients, 5 to 13 were followed over long-term follow-up studies (Velasco et al., 1993 ; 1995 ; 2000ab, 2006). Overall, the procedure was reported to be beneficial and generally well-tolerated, although a central nystagmus was induced in some cases (Taylor et al., 2000). A few patients were explanted because of repeated and multiple skin erosions (Velasco et al., 2006). It is interesting to note that a decrease of 80% of seizures were observed on average in patients with generalized tonic-clonic seizures and atypical absences of the Lennox-Gastaut syndrome, with a global improvement of patients in their ability scale scores (Velasco et al., 2006). By contrast, no improvements were found for either complex partial seizures or focal spikes in temporal regions. The best clinical results were seen when both electrodes contacts were located within the CM on both sides and when stimulation at 6-8 Hz and 60 Hz induced recruiting responses and regional DC shifts, respectively (Velasco et al., 2000a). Two hours of daily 130-Hz stimulation sessions (1-minute on, 4 minutes off), alternating the right and left CM were used. However, continuous bilateral stimulation led to faster and more significant results (Velasco et al. 2001b). As for AN stimulation, persistent antiepileptic effects were found 3 months or more after discontinuation of the stimulation (« off effect »), and possible plasticity which develops during the stimulation procedure was suggested (Velasco et al. 2001b). No such seizure suppression was found in a small placebo-controlled study conducted in 7 patients with mesial temporal lobe epilepsy. In this study, no statistically significant difference from the baseline in frequency of tonic-clonic seizures when the stimulator was on versus off (Fisher et al., 1992). In the open-label follow-up phase, however, 3 of 6 patients reported at least a 50% decrease in seizure frequency.

Up to now, very few animal studies have examined the role of the CM or of the parafascicular nucleus (PF) of the thalamus - which has similar connections - in the control of epileptic seizures. In a genetic model of absence epilepsy in the rat (GAERS), pharmacological activation of the PF was found to suppress spike-and-wave discharges (Nail-Boucherie et al., 2005). More recently, 130-Hz stimulation of this structure was reported to interrupt focal hippocampal seizures in a mouse model of mesiotemporal lobe epilepsy (Langlois et al., in preparation). Because of its unique location between cortical and limbic structures and the basal ganglia (see below), the CM/PF nuclei could well constitute an interesting target for DBS. More animal studies are clearly required to understand the role of this structure in the modulation of epileptic seizures.

2.3 - Basal ganglia

Since the beginning of the 1980s, experimental animal studies have suggested the existence of a “nigral control” of epileptic seizures (for review see Gale, 1995; Depaulis et al., 1994). Inhibition of the Substantia Nigra pars Reticulata (SNR) has potent anti-epileptic effects in different animal models of epilepsy (Deransart and Depaulis, 2002) and the GABAergic SNR output appears to be a critical relay in this control (Depaulis et al., 1990; Paz et al., 2005; 2007). Local manipulations of the basal ganglia that lead to an inhibition of the SNR neurons (e.g., activation of the striatum or pallidum, inhibition of the sub-thalamic nucleus) also had significant anti-epileptic effects (for review see Deransart and Depaulis, 2002), suggesting that different striato-nigral circuits are involved in the control of epileptic seizures. In humans, EEG, clinical and imaging data also support the involvement of the basal ganglia in the propagation and/or the control of epileptic discharges (Biraben et al., 2004; Bouilleret et al., 2008; Vercueil and Hirsch, 2002). Altogether, experimental and clinical data suggest a privileged role for the basal ganglia in the control of generation and/or spread of epileptic discharges in the cortex. Paradoxically, the therapeutic relevance of such findings was rarely considered until the 1990s.

2.3.a - *Caudate nucleus (CN)*

Following experimental evidence that stimulation of the caudate nucleus (CN) has antiepileptic properties in different animal models of seizures (La Grutta et al., 1971, 1988 ; Mutani, 1969 ; Oakley and Ojemann, 1982 ; Psatta, 1983), Chkhenkeli and his group, as well as Sramka and colleagues, were the first to suggest the beneficial effect of striatal low-frequency stimulation (below 50 Hz) in epileptic patients (Chkhenkeli, 1978 ; Sramka et al., 1980). A decrease in focal and generalized discharges was observed in 57 patients bilaterally stimulated at low frequency (4–6Hz) in the CN (Chkhenkeli and Chkhenkeli, 1997). The study, however, was not controlled and the effects on seizures were not assessed. Interestingly, epileptic activity was worsened by stimulating the CN at higher frequency, a finding that was also reported in the aluminium-hydroxide monkey model of motor seizures (Oakley and Ojemann, 1982). Therefore, if one assumes that low-frequency stimulation is excitatory and high-frequency stimulation is inhibitory, these clinical data are in agreement with animal data (see Deransart and Depaulis, 2002). Indeed, activation of the striatum inhibits the SNR through GABAergic projections and therefore leads to seizure suppression (Deransart et al., 1998). Although further studies are needed, these results highlight the ability of the basal ganglia system to modulate cortical epileptogenicity.

2.3.b - Subthalamic nucleus (STN)

In 1998, Vercueil et al. (1998) were the first to show that 130-Hz stimulation of the subthalamic nucleus (STN) could interrupt absence seizures in GAERS, a well-established genetic model of absence epilepsy (Danober et al., 1998; Marescaux et al. 1992). Since then, high-frequency stimulation of the subthalamic nucleus has been reported to protect against seizures induced by local kainate injection in the amygdala (Bressand et al., 1999; Loddenkemper et al., 2001; Usui et al., 2005) or by fluorothyl inhalation (Veliskova et al., 1996). This is in agreement with the antiepileptic effects reported after pharmacological inhibition of the STN on seizures induced by amygdala kindling (Deransart et al., 1998a), intravenous bicuculline or by its focal application into the anterior piriform cortex (Dybdal and Gale, 2000) and in GAERS (Deransart et al., 1996).

This led the group of Benabid at Grenoble University Hospital to perform the first STN stimulation in a 5-year-old girl with pharmacologically-resistant inoperable epilepsy caused by a focal centroparietal dysplasia (Benabid et al., 2002). Later, 11 additional

patients suffering from different forms of epilepsy received high frequency STN stimulation at different institutions (Chabardès et al., 2002 ; Loddenkemper et al., 2001 ; Vesper et al., 2007). Overall, seizure occurrence was reduced by at least 50% in 7/12 cases, and the stimulation was well tolerated. Good responders suffered from very different epilepsy types including focal epilepsy, Dravet syndrome, Lennox-Gastaut syndrome and progressive myoclonic epilepsy. Surgical complications occurred in 2 patients, including infection of the generator in one, and a postimplantation subdural hematoma in another who later underwent surgical treatment, without sequelae (Chabardès et al., 2002). Bilateral stimulation appeared more effective than unilateral stimulation, in agreement with experimental data (Depaulis et al., 1994). However, whether it should be applied continuously or intermittently remains questionable (Chabardès et al., 2002). Furthermore, whether the optimal target in epileptic patients is the STN itself or, as is suggested in some patients, the SNR, remains an important issue (see below - Chabardès et al., 2002 ; Vesper et al., 2007). A double-blind cross-over multicentric study is in progress in France (STIMEP) and aims at evaluating the clinical effect of 130-Hz stimulation of the STN/SNR in patients with ring chromosome 20 epilepsy. These patients suffer from very long lasting epileptic seizures, evolving often into status epilepticus and are difficult to control with antiepileptic drugs. They exhibit a deficit of dopaminergic activity in the striatum as compared with normal subjects (Biraben et al., 2004), a finding which is in accordance with the critical role of striatal dopamine in the control of seizures (Deransart et al., 2000).

2.3.c – Substantia Nigra pars Reticulata (SNR)

In 1980, Gale and Iadarola were the first to correlate an increase of GABA in the SNR with antiepileptic effects (Gale and Iadarola, 1980). Later, they showed that the potentiation of the GABAergic neurotransmission within the SNR, by bilateral microinjections of GABA-mimetic drugs, suppressed convulsions in various models of generalized seizures in the rat (Iadarola and Gale, 1982). The possibility that seizures are controlled by the SNR also emerged from pharmacological studies in GAERS showing that a bilateral inhibition of SNR suppresses cortical Spike-and-Waves discharges (SWDs) (Depaulis et al., 1988, 1989; Deransart et al., 1996, 1998, 2001). Since then, several studies have confirmed that inhibition of the SNR has a

potent anti-epileptic effects in different animal models of epilepsy (Depaulis et al., 1994; Deransart and Depaulis, 2002; Paz et al., 2005; 2007).

In this context, it was shown that DBS applied to the SNR, also suppressed generalized convulsive seizures induced by fluorothyl inhalation (Velisek et al., 2002), amygdala-kindled seizures (Morimoto and Goddard, 1987; Shi et al., 2006), absence seizures in GAERS (Feddersen et al., 2007) and also focal seizures in kainate treated mice (Deransart et al., 2004). In the model of generalized convulsive seizures induced by fluorothyl inhalation, bilateral and bipolar 130Hz SNR stimulation had anticonvulsant effects in both adults and infant rats (Velisek et al., 2002). In amygdala-kindling, such stimulations were shown to induce a long lasting suppression of antiepileptogenesis (Shi et al., 2006). In GAERS, bilateral, bipolar, and monophasic SNR stimulations at a frequency of 60Hz and a pulse width of 60 μ s were defined as the optimal conditions to interrupt ongoing absence seizures without motor side effects (Feddersen et al., 2007). The threshold to interrupt epileptic seizures was lower using SNR stimulation compared to STN stimulation, using the same model and stimulation parameters. However, this last study showed that continuous stimulation fail to control the occurrence of seizures, in agreement with previous reports (Vercueil et al., 1998) and suggested that a refractory period of about 60 sec exists during which any stimulation is without effect. This study also showed that *continuous* stimulation of the SNR could even aggravate seizure occurrence. Adaptive stimulation may allow to alleviate this problem and to further specify the existence of a refractory period (see below).

3 - Stimulation at seizure focus

Stimulating the epileptogenic cortex to interrupt epileptic seizures may appear paradoxical. Indeed, « stimulation » classically means « excitation » and the epilepsies are characterized by a pathological hyperexcitability and hypersynchrony of cortical neurons. The effects provoked by cortical stimulation, however, depend on the stimulation parameters used, the region which is stimulated, as well as the way that the stimulation is delivered (indirectly or directly). Furthermore, cortical stimulation is generally used to map functions in eloquent brain. It is known that cortical stimulation can evoke focal after-discharges that may evolve into clinical seizures. It has been shown that afterdischarges elicited by electrical stimulation via

subdural electrodes can be interrupted by the application of brief bursts of 50-Hz electrical stimulation through subdural electrode contacts (Lesser et al. 1999). To date, a few studies have been conducted, including a limited number of patients, and therapeutic results are equivocal at best.

Several preclinical studies have found potential antiepileptic effects of brain stimulation in animal models. Notably, low-frequency (1 Hz) stimulation applied after kindling stimulation of the amygdala was found to inhibit the development of afterdischarges, an effect named *quenching* (Weiss et al., 1995). This quenching effect seems effective in adult as well as immature rats (Velisek et al., 2002). Interestingly, when applied immediately *before* the kindling stimulus, preemptive 1 Hz sine wave stimulation was also effective, thus suggesting some potential benefit for seizure prevention (Goodman et al., 2005). Other regions such as the hippocampus (Barbarosie and Avoli, 1997), the central piriform cortex (Yang et al., 2006; Zhu-ge et al., 2007) or the cerebral fastigial nucleus (Wang et al., 2008) may also appear as potentially effective targets for 1-Hz stimulation treatment of epilepsy. In general these data suggest that 1-Hz stimulation inhibits both acquisition and expression of kindling seizure by preventing afterdischarge generation and propagation in rat. Unexpectedly, such effects are also observed in the cerebral fastigial nucleus, suggesting that targets outside the limbic system may have a significant antiepileptic action.

In humans, both low- (1-Hz) and medium- (50 Hz) frequency stimulation have proven effective to reduce interictal epileptiform discharges (Kinoshita et al., 2005b; Yamamoto et al., 2002). Therapeutic stimulation, however, was applied at high frequency in almost all studies. The first attempt of therapeutic stimulation of temporal lobe structures was reported in 1980, in 3 patients, without clear benefit (Sramka et al., 1980). More recently, several investigators have tried continuous scheduled stimulation of epileptic foci, including hypothalamic hamartoma (Kahane et al., 2003), neocortical structures (Elisevich et al., 2006) and, mostly, mesio-temporal lobe (Tellez-Zenteno et al., 2006 ; Velasco et al., 2000c ; 2007 ; Vonck et al., 2002). The first pilot study of mesio-temporal lobe stimulation, conducted in 10 patients studied by intracranial electrodes before surgery, showed that stimulation stopped seizures and decreased the number of interictal EEG spikes in the 7 patients where the stimulated electrode was placed within the hippocampus or hippocampal gyrus

(Velasco et al., 2000c). There were no side-effects on language and memory, and no histological damages were found in the stimulated tissue. Whether such an antiepileptic effect could be observed over a more prolonged stimulation procedure was later evaluated in a small open series conducted in 3 patients, all of whom exhibited more than 50% of seizure reduction after a mean follow-up of 5 months, without adverse events (Vonck et al., 2002).

Following this, 2 additional trials of hippocampal stimulation were conducted, leading to opposite results. In one double-blind study, the seizure outcome was significantly improved in all 9 patients over a long-term follow-up (Velasco et al., 2007), which showed more than 95% seizure reduction in the 5 patients with normal MRI, and 50-70% seizure reduction in the 4 patients who had hippocampal sclerosis. No adverse events were found but 3 patients were explanted after 2 years due to skin erosion in the trajectory system. It was suggested that beneficial effects of stimulation were associated with a high GABA tissue content and a low rate of cell loss (Cuellar-Herrera et al., 2004). By contrast, seizure frequency was reduced by only 15% in average in the 4 patients of the double-blind, multiple cross-over, randomized study of Tellez-Zenteno et al. (2006). Additionally, effects seemed to carry over into the off period, thus raising the issue of an implantation effect. Yet, no adverse events were found. Overall, stimulation of hippocampal foci shows beneficial trends, but whether the effect is significant, and of clear clinical relevance, remains debatable.

Currently, a randomized controlled trial of hippocampal stimulation for temporal lobe epilepsy (METTLE) is recruiting patients to determine whether unilateral hippocampal electrical stimulation is safe and more effective than simply implanting an electrode in the hippocampus without electrical stimulation, or treating with medical therapy alone. A prospective randomized controlled study of neurostimulation in the medial temporal lobe for patients with medically refractory medial temporal lobe epilepsy is also currently recruiting patients for a controlled randomized stimulation versus resection (CoRaStiR) study (www.clinicaltrials.gov).

4 - Adaptative stimulation

Continuous scheduled brain stimulation, whatever the target (DBS, cortical stimulation), has appeared to be safe and of potential benefit in treating medically

intractable epilepsies (see above). Limited, but growing data suggests that responsive (seizure-triggered) stimulation might also be effective (Morrel, 2006). Such a strategy is distinct from continuous scheduled stimulation as it aims at blocking seizures when they occur, rather than at decreasing cortical excitability chronically. It is motivated by the reduction of power consumption, the paroxysmal nature of the seizures and the possible behavioural side-effects induced by chronic stimulations. Also, it has been suggested that continuous stimulations may aggravate seizures in animals (Feddersen et al., 2007). Seizure-triggered stimulation requires an implanted stimulating device coupled with real-time signal analysis techniques. Usually, a seizure detection algorithm allows the delivery of a stimulation to interrupt seizure prior to, or concomitantly to, the onset of clinical symptoms. A number of algorithms to detect seizures do exist (see for instance Osorio et al., 2002; Grewal and Gotman, 2005). The main stumbling block, as for continuous stimulation, is to find, ideally following an automatic search, optimal stimulation parameters to abort seizures. To our knowledge, existing literature about automatic seizure-triggered stimulation in animal models *in vivo* is rather limited. Using similar techniques as VNS therapy, Fanselow and colleagues have shown a reduction of pentylenetetrazole-induced seizure activity in awake rats by seizure-triggered trigeminal nerve stimulation (Fanselow et al., 2000). Interestingly, seizure-triggered stimulation was more effective than the stimulation protocol involving a fixed duty cycle, in terms of the percent seizure reduction per second of stimulation (up to 78%). Currently, a preliminary study in Grenoble (France) is testing a new technology based on stimulation combined to seizure-detection to interrupt absence seizures in GAERS (Saillet et al., submitted). This should allow to better determine the optimal target and parameters of stimulation required by such technology.

In humans, responsive stimulation can shorten or terminate electrically-elicited afterdischarges using brief bursts of 50-Hz electrical stimulation (Lesser et al., 1999), the effect being greater at primary sites than at adjacent electrodes (Motamedi et al., 2002). Preliminary trials of responsive stimulation, however, did not consistently use a similar paradigm (Kossoff et al., 2004 ; Fountas et al., 2005 ; Osorio et al., 2005). The effects of responsive stimulation were first evaluated in 4 patients using an external neurostimulator, which proved effective at automatically detecting electrographic seizures, delivering targeted electrical stimuli, and altering or suppressing ictal discharges (Kossoff et al., 2004). Another feasibility study

confirmed these results using a cranially implantable device in 8 patients (Fountas et al., 2005). Detection and stimulation were performed using electrodes placed over the seizure focus, and 7 of the 8 patients exhibited more than a 45% decrease in their seizure frequency, with a mean follow-up time of 9.2 months. In the third pilot study, conducted in 8 patients, stimulation was delivered either directly to the epileptogenic zone (local closed-loop, n=4), or indirectly through the anterior thalami (remote closed-loop, n=4), depending on whether the epileptogenic zone was single, or multiple (Osorio et al., 2005). On average, a 55.5% and 40.8% decrease of seizure frequency was observed in the local closed-loop group and in the remote closed-loop group, respectively. Overall, none of the 20 patients enrolled in these 3 pilot studies had adverse events. Although promising, this new therapy needs further evaluation and a multi-institutional prospective clinical trial is underway in the USA. The Responsive Neurostimulation System (RNS), sponsored by NeuroPace Inc., is designed to continuously monitor brain electrical activity from the electrodes and, after identifying the "signature" of a seizure's onset, deliver brief and mild electrical stimulation with the intention of suppressing the seizure. The purpose of the RNS System Pivotal Clinical Investigation is to assess the safety and to demonstrate that the RNS System is effective as an add-on (adjunctive) therapy in reducing the frequency of seizures in individuals with partial onset seizures that are refractory to two or more AED medications. Whether, in the near future, closed-loop stimulators will be able to react using seizure-prediction algorithms represents a particularly challenging issue.

5 - Conclusions

Neurostimulation in non-surgically remediable epileptic patients represents an emerging treatment. It has the advantage of reversibility and adjustability, but remains palliative so that surgical resection remains the gold standard treatment of drug-resistant epilepsies whenever this option is possible. Stimulation techniques must be considered experimental although several controlled studies are currently under investigation. Notably, results of direct brain stimulation, although encouraging, are not conclusive and further investigations are required to evaluate the real benefit of this emerging therapy, in as much as the risks of haemorrhage and infection,

although low (around 5%), do exist. However, pathological examination in post-mortem studies and temporal lobe resection, in Parkinson's disease or epilepsy, suggest that chronic stimulation does not induce neural injury and can be delivered safely (Haberler et al., 2000 ; Pilitsis et al., 2008 ; Velasco et al., 2000c). In any case, seizure types or epileptic syndromes which may respond to stimulation should be identified, as well as the type of stimulation that is likely to be of potential efficacy depending on the patient's characteristics. This requires to improve our knowledge on the neural circuits in which seizures start and propagate, to better understand the precise mechanisms of the supposed effect of neurostimulation, and to search for optimal stimulation parameters. The development of experimental research in this field, as well as rigorous clinical evaluation, is essential for further improvements in clinical efficacy.

References

Akamatsu N, Fueta Y, Endo Y, Matsunaga K, Uozumi T, Tsuji S. Decreased susceptibility to pentylenetetrazole-induced seizures after low frequency transcranial magnetic stimulation in the rat. *Neurosci Lett* 2001; 310:153-156.

Andy OJ, Jurko MF. Seizure control by mesothalamic reticular stimulation. *Clin Electroencephalography* 1986 ; 17 : 52-60.

Arduini D, Lary Bounes GC. Action de la stimulation électrique de la formation réticulaire du bulbe et des stimulations sensorielles sur les ondes strychniques. *Electroencephalogr Clin Neurophysiol* 1952; 4: 502-12.

Barbarosie M, Avoli M. CA3-driven hippocampal-entorhinal loop controls rather than sustains in vitro limbic seizures. *J Neurosci* 1997; 17 : 9308-9314.

Benabid AL, Koudsié A, Benazzouz A, Vercueil L, Fraix V, Chabardès S, Lebas JF, Pollak P. Deep brain stimulation of the corpus luyi (subthalamic nucleus) and other targets in Parkinson's disease. Extension to new indications such as dystonia and epilepsy. *J Neurol* 2001; 248 (suppl 3): III37-47.

Benabid AL, Minotti L, Koudsie A, de Saint Martin A, Hirsch E. Antiepileptic effect of high-frequency stimulation of the subthalamic nucleus (corpus luyi) in a case of medically intractable epilepsy caused by focal dysplasia : a 30-month follow-up : technical case report. *Neurosurgery* 2002; 50: 1385–1391.

Benazzouz A, Piallat B, Pollak P, Benabid AL. Responses of substantia nigra pars reticulata and glomus pallidus complex to high frequency stimulation of the subthalamic nucleus in rat: electrophysiological data. *Neurosci Lett* 1995; 189 : 77-80.

Biraben A, Semah F, Ribeiro MJ, Douaud G, Remy P, Depaulis A. PET evidence for a role of the basal ganglia in patients with ring chromosome 20 epilepsy. *Neurology* 2004; 63: 73-77.

Bouilleret V, Semah F, Chassoux F, Mantzaridez M, Biraben A, Trebossen R, Ribeiro MJ. Basal ganglia involvement in temporal lobe epilepsy: a functional and morphologic study. *Neurology* 2008; 70:177-184.

Brasil-Neto JP, de Araujo DP, Teixeira WA, Araujo VP, Boechat-Barros R. *Arq Neuropsiquiatr* 2004 ; 62 : 21-25.

Bressand K, Dematteis M, Kahane P, Benazzouz A, Benabid AL. Involvement of the subthalamic nucleus in the control of temporal lobe epilepsy: study by high frequency stimulation in rats. *Soc Neurosci* 1999 25:1656.

Cantello R, Rossi S, Varrasi C, Ulivelli M, Civardi C, Bartalini S, Vatti G, Cincotta M, Borghoresi A, Zaccara G, Quartarone A, Crupi D, Langana A, Inghilleri M, Giallonardo AT, Berardelli A, Pacifici L, Ferreri F, Tombini M, Gilio F, Quarato P, Conte A, Manganotti P, Bongiovanni LG, Monaco F, Ferrante D, Rossini PM. Slow repetitive TMS for drug-resistant epilepsy : clinical and EEG findings of a placebo-controlled trial. *Epilepsia* 2007; 48 : 366-374.

Chabardès S, Kahane P, Minotti L, Koudsie A, Hirsch E, Benabid A-L. Deep brain stimulation in epilepsy with particular reference to the subthalamic nucleus. *Epileptic disord* 2002; 4 (suppl 3): 83–93.

Chen R, Classen J, Gerloff C, Celnik P, Wassermann EM, Hallett M, Cohen LG. Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation. *Neurology* 1997; 48: 1398-1403.

Chkhenkeli SA. The inhibitory influence of the nucleus caudatus electrostimulation on the human's amygdalar and hippocampal activity at temporal lobe epilepsy. *Bull Georgian Acad Sci* 1978; 4/6: 406-11.

Chkhenkeli SA, Chkhenkeli IS. Effects of therapeutic stimulation of nucleus caudatus on epileptic electrical activity of brain in patients with intractable epilepsy. *Stereotact Funct Neurosurg* 1997; 69: 221-224.

Cooke PM, Snider RS. Some cerebellar influences on electrically-induced cerebral seizures. *Epilepsia* 1955; 4: 19-28.

Cooper I. Cerebellar stimulation in man. New York: Raven Press, 1978: 1–212.

Cooper IS, Upton ARM. The effect of chronic stimulation of cerebellum and thalamus upon neurophysiology and neurochemistry of cerebral cortex. In: Lazorthes Y, Upton ARM, eds. *Neurostimulation: an overview*. New York: Futura, 1985: 207-211.

Cooper IS, Amin I, Riklan M, Waltz JM, Poon TP. Chronic cerebellar stimulation in epilepsy. Clinical and anatomical studies. *Arch Neurol* 1976; 33: 559-70.

Cooper IS, Amin I, Gilman S. The effect of chronic cerebellar stimulation upon epilepsy in man. *Trans Am Neurol Assoc* 1973; 98: 192-6.

Cuellar-Herrera M, Velasco M, Velasco F, Velasco AL, Jimenez F, Orozco S, Briones M, Rocha L. Evaluation of GABA system and cell damage in parahippocampus of patients with temporal lobe epilepsy showing antiepileptic effects after subacute electrical stimulation. *Epilepsia* 2004; 45: 459-466.

Danober L, Deransart C, Depaulis A, Vergnes M, Marescaux C. Pathophysiological mechanisms of genetic absence epilepsy in rat. *Prog Neurobiol* 1998; 55: 27-57.
Davis R, Emmonds SE. Cerebellar stimulation for seizure control: 17-year study. *Stereotact Funct Neurosurg* 1992; 58: 200–208.

Depaulis A, Vergnes M, Depaulis A. Endogenous control of epilepsy: the nigral inhibitory system. *Prog Neurobiol* 1994; 42: 33-52.

Deransart C, Depaulis A. The control of seizures by the basal ganglia? A review of experimental data. *Epileptic Disord* 2002; 4 (suppl 3): S61-S72.

Deransart C, Marescaux C, Depaulis A. Involvement of nigral glutamatergic inputs in the control of seizures in a genetic model of absence epilepsy in the rat. *Neuroscience* 1996; 71: 721-728.

Deransart C, Lê BT, Marescaux C, Depaulis A. Role of the subthalamo-nigral input in the control of amygdale-kindled seizures in rat. *Brain Res* 1998a; 807: 78-83.

Deransart C, Riban V, Lê BT, Marescaux C, Depaulis A. Dopamine in the nucleus accumbens modulates seizures in a genetic model of absence epilepsy in the rat. *Neuroscience* 2000; 100: 335-344.

Deransart C, Depaulis A (2004) Le concept de contrôle nigral des épilepsies s'applique-t-il aux épilepsies partielles pharmacorésistantes? *Epilepsies* 16(2) 75-82.

Dow RS, Fernandez-Guardiola A, Manni E. The influence of the cerebellum on experimental epilepsy. *Electroencephalogr Clin Neurophysiol* 1962; 14: 383-398.

Duprez TP, Serieh BA, Raftopoulos C. Absence of memory dysfunction after bilateral mammillary body and mammillothalamic tract electrode implantation: preliminary experience in three patients. *AJNR Am J Neuroradiol* 2005; 26: 195-197.

Ebner TJ, Bantli H, Bloedel JR. Effects of cerebellar stimulation on unitary activity within a chronic epileptic focus in a primate. *Electroencephalogr Clin Neurophysiol* 1980; 49: 585-599.

Elisevich K, Jenrow K, Schuh L, Smith B. Long-term electrical stimulation-induced inhibition of partial epilepsy. Case report. *J Neurosurg* 2006; 105: 894-897.

Fanselow EE, Reid AP, Nicolelis MA. Reduction of pentylenetetrazole-induced seizure activity in awake rats by seizure-triggered trigeminal nerve stimulation. *J Neurosci*. 2000; 20(21):8160-8.

Feddersen B, Vercueil L, Noachtar S, David O, Depaulis A, Deransart C. Controlling seizures is not controlling epilepsy: a parametric study of deep brain stimulation for epilepsy. *Neurobiol Dis* 2007; 27: 292-300.

Feger J, Robledo P. The effects of activation or inhibition of the subthalamic nucleus on the metabolic and electrophysiological activities within the pallidal complex and the substantia nigra in the rat. *Eur J Neurosci* 1991; 3: 947-952.

Fisher RS, Uematsu S, Krauss GL, Cysyk B, McPherson R, Lesser RP, Gordon B, Schwerdt P, Rise M. Placebo-controlled pilot study of centromedian thalamic stimulation in treatment of intractable seizures. *Epilepsia* 1992; 33: 841-851.

Fountas KN, Smith JR, Murro AM, Politsky J, Park YD, Jenkins PD. Implantation of a closed-loop stimulation in the management of medically refractory focal epilepsy: a technical note. *Stereotact Funct Neurosurg* 2005; 83: 153-158.

Fregni F, Otachi PT, Do Valle A, Boggio PS, Thut G, Rigonatti SP, Pascual-Leone A, Valente KD. A randomized clinical trial of repetitive transcranial magnetic stimulation in patients with refractory epilepsy. *Ann Neurol* 2006; 60: 447-455.

Gale K, Iadarola MJ. Seizure protection and increased nerve-terminal GABA: delayed effects of GABA transaminase inhibition. *Science* 1980; 208: 288-291.

Goodman JH, Berger RE, Tcheng TK. Preemptive low-frequency stimulation decreases the incidence of amygdala-kindled seizures. *Epilepsia* 2005; 46: 1-7.

Grewal S, Gotman J. An automatic warning system for epileptic seizures recorded on intracerebral EEGs. *Clin Neurophysiol*. 2005;116(10):2460-72.

Haberler C, Alesch F, Mazal PR, Pilz P, Jellinger K, Pinter MM, Hainfellner JA, Budka H. No tissue damage by chronic deep brain stimulation in Parkinson's disease. *Ann Neurol* 2000; 48: 372-376.

Hamani C, Ewerton FI, Bonilha SM, Ballester G, Mello LE, Lozano AM. Bilateral anterior thalamic nucleus lesions and high-frequency stimulation are protective against pilocarpine-induced seizures and status epilepticus. *Neurosurgery* 2004; 54:191-195.

Hamani C, Hodaie M, Chiang J, del Campo M, Andrade DM, Sherman D, Mirski M, Mello LE, Lozano AM. Deep brain stimulation of the anterior nucleus of the thalamus: effects of electrical stimulation on pilocarpine-induced seizures and status epilepticus. *Epilepsy Res.* 2008 Feb;78(2-3):117-23

Hodaie M, Wennberg RA, Dostrovsky JO, Lozano AM. Chronic anterior thalamus stimulation for intractable epilepsy. *Epilepsia* 2002; 43: 603-608.

Iadarola MJ, Gale K. Substantia nigra: site of anticonvulsant activity mediated by gammaaminobutyric acid. *Science* 1982; 218 : 1237-1240.

Jasper H. Current evaluation of the concepts of centrencephalic and cortico-reticular seizures. *Electroencephalogr Clin Neurophysiol* 1991; 78: 2-11.

Jennum P, Klitgaard H. Repetitive transcranial magnetic stimulations of the rat. Effect of acute and chronic stimulations on pentylentetrazole-induced clonic seizures. *Epilepsy Res* 1996; 23: 115-122.

Joo EY, Han SJ, Chung S-H, Cho J-W, Seo DW, Hong SB. Antiepileptic effects of low frequency repetitive transcranial magnetic stimulation by different stimulation durations and locations. *Clinical Neurophysiology* 2007 ; 118 : 702-708.

Kahane P, Ryvlin P, Hoffmann D, Minotti L, Benabid AL. From hypothalamic hamartoma to cortex : what can be learnt from depth recordings and stimulation ? *Epileptic Disord* 2003; 5: 205-217.

Kerrigan JF, Litt B, Fisher RS, Cranstoun S, French JA, Blum DE, Dichter M, Shetter A, Baltuch G, Jaggi J, Krone S, Brodie MA, Rise M, Graves N. Electrical stimulation of the anterior nucleus of the thalamus for the treatment of intractable epilepsy. *Epilepsia* 2004 ; 45 : 346-354.

Kinoshita M, Ikeda A, Begum T, Yamamoto J, Hitomi T, Shibasaki H. Low-frequency repetitive transcranial magnetic stimulation for seizure suppression in patients with extratemporal lobe epilepsy – a pilot study. *Seizure* 2005a; 14: 387-392.

Kinoshita M, Ikeda A, Matsushashi M, Matsumoto R, Hitomi T, Begum T, Usui K, Takayama M, Mikuni N, Miyamoto S, Hashimoto N, Shibasaki H. Electric cortical stimulation suppresses epileptic and background activities in neocortical epilepsy and mesial temporal lobe epilepsy. *Clin Neurophysiol* 2005b; 116: 1291-1299.

Kobayashi M, Pascual-Leone A. Transcranial magnetic stimulation in neurology. *Lancet Neurol* 2003; 2: 145-156.

Kossoff EH, Ritzl EK, Politsky JM, Murro AM, Smith JR, Duckrow RB, Spencer DD, Bergey GK. Effect of an external responsive neurostimulator on seizures and electrographic discharges during subdural electrode monitoring. *Epilepsia* 2004; 45:1560-1567.

Krauss GL, Fisher RS. Cerebellar and thalamic stimulation for epilepsy. *Adv Neurol* 1993; 63: 231–245.

Kwan P, Brodie M. Early identification of refractory epilepsy. *N Engl J Med* 2000; 342: 314-319.

Lado FA. Chronic bilateral stimulation of the anterior thalamus of kainate-treated rats increases seizure frequency. *Epilepsia* 2006; 47: 27-32.

La Grutta V, Amato G, Zagami MT. The importance of the caudate nucleus in the control of convulsive activity in the amygdaloid complex and the temporal cortex of the cat. *Electroencephalogr Clin Neurophysiol* 1971; 31: 57-69.

La Grutta V, Sabatino M, Gravante G, Morici G, Ferraro G, La Grutta G. A study of caudate inhibition on an epileptic focus in the cat hippocampus. *Arch Int Physiol Biochim* 1988; 96: 113-120.

Lesser RP, Kim SH, Beyderman L, Miglioretti DL, Webber WR, Bare M, Cysyk B, Krauss G, Gordon B. Brief bursts of pulse stimulation terminate afterdischarges caused by cortical stimulation. *Neurology* 1999; 53: 2073-2081.

Lim SN, Lee ST, Tsai YT, Chen IA, Tu PH, Chen JL, Chang HW, Su YC, Wu T. Electrical stimulation of the anterior nucleus of the thalamus for intractable epilepsy : a long term follow-up study. *Epilepsia* 2007; 48: 342-347.

Lockard JS, Ojemann GA, Congdon WC, DuCharme LL. Cerebellar stimulation in alumina-gel monkey model: inverse relationship between clinical seizures and EEG interictal bursts. *Epilepsia* 1979; 20: 223-234.

Loddenkemper T, Pan A, Neme S, Baker KB, Rezai AR, Dinner DS, Montgomery EB Jr, Lüders HO. Deep brain stimulation in epilepsy. *J Clin Neurophysiol* 2001; 18: 514-532.

Majkowski J, Karliński A, Klimowicz-Młodzik I. Effect of cerebellar stimulation of hippocampal epileptic discharges in kindling preparation. *Monogr Neural Sci* 1980; 5: 40-45.

Marescaux C, Vergnes M, Depaulis A. Genetic absence epilepsy in rats from strasbourg. *J Neural Transm Suppl* 1992; 35: 37-69.

Menkes DL, Gruenthal M. Slow-frequency repetitive transcranial magnetic stimulation in a patient with focal cortical dysplasia. *Epilepsia* 2000; 41: 240-42.

Mirski MA, Ferrendelli JA. Interruption of the mamillothalamic tract prevents seizures in guinea pigs. *Science* 1984; 226: 72-74.

Mirski MA, Ferrendelli JA. Anterior thalamic mediation of generalized pentylenetetrazol seizures. *Brain Res* 1986a; 399: 212-223.

Mirski MA, Ferrendelli JA. Selective metabolic activation of the mammillary bodies and their connections during ethosuximide-induced suppression of pentylenetetrazol seizures. *Epilepsia* 1986b; 27: 194-203.

Mirski MA, Fisher RS. Electrical stimulation of the mammillary nuclei increases seizure threshold to pentylenetetrazol in rats. *Epilepsia* 1994; 35: 1309-1316.

Mirski MA, Rossell LA, Terry JB, Fisher RS. Anticonvulsant effect of anterior thalamic high frequency electrical stimulation in the rat. *Epilepsy Res* 1997; 28: 89-100.

Misawa S, Kuwabara S, Shibuya K, Mamada K, Hattori T. Low-frequency transcranial magnetic stimulation for epilepsy partialis continua due to cortical dysplasia. *J Neurol Sci* 2005; 234: 37-39.

Morrell M. Brain stimulation for epilepsy : can scheduled or responsive neurostimulation stop seizures ? *Curr Opin Neurol* 2006; 19: 164-168.

Motamedi GK, Lesser RP, Miglioretti DL, Mizuno-Matsumoto Y, Gordon B, Webber WR,

Jackson DC, Sepkuty JP, Crone NE. Optimizing parameters for terminating cortical afterdischarges with pulse stimulation. *Epilepsia* 2002; 43: 836-846.

Mutani R. Experimental evidence for the existence of an extrarhinencephalic control of the activity of the cobalt rhinencephalic epileptogenic focus, part 1: the role played by the caudate nucleus. *Epilepsia* 1969; 10: 337–350.

Mutani R, Bergamini L, Doriguzzi T. Experimental evidence for the existence of an extrarhinencephalic control of the activity of the cobalt rhinencephalic epileptogenic focus. Part 2. Effects of the paleocerebellar stimulation. *Epilepsia* 1969; 10: 351-362.

Nail-Boucherie K, Lê-Pham BT, Gobaille S, Maitre M, Aunis D, Depaulis A. Evidence for a role of the parafascicular nucleus of the thalamus in the control of epileptic seizures by the superior colliculus. *Epilepsia* 2005; 46: 141-145.

Nanobashvili Z, Chachua T, Nanobashvili A, Bilanishvili I, Lindvall O, Kokaia Z. Suppression of limbic motor seizures by electrical stimulation in thalamic reticular nucleus. *Exp Neurol* 2003; 181: 224-230.

Oakley JC, Ojemann GA. Effects of chronic stimulation of the caudate nucleus on a preexisting alumina seizure focus. *Exp Neurol* 1982; 75:360–67.

Oommen J, Morrell M, Fisher RS. Experimental electrical stimulation for epilepsy. *Curr Treat Options Neurol* 2005 ; 7 : 261-271.

Osorio I, Frei MG, Giftakis J, Peters T, Ingram J, Turnbull M, Herzog M, Rise MT, Schaffner S, Wennberg RA, Walczak TS, Risinger MW, Ajmone-Marsan C. Performance reassessment of a real-time seizure-detection algorithm on long ECoG series. *Epilepsia*. 2002;43(12):1522-35.

Osorio I, Frein MG, Sunderam S, Giftakis J, Bhavaraju NC, Schaffner SF, Wilkinson SB. Automated seizure abatement in humans using electrical stimulation *Ann Neurol* 2005; 57: 258-268

Osorio I, Overman J, Giftakis J, Wilkinson SB. High frequency thalamic stimulation for inoperable mesial temporal epilepsy. *Epilepsia* 2007; 48: 1561-1571.

Paz JT, Deniau JM, Charpier S. Rhythmic Bursting in the Cortico-Subthalamo-Pallidal Network during Spontaneous Genetically Determined Spike and Wave Discharges. *J Neurosci* 2005; 25: 2092-2101.

Paz JT, Chavez M, Sallet S, Deniau JM, Charpier S. Activity of ventral medial thalamic neurons during absence seizures and modulation of cortical paroxysms by the nigrothalamic pathway. *J Neurosci* 2007; 27: 929-941.

Pilitsis JG, Chu Y, Kordower J, Bergen CD, Cochran EJ, Bakay RA. Postmortem study of deep brain stimulation of the anterior thalamus: case report. *Neurosurgery* 2008; 62: 530-532.

Polkey CE. Alternative surgical procedures to help drug-resistant epilepsy – a review. *Epileptic Disord* 2003 ; 5 : 63-75.

Psatta DM. Control of chronic experimental focal epilepsy by feedback caudatum stimulations. *Epilepsia* 1983; 24: 444-454.

Rotenberg A, Muller P, Birnbaum D, Harrington M, Riviello JJ, Pascual-Leone A, Jensen FE.

Seizure suppression by EEG-guided repetitive transcranial magnetic stimulation in the rat. *Clin Neurophysiol* 2008; 119:2697-2702.

Saillet S, Charvet G, Gharbi S, Depaulis A, Guillemaud R, David O. Closed loop control of seizures in a rat model of absence epilepsy using the BioMEATM system. *IEEE Neural Eng.* Submitted

Santiago-Rodriguez E, Cardenas-Morales L, Harmony T, Fernandez-Bouzas A, Porras-Kattz E, Hernandez A. Repetitive transcranial magnetic stimulation decreases the number of seizures in patients with focal neocortical epilepsy. *Seizure* 2008 ; may 19 [Epub ahead of print].

Semah F. PET imaging in epilepsy: basal ganglia and thalamic involvement. *Epileptic Disord* 2002; 4 (suppl 3): S55-S60.

Shi LH, Luo F, Woodward D, Chang JY. Deepbrain stimulation of the substantia nigra pars reticulata exerts long lasting suppression of amygdale-kindled seizures. *Brain Res* 2006; 1090 (1): 202-207.

Sramka M, Fritz G, Gajdosova D, Nadvornik P. Central stimulation treatment of epilepsy. *Acta Neurochir Suppl* 1980; 30: 183-187.

Takebayashi S, Hashizume K, Tanaka T, Hodozuka A. The effect of electrical stimulation and lesioning of the anterior thalamic nucleus on kainic acid-induced focal cortical seizure status in rats. *Epilepsia*. 2007a Feb;48(2):348-58.

Takebayashi S, Hashizume K, Tanaka T, Hodozuka A. Anti-convulsant effect of electrical stimulation and lesioning of the anterior thalamic nucleus on kainic acid-induced focal limbic seizure in rats. *Epilepsy Res*. 2007b May;74(2-3):163-70.

Tassinari CA, Cincotta M, Zaccara G, Michelucci R. Transcranial magnetic stimulation and epilepsy. *Clin Neurophysiol* 2003; 114: 777-798.

Taylor RB, Wennberg RA, Lozano AM, Sharpe JA. Central nystagmus induced by deep-brain stimulation for epilepsy. *Epilepsia* 2000; 41: 1637-1641.

Tellez-Zenteno JF, McLachlan RS, Parrent A, Kubu CS, Wiebe S. Hippocampal electrical stimulation in mesial temporal lobe epilepsy. *Neurology* 2006; 66: 1490-1494.

Tergau F, Naumann U, Paulus W, Steinhoff BJ. Low-frequency repetitive transcranial magnetic stimulation improves intractable epilepsy. *Lancet* 1999; 353: 2209.

Theodore WH, Fisher RS. Brain stimulation for epilepsy. *Lancet Neurol* 2004; 3: 111-118.

Theodore WH, Hunter K, Chen R, et al. Transcranial magnetic stimulation for the treatment of seizures: a controlled study. *Neurology* 2002; 59: 560-562.

Usui N, Maesawa S, Kajita Y, Endo O, Takebayashi S, Yoshida J. Suppression of secondary generalization of limbic seizures by stimulation of subthalamic nucleus in rat. *J Neurosurg* 2005; 102 (6): 1122-1129.

Van Buren JM, Wood JH, Oakley J, Hambrecht F. Preliminary evaluation of cerebellar stimulation by double blind stimulation and biological criteria in the treatment of epilepsy. *J Neurosurg* 1978; 48: 407-16.

van Rijckevorsel K, Abu Serieh B, de Tourtchaninoff M, Raftopoulos C. Deep EEG

recordings of the mammillary body in epilepsy patients. *Epilepsia* 2005; 46: 781-785.

Velasco F, Velasco M, Cepeda C, Munoz H. Wakefulness-sleep modulation of thalamic multiple unit activity and EEG in man. *Electroencephalogr Clin Neurophysiol* 1979; 47: 597-606.

Velasco F, Velasco M, Ogarrio C, Fanghanel G. Electrical stimulation of the centromedian thalamic nucleus in the treatment of convulsives seizures: a preliminary report. *Epilepsia* 1987; 28: 421-430.

Velasco F, Velasco M, Velasco AL, Jimenez F. Effect of chronic electrical stimulation of the centromedian thalamic nuclei on various intractable seizure patterns, I: clinical seizures and paroxysmal EEG activity. *Epilepsia* 1993; 34: 1052-1064.

Velasco F, Velasco M, Velasco AL, Jimenez F, Marquez I, Rise M. Electrical stimulation of the centromedian thalamic nucleus in control of seizures : long term studies. *Epilepsia* 1995 ; 36 : 63-71.

Velasco F, Velasco M, Jimenez F, Velasco AL, Brto F, Rise M, Carrillo-Ruiz JD. Predictors in the treatment of difficult to control seizures by electrical stimulation of the centromedian thalamic nucleus . *Neurosurgery* 2000a ; 47: 295-305.

Velasco M, Velasco F, Velasco AL, Jimenez F, Brito F, Marquez I. Acute and chronic electrical stimulation of the centromedian thalamic nucleus: modulation of reticulo-cortical systems and predictor factors for generalized seizure control. *Arch Med Res* 2000b; 31:304-315.

Velasco M, Velasco F, Velasco AL, Boleaga B, Jimenez F, Brito F, Marquez I. Subacute electrical stimulation of the hippocampus blocks intractable temporal lobe seizures and paroxysmal EEG activities. *Epilepsia* 2000c; 41: 158-169.

Velasco F, Velasco M, Jimenez F, Velasco AL, Marquez I. Stimulation of the central median thalamic nucleus for epilepsy. *Stereotact Funct Neurosurg* 2001a; 77: 228–232.

Velasco M, Velasco F, Velasco AL. Centromedian-thalamic and hippocampal electrical stimulation for the control of intractable epileptic seizures. *J Clin Neurophysiol* 2001b; 18: 495-513.

Velasco F, Velasco M, Jimenez F, Velasco AL, Rojas B. Centromedian nucleus stimulation for epilepsy. Clinical, electroencephalographic, and behavioral observations. *Thalamus & Related systems* 2002 ; 1: 387-398.

Velasco F, Carrillo-Ruiz JD, Brto F, Velasco M, Velasco A.L., Marquez I, Davis R. double-blind, randomized controlled pilot study of bilateral cerebellar stimulation for treatment of intractable motor seizures. *Epilepsia* 2005; 46: 1071-1081.

Velasco AL, Velasco F, Jimenez F, Velasco M, Casro G, Carrillo-Ruiz JD, Fanghanel G, Boleaga B. Neuromodulation of the centromedian thalamic nuclei in the treatment of generalized seizures and the improvement of the quality of life in patients with Lennox-Gastaut syndrome. *Epilepsia* 2006; 47: 1203-1212.

Velasco AL, Velasco F, Velasco M, Trejo D, Castro G, Carrillo-Ruiz JD. Electrical stimulation of the hippocampal epileptic foci for seizure control : a double-blind, long-term follow-up study. *Epilepsia* 2007; 48: 1895-1903.

Velisek L, Veliskova J, Moshe S L. Electrical stimulation of substantia nigra pars reticulata is

anticonvulsant in adult and young male rats. *Exp Neurol* 2002; 173 (1): 145-152.

Velisek L, Velsikova J, Stanton PK. Low-frequency stimulation of the kindling focus delays basolateral amygdala kindling in immature rats. *Neurosci Lett* 2002 ; 326 ; 61-63.

Veliskova J, Claudio OI, Galanopoulou AS, Kyrozis A, Lado FA, Ravizza T, Velisek L, Moshe SL. Developmental aspects of the basal ganglia and therapeutic perspectives. *Epileptic Disord* 2002; Suppl 3: S73-82.

Vercueil L, Hirsch E. Seizures and the basal ganglia: a review of the clinical data. *Epileptic Disord* 2002; 4 (suppl 3): S47-S54.

Vercueil L., Benazzouz A., Deransart C., Bressand K., Marescaux C., Depaulis A., Benabid A.L. High-frequency stimulation of the sub-thalamic nucleus suppresses absence seizures in the rat: comparison with neurotoxic lesions. *Epilepsy Res* 1998; 31: 39-46.

Vesper J, Steinhoff B, Rona S, Wille C, Bilic S, Nikkhah G, Ostertag C. Chronic high-frequency deep brain stimulation of the STN/SNr for progressive myoclonic epilepsy. *Epilepsia* 2007; 48: 1984-1989.

Vonck K, Boon P, Achten E, De Reuck J, Caemaert J. Long-term amygdalohippocampal stimulation for refractory temporal lobe epilepsy. *Ann Neurol* 2002; 52: 556-565.

Vonck K, Boon P, Van Roost D. Anatomical and physiological basis and mechanism of action of neurostimulation for epilepsy. *Acta Neurochir* 2007; 97 (suppl): 321-328.

Wang S, Wu DC, Ding MP, Li Q, Zhuge ZB, Zhang SH, Chen Z. Low-frequency stimulation of cerebellar fastigial nucleus inhibits amygdaloid kindling acquisition in sprague-dawley rats. *Neurobiol Dis* 2008; 29 (1): 52_58.

Wassermann EM, Lisanby SH. Therapeutic application of repetitive transcranial magnetic stimulation: a review. *Clin Neurophysiol* 2001; 112: 1367-1377.

Weiss SRB, Li XL, Rosen JB, Li H, Heynen T, Post RM. Quenching : inhibition of the development and expression of amygdala kindled seizures with low frequency stimulation. *Neuroreport* 1995; 4: 2171-2176.

Wright GD, Mc Lellan DL, Brice JG. A double-blind trial of chronic cerebellar stimulation in twelve patients with severe epilepsy. *J Neurol Neurosurg Psychiatry* 1984; 47: 769-74.

Yamamoto J, Ikeda A, Satow T, Takeshita K, Takayama M, Matsushashi M, Matsumoto R, Ohara S, Mikuni N, Takahashi J, Miyamoto S, Taki W, Hashimoto N, Rothwell JC, Shibasaki H. Low-frequency electric cortical stimulation has an inhibitory effect on cortical focus in mesial temporal lobe epilepsy. *Epilepsia* 2002 ; 43 : 491-495.

Yang LX, Jin CL, Zhu-Ge ZB, Wang S, Wei EQ, Bruce IC, Chen Z. Unilateral low-frequency stimulation of central piriform delays seizure development induced by amygdaloid-kindled in rats. *Neuroscience* 2006; 138: 1089-1096.

Zhu-Ge ZB, Zhu YY, Wu DC, Wang S, Liu LY, Hu WW, Chen Z. Unilateral low-frequency stimulation of central piriform cortex inhibits amygdaloid-kindled seizures in Sprague-Dawley rats. *Neuroscience* 2007; 146: 901-906.

Zumsteg D, Lozano AM, Wennberg RA. Mesial temporal inhibition in a patient with deep brain stimulation of the anterior thalamus for epilepsy. *Epilepsia* 2006; 47: 1958-1962.

Original Publications:

1. **Feddersen B**, Bender A, Arnold S, Klopstock T, Noachtar S.
Aggressive confusional state as a clinical manifestation of status epilepticus in MELAS.
Neurology 2003; 61: 1149-1150.
2. Bender A, Jäger G, Scheuerer W, **Feddersen B**, Kaiser R, Pfister HW.
Two severe cases of tick-borne encephalitis despite complete active vaccination – the significance of neutralizing antibodies.
J Neurol 2004; 251: 353-354.
3. **Feddersen B**, Herzer R, Hartmann U, Gaab MR, Runge U.
On the psychopathology of temporal lobe epilepsy.
Epilepsy Behav 2005; 6: 43-49.
4. **Feddersen B**, Klopstock T, Noachtar S.
Hyperhidrosis in Parkinson`s Disease.
Neurology 2005; 64: 571.
5. Schneider I, Tirsch WS, Faus-Keßler T, Becker L, Kling E, Austin Busse RL, Bender A, **Feddersen B**, Tritschler J, Fuchs H, Gailus-Durner V , KH Englmeier, de Angelis MH, Klopstock T.
Systematic, standardized and comprehensive neurological phenotyping of inbred mice strains in the German Mouse Clinic.
J Neurosci Methods 2006; 157: 82-90.
6. Herberger S, Linn J, Pfefferkorn T, **Feddersen B**, Göhringer T, Winkler F, Straube A, Danek A.
«Reversibles posteriores» Leukenzephalopathie-Syndrom. Eine unglückliche Begriffsprägung für eine komplexe Erkrankung
Nervenarzt 2006; 77: 1218-1222.
7. **Feddersen B**, Straube A, Mayer TE.
Bradycardia after Coiling of Giant Vertebral Aneurysm.

Arch Neurol 2006; 63: 1496.

8. Litscher G, Hadolt I, Ausserer H, **Feddersen B**.
Prognostic value of cerebral near-infrared spectroscopy and cerebral blood flow velocity for developing acute mountain sickness at high altitudes.
J Near Infrared Spectrosc 2006; 14: 301-306.
9. O'Dwyer R, Silva Cunha JP, Vollmar C, Mauerer C, **Feddersen B**, Burgess RC, Ebner A, Noachtar S.
Lateralizing Significance of Quantitative Analysis of Head Movements before Secondary Generalization of Seizures of Patients with Temporal Lobe Epilepsy.
Epilepsia. 2007; 48: 524-530.
10. **Feddersen B**, Ausserer H, Neupane P, Thanbichler F, Depaulis A, Waanders R, Noachtar S.
Right Temporal Cerebral Dysfunction Heralds Symptoms of Acute Mountain Sickness.
J Neurol 2007; 254: 359-363.
11. Bender A, Schulte-Altedorneburg G, Mayer TE, Pfefferkorn T, Birnbaum T, **Feddersen B**, Bruckmann H, Pfister HW, Straube A.
Functional outcome after severe cerebral venous thrombosis.
J Neurol 2007; 254: 465-470.
12. Pfefferkorn T, **Feddersen B**, Schulte-Altedorneburg G, Pfister HW.
Tick-borne encephalitis with polyradiculitis documented by MRI.
Neurology 2007; 68: 1232-1233.
13. **Feddersen B**, Vercueil L, Noachtar S, David O, Depaulis A, Deransart C.
Controlling seizures is not controlling epilepsy: a parametric study of deep brain stimulation for epilepsy.
Neurobiol Dis 2007; 27: 292-300.

14. Engelhardt H*, **Feddersen B***, Boetzel K, Noachtar S.
The influence of caloric nystagmus on flash evoked and transient steady-state potentials.
Clin Neurophysiol 2007; 118: 2282–2286.
15. **Feddersen B**, Linn J, Klopstock T.
“Puppy Sign” indicating bilateral dissection of internal carotid arteries.
J Neurol Neurosurg Psychiatry 2007; 78; 1055.
16. Vollmar C*, **Feddersen B***, Beckmann BM, Kääh S, Noachtar S.
Seizures on hearing the alarm clock.
Lancet 2007; 370: 2172.
17. Noachtar S, Bilgin O, Rémi J, Chang N, Midi I, Vollmar C, **Feddersen B**.
Interictal regional polyspikes in noninvasive EEG suggest cortical dysplasia as etiology of focal epilepsies.
Epilepsia 2008; 49: 1011-1017.
18. **Feddersen B**, Ausserer H, Haditsch B, Frisch H, Noachtar S, Straube A.
Brain Natriuretic Peptide at Altitude: Relationship to Diuresis, Natriuresis, and Mountain Sickness.
Aviat Space Environ Med. 2009; 80: 108-111.
19. **Feddersen B***, de la Fontaine L*, Sass JO, Lutz J, Abicht A, Klopstock T, Verma IC, Meisenzahl E, Pogarell O.
Mitochondrial Neurogastrointestinal Encephalomyopathy (MNGIE) Mimicking Anorexia Nervosa.
Am J Psych 2009; 166: 494-495.

* shared first authorship

20. **Feddersen B**, Remi J, Kilian M, Vercueil L, Deransart C, Depaulis A, Noachtar S.

Does ictal dystonic posturing has an inhibiting effect on seizure propagation in focal epilepsies?

Epilepsia submitted as full-length original research article.

21. **Feddersen B**, Meier R, Deransart C, Depaulis A. EEG Changes Between Left and Right Substantia Nigra Heralds the Occurrence of Generalized Seizures in a model of GAERS. Epilepsia in preparation as short communication.

Book chapters:

1. **Feddersen B**, Ausserer H, Neupane P, Noachtar S. Changes in EEG background activity during sojourns at high altitudes. In: Waanders R, Frisch H, Schobersberger W, Berghold F (Hrsg.) Jahrbuch 2003 der ÖGAHM; Raggl digital Graphik, Innsbruck: 85-90.
2. Ausserer H, Sattelmayer V, Neupane P, **Feddersen B**. Cerebral Circulation at High Altitudes. In: Waanders R, Frisch H, Schobersberger W, Berghold F (Hrsg.) Jahrbuch 2003 der ÖGAHM; Raggl digital Graphik, Innsbruck: 79-83.
1. Winkler PA, **Feddersen B**, Noachtar S. Epilepsietherapie in der Hirntumorbehandlung. In: Tumorzentrum München (Hrsg.) Manual Hirntumoren und primäre Tumoren des Rückenmarkes. W. Zuckerschwerdt Verlag, München 2004, 58-62.
2. **Feddersen B**, Grau S, Schankin C, Kreth S, Winkler PA, Noachtar S, Straube A. Symptomatische Therapie bei Tumoren des ZNS. In: Tumorzentrum München (Hrsg.) Manual Hirntumoren und primäre Tumoren des Rückenmarkes. W. Zuckerschwerdt Verlag, München 2007, :64-76.
3. Langlois M, SAILLET S, **Feddersen B**, Minotti L, Vercueil L, Chabardès S, David O, Depaulis A, Kahane P, Deransart C. Deep brain stimulation in epilepsy: experimental and clinical data. In: Deep Brain Stimulation. Editors: Mark H. Rogers and Paul B. Anderson. Nova Science Publishers, Inc. 2009, in press.

Abstracts:

1. **Feddersen B**, Runge U, Herzer R, Gaab MR. Concerning psychopathology in focal epilepsies with unilateral temporal focus. *Epilepsia* 2000; 41; Suppl. 7: 201.
2. **Feddersen B**, Runge U, Herzer R, Gaab MR. Psychopathology in temporal lobe epilepsy. *J Neurol* 2001; 248; Suppl. 2: II/189.
3. **Feddersen B**, Arnold S, Bender A, Noachtar S. Initial manifestation of MELAS as confusional state due to focal status epilepticus. *J Neurol* 2002; 249; Suppl. 1: I/78.
4. **Feddersen B**, Bender A, Scheuerer W, Arnold S, Noachtar S. Non-Convulsive Status Epilepticus: Semiology, EEG, Etiology. *J Neurol* 2003; 250; Suppl. 3: III/112.
5. **Feddersen B**, Arnold S, Vollmar C, Noachtar S. Semiology, EEG and Etiology of Non-Convulsive Status Epilepticus. *Epilepsia* 2003; 44; Suppl. 9: 177.
6. Cunha JPS, Vollmar C, Li Z, **Feddersen B**, Noachtar S. A new video-processing method for quantitative evaluation of seizure semiology. *Epilepsia* 2003; 44; Suppl. 9: 8.
7. **Feddersen B**, Deransart C, Vercueil L, Noachtar S, Depaulis A. High-frequency stimulation of the substantia nigra pars reticulata suppresses absence seizures in a genetic model of absence epilepsy in the rat. *Epilepsia* 2004; 45; Suppl. 3: 118.
8. Deransart C, **Feddersen B**, Minotti L, Depaulis A. Nigral control of epilepsies: does this concept also apply to focal seizures? *Epilepsia* 2004; 45; Suppl. 3: 118.

9. Ausserer H, Neupane P, Waanders R, Ascher R, Bitzer O, Pfefferkorn T, **Feddersen B**. Acute mountain sickness is preceded by early impairment of cerebral autoregulation. *High Alt Med Biol* 2004; 5: 202.

10. **Feddersen B**, Ausserer H, Neupane P, Thanbichler F, Dugas M, Waanders R, Noachtar S. Right Temporal Cerebral Dysfunction Measured By EEG Predicts Occurrence Of Symptoms Of Acute Mountain Sickness. *High Alt Med Biol*. 2004; 5: 213.

11. **Feddersen B**, Deransart C, Vercueil L, Noachtar S, Depaulis A. A parametrical study of the antiepileptic effects of high-frequency stimulation of the substantia nigra pars reticulata in a genetic model of absence epilepsy in the rat. *Epilepsia* 2004; 45; Suppl. 7: 41-42.

12. Wagner P, Cunha J, Maurer C, Vollmar C, **Feddersen B**, Noachtar S. Comparison of quantified ipsilateral and contralateral head movements in patients with frontal and temporal lobe epilepsies. *Epilepsia* 2004; 45; Suppl. 7: 269.

13. Meier A, Cunha J, Maurer C, Vollmar C, **Feddersen B**, Noachtar S. Quantified analysis of wrist and trunk movements differentiates between hypermotor and automotor seizures. *Epilepsia* 2004; 45; Suppl. 7: 83.

14. **Feddersen B**, Deransart C, Vercueil L, Noachtar S, Depaulis A. Definition of optimal parameters in electrical stimulation of substantia nigra pars reticulata to suppress seizures in "Genetic Absence Epilepsy Rats from Strasbourg (GAERS)". *J Neurol* 2005; 252; Suppl. 2: II/14-15.

15. **Feddersen B**, Deransart C, Vercueil L, Noachtar S, Depaulis A. High frequency stimulation of the Substantia nigra pars reticulata (SNr) to suppress seizures in the "Genetic Absence Epilepsy Rats from Strasbourg (GAERS)" - Evaluation of optimal protocols for chronic stimulation. *Epilepsia* 2005; 46; Suppl. 6: 205-206.

16. Ulowetz S, Cunha J, Mauerer C, Vollmar C, **Feddersen B**, Noachtar S. Quantitative movement analysis of extent of wrist movements identifies hypermotor seizures in a non-selected sample of focal epileptic motor seizures. *Epilepsia* 2005; 46; Suppl. 6: 157.
17. Noachtar S, Chang N, Vollmar C, Mauerer C, **Feddersen B**, Arnold S. Non-invasively recorded regional polyspikes are suggestive of cortical dysplasia as aetiology of focal epilepsies. *Epilepsia* 2005; 46; Suppl. 6: 378.
18. **Feddersen B**, Ausserer H, Thanbichler F, Neupane P, Waanders R, Noachtar S. Right Temporal Cerebral Dysfunction Heralds Symptoms of Acute Mountain Sickness. *Klin Neurophysiol* 2006; 37: 35.
19. Noachtar S, Baykan B, Aykutlu E, **Feddersen B**, Desudchit T, Ozel S, Lüders H. Analysis of seizures consisting mainly of alteration of consciousness: a video-EEG study of 388 seizures in 117 patients with generalized and focal epilepsies. *Klin Neurophysiol* 2006; 37: 73-74.
20. Vollmar C, Stredl I, **Feddersen B**, Mauerer C, Ricken J, Noachtar S. Results of EEG-video monitoring in temporal lobe epilepsy: do we need to record habitual seizures in all patients? *Epilepsia* 2006; 43; Suppl. 4: 35-36.
21. **Feddersen B**, Kilian M, Mauerer C, Vollmar C, Ricken J, Noachtar S. Seizures with version are more likely to generalize secondarily than seizures with dystonia: an EEG-video study on seizure evolution in temporal lobe epilepsy and the role of basal ganglia inhibition. *Epilepsia* 2006; 43; Suppl. 4: 248.
22. Rego R, Vollmar C, Mauerer C, **Feddersen B**, Scherg M, Noachtar S. EEG Frequency Analysis for Lateralization of Temporal Lobe Epilepsy. *Epilepsia* 2006; 43; Suppl. 4: 45-46.
23. **Feddersen B**, Kilian M, Mauerer C, Vollmar C, Ricken J, Noachtar S. Bei Patienten mit einer Temporallappenepilepsie generalisieren Versivanfälle

- häufiger als Anfälle mit einer Dystonie: eine Video-EEG Studie zur Rolle der Basalganglien auf die Anfallsevolution. *Klin Neurophysiol* 2007; 38: 43.
24. **Feddersen B**, Bernhard C, Stoyke C, Remi J, Vollmar C, Noachtar S. The analysis of seizure semiology identifies patients with bilateral temporal lobe epilepsy. *Epilepsia* 2007; 48; Suppl. 3: 37.
25. **Feddersen B**, Kilian M, Deransart C, Noachtar S. In temporal lobe epilepsy seizures with dystonia are less likely to generalize secondarily than seizures with version. *Epilepsia* 2007; 48; Suppl. 3: 34.
26. **Feddersen B**, Remi J, Kilian M, Stoyke C, Noachtar S. Verhindert bei fokalen Anfällen die Anfallsausbreitung in die Basalganglien eine sekundäre Generalisierung? *Aktuelle Neurologie* 2008; 35; Suppl. 1: 58.
27. **Feddersen B**, Einhellig M, Vollmar C, Remi J, Stoyke C, Noachtar S. The role of Levetiracetam in treatment of status epilepticus: review of 77 patients. Abstract Book, European Congress on Epileptology 21.-25.9.2008: 221.
28. **Feddersen B**. EEG und mehr. *Klinische Neurophysiologie* 2009; 40: 50.
29. Neugebauer H, Winkler T, **Feddersen B**, Pfefferkorn T, Noachtar S, Pfister HW. Fallbericht: Up-Beat-Nystagmus als Ausdruck eines durch Phosostigmingabe induzierten rechtsseitigen okzipitalen Status epilepticus und dessen Sistieren nach Gabe von Lorazepam. *Klinische Neurophysiologie* 2009; 40: 70.
30. **Feddersen B**, Meier R, Noachtar S, Depaulis A. Changes in coherence between left and right substantia nigra heralds the occurrence of generalized seizures in genetic absence epilepsy rats from Strasbourg. *Klinische Neurophysiologie* 2009; 40: 87.

Letters:

1. **Feddersen B**, Ausserer H. Projekt Silberpyramide 2002; Projektbeschreibung anlässlich der Verleihung des wissenschaftlichen Förderpreis 2002. Alpinmedizinischer Rundbrief 28; Januar 2003: 10-13.
2. **Feddersen B**, Ausserer H. EEG und transkranielle Dopplersonographie in Relation zur AMS. Alpinmedizinischer Rundbrief 29; August 2003: 34.
3. **Feddersen B**, Köhrer M, Ausserer H. Internationales Höhenlungenödem Register. Alpinmedizinischer Rundbrief 32; März 2005: 11.
4. Ausserer H, Köhrer M, **Feddersen B**. Das Golmud-Lhasa-Railway Projekt - Mit dem Zug aufs Dach der Welt. Alpinmedizinischer Rundbrief 32; März 2005: 10.

Oral presentations:

1. **Feddersen B**. Sinus cavernosus Syndrom mit multiplen Hirninfarkten bei vorbestehendem myelodysplastischen Syndrom. 19. Arbeitstagung für Neurologische Intensiv- und Notfallmedizin, Kassel 2002.**Feddersen B**. Nicht konvulsiver Status epilepticus: Semiologie, EEG, Ätiologie. 20. Arbeitstagung für Neurologische Intensiv- und Notfallmedizin, Augsburg 2003.
3. **Feddersen B**. EEG und transkranielle Dopplersonographie in Relation zu AMS. Höhenmedizinisches Wochenendseminar, Brand/Vorarlberg 2003.
4. **Feddersen B**. Non-convulsive status epilepticus: Semiology, EEG & Etiology. Thirteenth Meeting of the European Neurological Society, Istanbul 2003.
5. **Feddersen B**. Visualization of interictal spikes as measured with subdural EEG electrodes using functional magnetic resonance imaging (fMRI). Thirteenth Meeting of the European Neurological Society, Istanbul 2003.

6. **Feddersen B.** Basalganglienstimulation bei Epilepsie. Epilepsie-Kolloquium der Universität München, Klinikum Grosshadern 3.2.2004.
7. **Feddersen B.** Right temporal EEG predicts occurrence of acute mountain sickness. VI World Congress on Mountain Medicine & V Annual Chinese High Altitude Medicine, Qinghai China – Lhasa Tibet 2004.
8. **Feddersen B.** Semiologie des sogenannten „Nicht konvulsiven“ Status epilepticus. Epilepsie-Kolloquium der Universität München, Klinikum Grosshadern 10.5.2005.
9. **Feddersen B.** Definition of optimal parameters in electrical stimulation of substantia nigra pars reticulata to suppress seizures in “Genetic Absence Epilepsy Rats from Strasbourg (GAERS)” Fifteenth Meeting of the European Neurological Society, Vienna 2005.
10. **Feddersen B.** Tiefe Hirnstimulation zur Unterdrückung von epileptischen Anfällen. Institut für Chirurgische Forschung, Universität München 13.6.2005.
11. **Feddersen B.** Wie entsteht das EEG. EEG und Epilepsie Seminar Kloster Seeon 16.9.2005.
12. **Feddersen B.** Das EEG bei generalisierten Epilepsien. EEG und Epilepsie Seminar Kloster Seeon 17.9.2005.
13. **Feddersen B.** Epilepsiechirurgische Fälle. EEG und Epilepsie Seminar Kloster Seeon 17.9.2005.
14. **Feddersen B.** Interiktales EEG bei Epilepsie. EEG und Epilepsie Fortbildung München-Mainz, Klinikum Grosshadern, Universität München 4.11.2005.
15. **Feddersen B.** Tiefe Hirnstimulation bei Epilepsie. Institut für Chirurgische Forschung, Universität München 12.12.2005.

16. **Feddersen B.** Aktivierungsmethoden im EEG. 15. Münchner Intensiv EEG Seminar, Klinikum Grosshadern, Universität München 28.6.2006.
17. **Feddersen B.** Basalganglienstimulation und Epilepsie. III. Symposium Forschung in der Neurologie, Klinikum Grosshadern, Universität München 25.7.2006.
18. **Feddersen B.** Das EEG bei generalisierten Epilepsien. EEG und Epilepsie Seminar Kloster Seeon 13.10.2006.
19. **Feddersen B.** Epilepsiechirurgische Fälle. EEG und Epilepsie Seminar Kloster Seeon 14.10.2006.
20. **Feddersen B.** Epilepsiechirurgische Fälle. EEG und Epilepsie Seminar Oberstdorf 3.3.2007.
21. **Feddersen B.** Kasuistik. 307. Nervenärztliches Kolloquium, Psychiatrische Klinik, Universität München 12.9.2007.
22. **Feddersen B.** Status epilepticus Fälle. EEG und Epilepsie Seminar Kloster Seeon 13.10.2007.
23. **Feddersen B.** Das EEG bei generalisierten Epilepsien. EEG und Epilepsie Seminar Kloster Seeon. 13.10.2007.
24. **Feddersen B.** Behandlung von Epilepsien nach SHT. Berufsgenossenschaftliche Unfallklinik Murnau 7.11.2007.
25. **Feddersen B.** Vagusstimulation bei Epilepsie. Fortbildungsveranstaltung München – Tübingen. Neurologische Klinik Tübingen, Universität Tübingen 19.4.2008.
26. **Feddersen B.** Das EEG bei generalisierten Epilepsien. EEG und Epilepsie Seminar Kloster Seeon 31.10.2008.

27. **Feddersen B.** Status epilepticus Fälle. EEG und Epilepsie Seminar Kloster Seeon 01.11.2008.
28. **Feddersen B.** Nicht-convulsiver Status epilepticus. Neurobiologisches Kolloquium, Neurologische Klinik, Universität München. 04.02.2009.
29. **Feddersen B.** EEG und mehr. 53. Jahrestagung der Deutschen Gesellschaft für Klinische Neurophysiologie, München 27.03.2009.

Grants and awards:

1. **Feddersen B.**, Ausserer H, Hadolt I, Sattelmeyer V, Neupane P, Glück M, Vogelheinrich K, Ascher R, Bitzer O, Waanders R, Noachtar S. Wissenschaftlicher Förderpreis 2002 der Österreichischen Gesellschaft für Alpin und Höhenmedizin.
2. **Feddersen B.** Fellowship of the European Neurological Society 2003 (12 months).
3. **Feddersen B.** Young Investigator Award 2005 of the International League against Epilepsy.
4. Steinmann S, **Feddersen B.** Wissenschaftspreis der Deutschen Gesellschaft für Berg- und Expeditionsmedizin 2006/2007.

ANNEXE

Here, the original publications related to the field of EEG and epilepsy are presented.

Aggressive confusional state as a clinical manifestation of status epilepticus in MELAS

B. Feddersen, MD; A. Bender, MD; S. Arnold, MD;
T. Klopstock, MD; and S. Noachtar, MD

Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS)¹ is caused by mutations in the mitochondrial DNA (mtDNA), the most common at nucleotide 3243 in the tRNA^{Leu(UUR)}.² Although early development is typically normal, stroke-like episodes and seizures may occur in childhood or young adult life. Patients also may have short stature, exercise intolerance, hearing loss, dementia, pigmentary retinal degeneration, and migraine-like headache.

Patients and methods. *Patient 1.* A 43-year-old man had bilateral sensorineural hearing loss since adolescence and focal epilepsy since age 42 years. Before admission he had had transient left arm paresthesias and his wife had noted confusion and aggressive behavior. Neurologic examination revealed mild left arm paresis. The patient was aggressive and confused. Brain CT showed an inhomogeneous hypodensity in the right parietal region. MRI revealed cortical and subcortical hyperintensities in T2- and perfusion/diffusion-weighted images in the right parietal region; these findings were recent and compatible with MELAS. The EEG during the status showed right parietal sharp waves at a frequency of 0.5 to 2 Hz and rhythmic theta and delta waves alternating with periodic polymorphic complexes in a waxing and waning manner at a frequency of 0.5 to 1.5 Hz in the same region. After a loading dose of phenytoin (PHT) 750 mg followed by the administration of PHT 400 mg/bid, the patient's clinical condition improved. An EEG 7 days later was free of epileptiform discharges. Muscle biopsy showed about 5% ragged red fibers. PCR analysis from muscle DNA revealed the MELAS mutation at bp3243 of the mtDNA.

Patient 2. A 57-year-old woman had migraine-like headache, aphasia, and confusion. Because of bilateral sensorineural deafness she had a left cochlear implant. Neurologic examination revealed bilateral gaze-induced horizontal nystagmus, apraxia, aphasia, and confusion. The EEG showed waxing and waning repetitive sharp waves and high amplitude polymorphic complexes in the left occipital region at a frequency of 0.7 to 2 Hz. ECD-SPECT performed during the status epilepticus revealed a left occipital to occipitoparietal hyperperfusion (figure). The left-sided cochlear implant caused artifacts in the CT scans. Analysis of the CSF revealed elevated levels of lactate (4.14 mmol/L). A muscle biopsy showed about 7% ragged red fibers and the typical MELAS mutation at position 3243 of the mtDNA. Status epilepticus ceased after the patient was started on PHT (750 mg loading dose followed by 100 mg/bid) and clonazepam (2 mg/bid) treatment.

One month later she was readmitted because of recurrence of confusion and aggressive behavior. Repeat EEG showed a pattern similar to the previous one, but in the right occipital region. CT scans revealed new hypodensities in the area of the right middle cerebral artery. The patient recovered after additional doses of lorazepam and PHT.

Discussion. The pathophysiology that leads to epileptic activity in the brains of patients with certain mitochondrial diseases—e.g., MELAS, myoclonus epilepsy with ragged red fibers (MERRF), and Leigh syndrome—is not well understood. In other mitochondrial diseases, chronic progressive external ophthalmoplegia, and Kearns-Sayre syndrome, epilepsy is not a common clinical finding. One distinct difference may be that gray matter involvement is an early feature of the disease in MELAS and MERRF.³ Impairment of the oxidative phosphorylation could make the membrane potential unstable or lead to the generation of free radicals, and a disruption in the calcium homeostasis system.³

No studies have yet addressed the question of which antiepi-

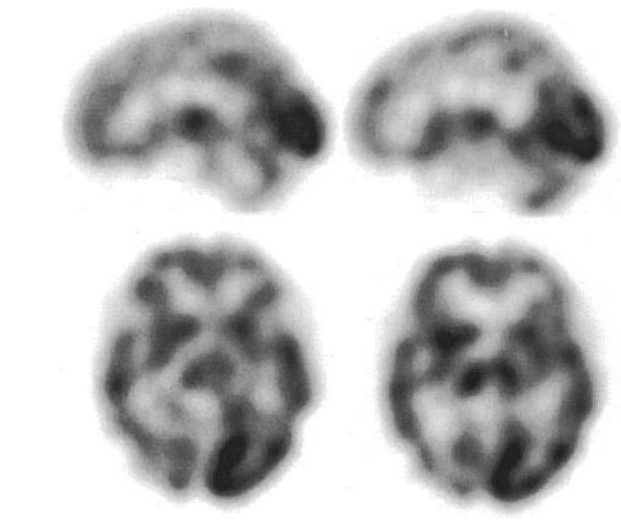


Figure. ECD-SPECT during status epilepticus reveals a left occipital parietal hyperperfusion in Patient 2.

leptic drug is best suited for chronic treatment of seizures in mitochondrial diseases. Valproate seems to be inappropriate, because it causes reduction of serum carnitine,⁴ inhibition of beta-oxidation and oxidative phosphorylation, and ultrastructural abnormalities of mitochondria with lipid deposition. Moreover, mitochondrial diseases may be considered a risk factor for valproate-induced liver failure.⁵ Although PHT also decreases serum carnitine levels,⁴ it is often used for treatment of status epilepticus. During status epilepticus the cerebral metabolism is increased. This has an even greater impact in patients with mitochondrial disease. In patients with MELAS, for example, neurons, which have to cope with an increased calcium influx during status epilepticus, are more likely to suffer from glutamatergic and calcium-induced excitotoxic cell damage, because their mitochondrial respiratory function and ATP availability are diminished. Impaired function of the calcium-ATPase results.⁶ Thus, rapid antiepileptic treatment of patients with MELAS with non-convulsive status epilepticus is important.

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References

1. Pavlakis SG, Phillips PC, DiMauro S, De Vivo DC, Rowland LP. Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes: a distinctive clinical syndrome. *Ann Neurol* 1984;16:481–488.
2. Hammanns SR, Sweeny MG, Hanna MG, et al. The mitochondrial DNA transfer RNA Leu(UUR) A 224 G (3243) mutation: a clinical and genetic study. *Brain* 1995;118:721–734.

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3. Cock H, Schapira AHV. Mitochondrial DNA mutations and mitochondrial dysfunction in epilepsy. *Epilepsia* 1999;40(suppl 3):33–40.
4. Campistol J, Chavez B, Vilaseca MA, Artuch R. Antiepileptic drugs and carnitine. *Rev Neurol* 2000;suppl 1:105–109.
5. Krahenbuhl S, Brandner S, Kleinle S, Liechti S, Straumann D. Mitochondrial diseases represent a risk factor for valproate-induced fulminant liver failure. *Liver* 2000;20:346–348.

6. Budd SL, Nicholls DG. Mitochondria, calcium regulation, and acute glutamate excitotoxicity in cultured cerebellar granule cells. *J Neurochem* 1996;67:2282–2291.

Hypersensitivity pneumonitis possibly caused by riluzole therapy in ALS

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Erik Verbeken, MD, PhD; and Wim Robberecht, MD, PhD

A 69-year-old man with sporadic amyotrophic lateral sclerosis (ALS) presented with complaints of increasing and disabling shortness of breath and dry cough for 3 months. A chest X-ray, taken for routine purposes 6 months before the start of symptoms, was normal.

The patient was diagnosed with ALS 33 months before presentation. Riluzole^{1,2} 50 mg twice daily was started 1 year later. He was treated with omeprazole 20 mg per day for more than 10 years, for a grade IV esophagitis. Ten days before the respiratory complaints started, omeprazole was switched to lansoprazole 15 mg per day.

After receiving antibiotics for a total of 20 days, without effect, the patient consulted a pulmonologist, who diagnosed him with pulmonary fibrosis. He was treated with methylprednisolone for 8 weeks (32 mg per day tapered every fortnight). This improved his general condition, but had only a minor effect on the coughing and dyspnea. After methylprednisolone was stopped, the complaints soon recurred and the patient presented himself to our clinic.

Clinical examination revealed ALS with predominant lower limb involvement: the patient was capable of walking with a walker, but was restricted to a wheelchair due to his dyspnea. The patient manifested an increased respiratory rate and use of accessory respiratory muscles. Lung auscultation was normal. Arterial blood gas at room air showed hypoxia (pH 7.49, oxygen tension 57 mm Hg, carbon dioxide tension 37 mm Hg). Laboratory tests revealed normal blood counts, normal liver and renal function and electrolytes, and increased erythrocyte sedimentation rate (63 mm/hour [normal value, 1 to 10 mm/hour]) and lactate dehydrogenase (701 U/L [normal value, 240 to 480 U/L]); antinuclear and antineutrophil cytoplasmic antibodies were negative. A chest X-ray was suggestive of interstitial lung disease (figure, A). Lung function measurements showed restrictive lung disease (forced vital capacity of 65% and total lung capacity of 57% of the predicted value) and a severe decrease of carbon monoxide diffusion (26% of the predicted value). Chest CT showed enlargement of the interlobular septa and bronchial structures (figure, C). Bronchoscopy results were normal. Broncho-alveolar lavage fluid stained negative for tuberculosis and contained no pathogenic bacteria or malignant cells. It contained 358 leukocytes per μ L (normal value, 50 to 250 per μ L), 51.5% of which were lymphocytes (normal value, 0.0 to 20.0%).

Thoracoscopic lung biopsy was performed, because less invasive technical investigations yielded no definite diagnosis and the patient was deteriorating. Anatomopathology revealed a picture suggestive of hypersensitivity pneumonitis (HP) (figure, E and F).

On the diagnosis of HP and exclusion of other potential causes, mainly by taking a detailed history of past and present exposures, riluzole and lansoprazole were discontinued and methylprednisolone 32 mg per day was restarted.

Three weeks later, the patient showed recovery from dyspnea and was walking with his walker again; the cough had disappeared. Control arterial blood gas showed complete normalization, control chest X-ray and CT showed significant resolution (figure 1, B and D), lung function showed partial recuperation (forced vital capacity of 78%), and carbon monoxide diffusion showed a significant increase to 40%.

Discussion. Neither the adverse events database of the distributor of riluzole (Aventis) nor the literature revealed reports of adverse events similar to the one reported here.^{3,4}

Omeprazole compromises the effect of riluzole by enhancing its metabolism, via induction of cytochrome p450 1A2, as can be read in the instruction leaflet of riluzole, supplied by Aventis. Lansoprazole does not have this effect. We hypothesize that the deleterious effect of riluzole in this patient only became apparent

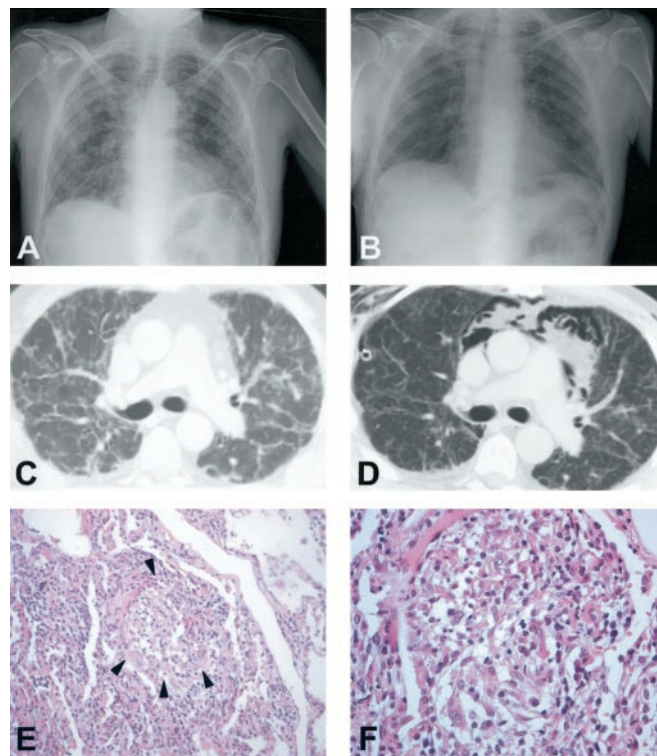


Figure. (A) Chest X-ray at presentation showed a normal mediastinum, normal lung hili, and a normal heart, but diffuse interstitial enhancement suggestive of interstitial lung disease. (B) Control chest X-ray, taken 3 weeks after cessation of riluzole therapy, showed resolution of the interstitial enhancement seen at presentation (see A). (C) Chest CT scan at presentation, at the level of the truncus pulmonalis, showed enlargement of the interlobular septa and bronchial structures (traction bronchiectasies). The lymph nodes are of normal size; there are no confluent alveolar infiltrates. (D) Control chest CT scan (level of the truncus pulmonalis), taken 3 months after cessation of riluzole, showed that the enlargement of interlobular septa and bronchial structures seen in C had diminished. (E) Pathologic examination of an open lung biopsy showed both the interstitial mononuclear infiltrate and loose epithelioid granulomas (a granuloma is delimited by the arrowheads), characteristic of hypersensitivity pneumonitis (hematoxylin-eosin [H-E], original magnification $\times 100$). (F) Detail of a loose epithelioid granuloma, as described in E (H-E, original magnification $\times 400$).

after switching omeprazole to lansoprazole, because this switch preceded the onset of symptoms in our patient by only 10 days. The prior 21 months of exposure to riluzole + omeprazole may have allowed the patient to develop a subclinical reaction to riluzole. That lansoprazole would be the cause of the HP is highly unlikely, in view of the short exposure to lansoprazole at the time of first symptoms (10 days) and the long-term widespread use of the compound without reports of similar adverse reactions.

The diagnosis of HP is supported by the biochemical, radio-

On the psychopathology of unilateral temporal lobe epilepsy

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Abstract

Personality adjustment of patients with unilateral temporal lobe epilepsy (TLE) was investigated in the light of special characteristics of the epilepsy process, psychosocial stressors, and the cognitive status of the patients. Thirty-seven patients with medically intractable unilateral temporal lobe epilepsy (16–55 years of age; 20 right temporal and 17 left temporal foci) were examined with standardized personality inventories (FPI, STAI, IPC, TSK) supplemented by a rating scale evaluated by the neuropsychologist (GEWLE). Patients with left temporal lobe epilepsy were characterized by increased emotional dependency, less externally judged composedness, increased depressive drive and mood, increased nervousness, increased search for information and exchange of disease experience, and greater tendency to persevere ($P < 0.05$). Cognitive status and psychosocial status did not significantly differ. The evaluation of personality adjustment contributes to the lateralization of the epileptogenic focus and reveals interesting patterns in the preoperative diagnostic puzzle, and in addition provides a strategy to individualize psychotherapeutic strategies.

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Keywords: Epilepsy; Temporal lobe; Psychopathology; Epilepsy surgery; Lateralization; Personality; Neuropsychology

1. Introduction

The first mention of a connection between epilepsy and interictal behavioral changes was in 400 BC, when Hippocrates noted that the mental status of patients declined between seizures [1]. Today, a nosologically unified concept of the disease and a precise definition of the forms of epilepsy and different seizure types have been established. The occurrence and degree of associated psychic disorders are attributed to a complex of different factors [2–9], which the disease process and the degree of psychosocial stressors influence [10–12]. At the end of the seventies, further impulses for a new orientation of epilepsy research came from the development and increasing integration of modern clinical-

psychological methods and concepts [13–19], which were complemented by specific neuropsychological investigative strategies. The new method of focus localization in epilepsy surgery rekindled the discussion of psychopathological factors, especially in connection with temporal lobe epilepsy [20–29]. However, the comparability of results from different studies is limited, because the methods and methodological levels used earlier differed, and all the various aspects of the disease were seldom taken into consideration.

The current study aims to objectify personality features of patients with unilateral left (LTLE) or right (RTLE) temporal lobe epilepsy to compare their profiles in the light of relevant cognitive parameters and psychosocial stressors, and to compare them with a healthy control group and a group of patients with idiopathic generalized epilepsy (GE) suffering from absences and generalized tonic-clonic seizures.

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2. Methods

2.1. Patients with drug-resistant TLE

The study included patients who had undergone a complete presurgical epilepsy diagnostic workup at the epilepsy center of the Department of Neurology, University of Greifswald, Germany (according to the current standards of the ILAE and the working group for presurgical epilepsy diagnosis [30]) and been diagnosed to have a unilateral temporal epileptogenic focus. Exclusion criteria were age under 16 years, reduced intelligence, aphasic disorders, previous brain surgery, left-handedness, and proof of right-sided speech dominance by the WADA test. Left-handed patients were excluded to keep the influence of primarily cerebral dominant patterns simple. A total of 37 patients participated; 17 had a left temporal and 20 a right temporal focus. None of the patients had discrete psychiatric disorders in the presurgical psychiatric evaluations (according to the ICD-10 classification). The evaluations were done with a structured interview using the AMDP system [31], Beck Depression Inventory [32], and SCL-90 [33]. The mean age was $32.7 (\pm 1.44)$ years. Table 1 lists the epilepsy-associated parameters.

2.2. Control groups

To establish whether the significant findings between LTLE and RTLE were related to the side of the seizure focus, we made comparisons with a group of healthy controls using the FPI-A-H, GEWLE, and IPC scales ($n = 225$, mean age = 38.23 ± 1.91 , females/males 109/116) and with a group of patients with idiopathic generalized epilepsy with absence and generalized tonic-clonic seizures using the FPI-A-H and GEWLE scales ($n = 38$, mean age = 35.41 ± 1.86 , females/males 19/19).

2.3. Personality inventories

Five personality inventories were used in the study. The Freiburg Personality Inventory/Form A (FPI-A) [34], comprises 10 subscales: Nervousness, Aggression,

Depression, Excitability, Sociability, Calmness, Dominance Inhibition, Openness, Extraversion, Emotional Lability. The FPI-A was extended by adding two scales: Activity and Perseverance/Circumstantiality (FPI-A-H). They include personality traits that Remschmidt described as a “nucleus” of the so-called epileptic change of character [15] and are still discussed as part of a temporal lobe personality [2,25,28,35]. Each of the additional scales consists of eight items constructed and selected by neuropsychiatric experts and partly taken from INR [36], a German adaptation of the well-known Eysencks Personality Inventory [37]. Both subscales proved reliable for quantifying self-reported aspects of motivation/extraversion/activity and aspects of perseverance/circumstantiality/pedantry in earlier investigations of epileptic syndromes [38]. To compensate for the disadvantages of self-rating, a foreign-rating scale was also used. This scale, the Greifswald Adjective List for Epilepsy Patients (GEWLE), allows for foreign judgments using 135 adjectives to specify the same 13 personality dimensions described in the FPI-A-H. Item construction and selection are based on psychopathological data in epilepsies (literature analysis) and on well-validated personality inventories such as the FPI [34], MMPI [39], and EWL [40]; the same neuropsychiatric experts evaluated it as well as the added FPI-A-H scales [10,38]. The neuropsychologist conducted the GEWLE in all patients; this scale reflects the patient’s behavior during cognitive testing (3–6 hours). Blinding refers to FPI self-rating and lateralization of the epileptogenic focus. Spielberger’s State-Trait Anxiety Inventory (STAI) [41] was also included to record anxiety and fear. In addition, individual psychological patterns of the patients with TLE were determined by using modern constructs of personality research such as “locus of control of reinforcement” with the IPC scale [42] and “coping with disease” by means of the Trierer Skalen zur Krankheitsbewältigung (TSK) [43]. The IPC contains the following subscales: (1) Internal Control Orientation, (2) External Control Orientation (Powerful Others), and (3) Chance Control Orientation. TSK is subdivided into coping scales, with (1) Past-Oriented Rumination, (2) Search for Social and Emotional Support, (3) Threat Defensiveness, (4) Search for Disease Information and Communication, and (5) Religiosity/Religious Reactions (see Table 2).

2.4. Cognitive measurement

From the extensive neuropsychological data collected on each patient during the presurgical epilepsy diagnostic workup, cognitive performance parameters were chosen, especially those connected with temporal and frontal neuropsychological functions, verbal and visual memory, attention, perceptual speed, flexibility, as well as general intelligence [44–55], (see Table 3).

Table 1
Epilepsy-associated parameters^a

	Left temporal lobe epilepsy	Right temporal lobe epilepsy
Localization of focus	17	20
Female/male	9/8	8/12
Age (years)	33.1 ± 1.94	32.1 ± 2.12
Age of manifestation (years)	14.8 ± 2.16	18.1 ± 2.06
Duration of epilepsy (years)	18.9 ± 2.45	14.0 ± 1.88
Syndrome of epilepsy	8/9	10/10
symptomatic/cryptogenic		
Seizure frequency (per month)	73 ± 22.84	44 ± 10.26

^a Data are given as means \pm SEM.

Table 2
Personality inventories

Questionnaire ^a	Subscales
FPI-A-H [10,34]	Nervousness, Aggression, Depression, Excitability, Sociability, Calmness, Dominance Inhibition, Openness, Activity, Perseverance, Extraversion, Emotional Lability Same as for FPI-A-H
GEWLE (foreign rating by the neuropsychologist [10,38])	State Anxiety, Trait Anxiety
STAI [63], German adaptation of State–Trait Anxiety Inventory [41]	Internal Control Orientation, External Control Orientation, (powerful others), Chance Control Orientation
IPC [42], German adaptation of IPC scales [64]	Coping scales, with Past-Oriented Rumination, Search for Social and Emotional Support, threat Defensiveness (“positive thinking”), Search for Disease Information and Communication, Religiosity Religious Reactions
TSK [43]	

^a FPI-A-H, Freiburger-Persönlichkeits-Inventar Form A-H; GEWLE, Greifswalder Eigenschaftswörterliste für Epilepsiekranken; STAI, State–Trait Anxiety Inventory; IPC, Fragebogen zur Kontrollüberzeugung; TSK, Trierer Skala zu Krankheitsbewältigung.

Table 3
Cognitive inventories

Test ^a	Functions
HAWIE/WIP (modified from WAIS [44])	Verbal and visual intelligence, digit span
Block design [45]	Block span
VLMT (German version of AVLT) [46]	Verbal memory
DCS [47]	Visual memory
d2 test [48]	Selective attention
ZZT, Tapping [49,50]	Speed
Word Association [51]	Verbal fluency
Stroop Test (quotient of difference interference–naming and reading performance) [52]	Perceptual speed, flexibility, speed-independent adaptability
Labyrinth Test [53]	Problem solving, planning

^a HAWIE, Hamburg-Wechsler-Intelligenztest für Erwachsene; WIP, reduzierter Wechsler Intelligenztest; WAIS, Wechsler Adult Intelligence Test; VLMT, verbaler Lern- und Merkfähigkeitstest; AVLT, Auditory Verbal Learning Test; DCS, Diagnosticum für Cerebralschädigung; ZZT, Zahlen-Zeige-Test.

2.5. Psychosocial stressors

Herzer and co-workers [10,38] developed an index of psychosocial stressors particularly for epileptic patients (BIPSY) on the basis of social anamnestic and biographical data as well as individual psychosocial conditions. This index includes risk factors for psychosocial and personality development such as low level of education, low level of professional qualification, and professional status of parents, two or more brothers and sisters, “broken home” situation, complicated relationship with parents and siblings, dysadaptability in kindergarten, problems at school (achievement and comportment), dissatisfaction with familial and professional development and situation, and the actual strain of epilepsy complications, familial illness, disturbed family relations, and conflicts in the professional sphere. Twenty-five risks are defined (BIPSY maximum = 25, mean value among mixed epileptic patients = 6.41 ± 5.26 (mean \pm SD) [10]). BIPSY was determined for each pa-

tient in a standardized interview, which took place 2 days after cognitive examination.

2.6. Data analysis

For statistical analysis, the Mann–Whitney *U* test was used for nonrelated samples, and the nonparametric Wilcoxon test for related samples. The statistical significance level was set at $P < 0.05$. For correlation analysis, Spearman’s correlation and logistic regression analysis were chosen. The lower limit of correlation was set at $r > 0.3$. Data are given as mean values \pm SEM when not stated otherwise. We performed the Friedmann analysis for several connected samples and continued the analysis only if the *P* value was lower than 0.05. According to Bender and Langer [56], this procedure can replace a Bonferroni correction to adjust the *P* value according to the number of analyses.

3. Results

3.1. Epileptic parameters

A significant difference could not be shown for any of the epileptic parameters besides the focus localization (LTLE/RTLE: age of manifestation $14.8 \pm 2.16/18.1 \pm 2.06$; duration of epilepsy $18.9 \pm 2.45/14.03 \pm 1.88$; frequency of seizures $73 \pm 22.84/44 \pm 10.26$) (see Table 1).

3.2. Personality inventories

Seventeen patients with LTLE gave themselves significantly higher scores on the FPI-A-H ($P < 0.05$) for Perseverance than did the 20 patients with RTLE (see Fig. 1A). This result was not confirmed on the foreign-rating scale GEWLE; however, Spearman’s correlation showed a positive correlation ($r = 0.3259$) between self-rating and foreign-rating scales. The local-

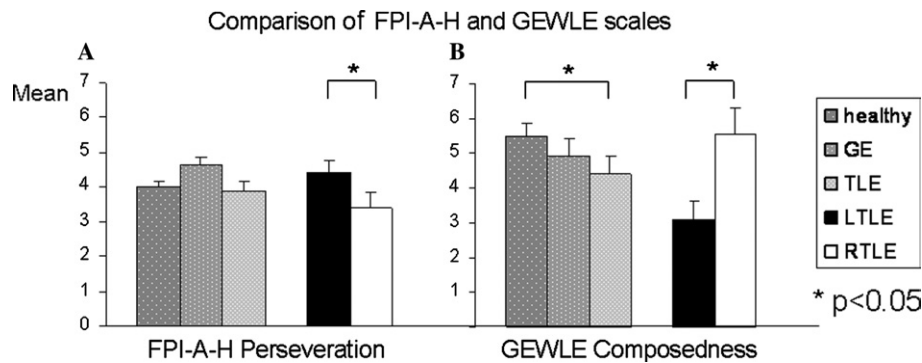


Fig. 1. (A) Patients with LTLE scored higher on the scale “perseverance” in the self-rating FPI-A-H. (B) Patients with TLE were considered to be less composed in the GEWLE than were healthy controls and patients with LTLE, and even less composed than patients with RTLE.

ization of focus also correlated with the self-rating ($r = -0.3674$) and foreign-rating ($r = -0.3282$) scales. Furthermore, patients with LTLE were considered to be significantly less composed in the GEWLE ($P < 0.05$), (see Fig. 1B). In this subscale, patients with TLE had lower scores compared with a healthy control group ($P < 0.05$). The total group of TLE patients did not differ, in the items found to be significantly different between LTLE and RTLE, from a control group of patients with idiopathic generalized epilepsy suffering from absence seizures and generalized tonic-clonic seizures on the FPI-A-H and GEWLE scales. In the area of control attributions, the IPC scores of patients with LTLE were significantly higher on the Powerlessness and External Locus of Control scale of the IPC ($P < 0.01$), (see Fig. 2). For TSK Coping Strategies, patients with LTLE had significantly higher scores ($P < 0.05$) on the Search for Disease Information and Communication scale (see Fig. 3). In a logistic regression analysis with a likelihood forward ratio, the parameters External Attribution/Powerlessness on the IPC, Composedness on the GEWLE, Depression and Excitability on the self-rating scale FPI-A-H, Search for Disease Information and Communication on the TSK, Nervousness on the foreign-GEWLE, and Activity on the self-rating scale FPI-A-H showed a real focus localization of 94.59% (35 of 37 patients were

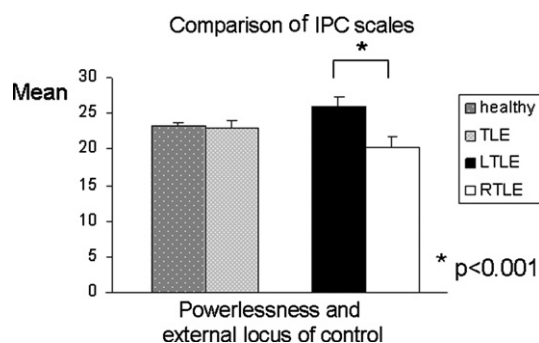


Fig. 2. Patients with LTLE gave themselves higher scores on the IPC scale “powerlessness and external locus of control.”

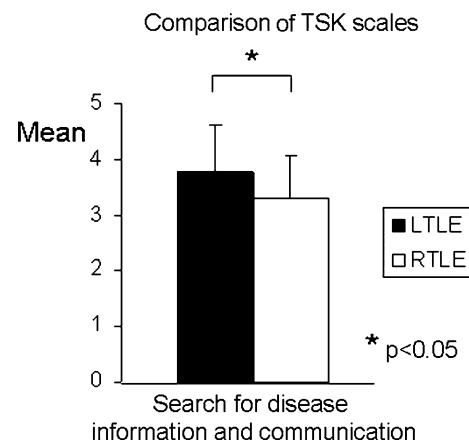


Fig. 3. Patients with LTLE had significantly higher scores on the TSK scale “search for disease information and communication.”

correctly localized). The significance of this model was $P < 0.0001$.

3.3. Cognitive measurement

No further differences could be confirmed for cognitive parameters between patients with LTLE and RTLE.

3.4. Psychosocial stressors

There was no difference in psychosocial stressors between the two groups. This was indicated by Spearman's correlation as well as the proof of significance, LTLE/RTLE: $6.53 \pm 0.84/6.85 \pm 1.12$.

4. Discussion

The patients with pharmacoresistant TLE showed less extraversion and higher emotional lability than did a healthy control group. The neuropsychologist also judged them to be more excitable, open, inhibited, emotionally labile, and less composed. These data indicate that the often-mentioned doubts that patients with

severe epilepsy lack the abilities of self-criticism and judgment [15] need to be revised. The greater openness may contribute to a higher grade of activation, reflecting the circumstances of presurgical video/EEG monitoring, which per se requires a certain degree of openness in view of the arduous diagnostic procedure.

A comparison of the self-rating scale FPI-A-H for the LTLE and RTLE groups revealed that LTLE patients had a conspicuously higher tendency toward perseverance, circumstantiality, and pedantry. The foreign-rating GEWLE showed that they were less composed. Correlation analysis of the personality features revealed a significantly positive correlation between the self-rated and foreign-rated perseverance scales. This indicates that the tendency to persevere, which was formerly considered a “nucleus” of the so-called epileptic change of character [1,16], seems to apply only to patients with left temporal focus and left temporal speech lateralization. The relevance of the perseverance tendency in LTLE is also underlined by the fact that the total group of patients with TLE did not deviate from the normal sample on the new FPI scale [38]. The differences in the foreign-rated scale on composedness may be influenced by the fact that the total group of patients with TLE had significantly lower scores than did a healthy control group. This is understandable when facing an unpredictable illness. In addition, patients with LTLE and left-sided speech dominance were more dependent on external influences; we were also able to substantiate a significantly higher external control attribution on the IPC. Their behavior thus seems to be more oriented to the environment, from which they need more signals to regulate their behavior. This, in turn, increases the impression of their persistence and fussiness.

The significantly more pronounced Search for Disease Information and Communication of patients with LTLE to cope with their chronic illness allows fine discrimination between patients with LTLE and those with RTLE by using the scales External Control Attribution (IPC), Composedness (GEWLE), Depression (FPI), Search for Information (TSK), Nervousness (GEWLE), and Activity (FPI-A-H). Fedio and Martin [27] have reported similar results following left-side lobectomy for patients, who considered themselves “brittle,” “overprecise,” “pedantic,” and “fixated on religious themes and their own destiny.”

The data in the literature are contradictory because of different methodological deficiencies, epileptic classifications, and patient selection criteria [27,28]. Contrary to others [54,55], we could not verify that patients with LTLE have a higher level of anxiety and more depression. However, we confirmed the interpretation that emotional-affective changes are typical of patients with TLE [2,9,13,20,28,35,57]. Our findings support the differentiation made by Bear and Fedio [28], i.e., patients with LTLE tend to be more reflexive and rational in thinking and

behavioral style and to exaggerate their own problems, whereas patients with RTLE react more emotionally affective and underestimate their own problems. This has not remained unchallenged [17,23,25,26,29].

The recorded cognitive parameters made a minor contribution with respect to left–right discrimination, a finding that differs from findings in the neuropsychological literature [12,18,19,58,59]. This disparity may be due to the epilepsy syndrome itself. Nine of seventeen in the LTLE group and 10 of 20 in the RTLE group had a cryptogenic epilepsy. The absence of structural defects in the medial temporal lobe, especially hippocampal sclerosis, which would have an impact on dysfunction of verbal memory, may contribute to the disparity. Nevertheless, these results indicate that electrophysiological disturbances in these regions may appear sooner than cognitive deficits. The equal distribution of the specific epileptic parameters and the psychosocial stressors in both TLE groups shows that the differences observed in the personality profiles of RTLE and LTLE patients cannot be made responsible for psychosocial risks or specific epileptic signs. Furthermore, the absence of differences between the total group of TLE and patients with idiopathic generalized epilepsy indicates that our findings contribute to the focus lateralization but not to the effects of unpredictable recurrence of seizures nor to comorbid psychiatric diseases.

Thus, our study provides new evidence that the lateralization of a temporal epileptic focus, in view of its proximity to the limbic system, the amygdala, and the frontal structures, has a direct influence on emotional-affective and social personal peculiarities. Moreover, it underlines the importance of current demands of epileptology, epilepsy surgery, and neuropsychology that studies of cognitive performance be complemented by emotional-affective, social, and neuropsychiatric parameters [60–62]. The individual patterns of these parameters may also directly contribute to the lateralization of the epileptogenic focus and may be used to individualize neuropsychological and psychotherapeutic treatment, especially after surgery.

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References

- [1] Stauder KH. *Konstitution und Wesensaenderung der Epileptiker*. Leipzig: Thieme; 1938.
- [2] Blumer D. Evidence supporting the temporal lobe epilepsy personality syndrome. *Neurology* 1999;53(Suppl. 2):9–12.
- [3] Wagner KD. *Anfallsranke Kinder in der Normalschule*. In: Wagner KD, editor. *Schulschwierigkeiten in der Beratungspraxis*. Leipzig: Barth; 1970.

- [4] Huber G. Psychosyndrome bei epilepsien. *Internist* 1977;18:62–6.
- [5] Goellnitz G. Neuropsychiatrie des Kindes- und Jugendalters. Jena: Fischer; 1975.
- [6] Diehl LW. Wesensaenderung bei Epilepsien?. *Psychiatr Neurol Med Psychol* 1978;30:239–47.
- [7] Rabending G. Epilepsien. Leipzig: Thieme; 1985.
- [8] Trimble MR. Psychiatrische und psychologische Aspekte der Epilepsie. In: *Psychiatrie der Gegenwart*. Bd. 6, Berlin/Heidelberg/New York: Springer-Verlag; 1988, p. 325–63.
- [9] Bromfield EB, Altshuler L, Leiderman DB. Cerebral metabolism and depression in patients with complex partial seizures. *Epilepsia* 1990;31:625–6.
- [10] Herzer H. Klinisch-psychologische Untersuchungen zur Psychopathologie bei Epilepsiesyndromen Psychol Habilitation, Greifswald; 1988.
- [11] Herzer H, Rabending G, Grimmberger M. Belastende Lebensereignisse und Epilepsieverlauf. Frankfurt/O. Unveroeff. Vortrag. VI. Arbeitstagung d. Sekt. Epilepsie d. Gesell. f. Neuroelektrodiagnostik d. DDR; 1985.
- [12] Perrine K, Kiolbasa T. Cognitive deficits in epilepsy and contribution to psychopathology. *Neurology* 1999;53(Suppl. 2):39–48.
- [13] Geschwind N. Behavioral changes in temporal lobe epilepsy. *Psychol Med* 1979;9:217–9.
- [14] Herzer H, Altenstein R, Grimmberger M. Beziehung zwischen automatisch analysierten quantitativen EEG-Daten und psychischen Leistungsparametern bei Epilepsiekranken. *Psychiatr Neurol Med Psychol* 1981;33:257–66.
- [15] Remschmidt H. Psychological studies of patients with epilepsy and popular prejudice. *Epilepsia* 1973;14:347–56.
- [16] Remschmidt H. Testpsychologische und experimentelle Untersuchungen zur Psychopathologie der Epilepsien. In: Penin H, editor. *Psychische Störungen bei Epilepsie*. Stuttgart/New York: Verlag Schattauer; 1973.
- [17] Nielsen H, Kristensen O. Personality correlates of sphenoidal EEG-foci in temporal lobe epilepsy. *Acta Neurol Scand* 1981;64:289–300.
- [18] Hermann BB. Deficits in neuropsychological functioning and psychopathology in persons with epilepsy: a rejected hypothesis revised. *Epilepsia* 1981;22:161–7.
- [19] Rausch R, Crandall PH. Psychological status related to surgical control of temporal lobe seizures. *Epilepsia* 1982;23:191–202.
- [20] Waxman SA, Geschwind N. The interictal behavior syndrome of temporal lobe epilepsy. *Arch Gen Psychiatry* 1975;32:1580–6.
- [21] Trimble MR. Anticonvulsants and psychopathology. In: Sackellares JC, Berent S, editors. *Psychological disturbances in epilepsy*. London: Butterworth–Heinemann; 1996.
- [22] Sackellares JC, Berent S. Psychosocial disturbances in epilepsy. London: Butterworth–Heinemann; 1996.
- [23] Schwartz JA. The social apraxia of epilepsy. In: Sackellares JC, Berent S, editors. *Psychosocial disturbances in epilepsy*. London: Butterworth–Heinemann; 1996. p. 159–70.
- [24] Altshuler LL, Devinsky O, Post RM, Theodore W. Depression, anxiety, and temporal lobe epilepsy: laterality of focus and symptoms. *Arch Neurol* 1990;47:284–8.
- [25] Devinsky O, Najjar S. Evidence against the existence of a temporal lobe epilepsy personality syndrome. *Neurology* 1999;53(Suppl. 2):13–25.
- [26] Schmitz EB, Moriarty J, Costa DC, Ring HA, Ell PJ, Trimble MR. Psychiatric profiles and patterns of cerebral blood flow in focal epilepsy: interactions between depression, obsessionality, and perfusion related to the laterality of the epilepsy. *J Neurol Neurosurg Psychiatry* 1997;62:458–63.
- [27] Fedio P, Martin A. Ideative-emotive behavioral characteristics of patients following left or right temporal lobectomy. *Epilepsia* 1983;25:117–30.
- [28] Bear D, Fedio P. Quantitative analysis of interictal behavior in temporal lobe epilepsy. *Arch Neurol* 1977;34:454–67.
- [29] Rodin E, Schmaltz S. The Bear–Fedio personality inventory and temporal lobe epilepsy. *Neurology* 1984;34:591–6.
- [30] Engel JR, Pedley TA. *Epilepsy a comprehensive textbook*. Philadelphia: Lippincott–Raven; 1998.
- [31] Haug HJ, Stieglitz RD. Das AMDP-System in der klinischen Anwendung und Forschung. Goettingen: Verlag Hogrefe; 1997.
- [32] Hautzinger M, Bailer M, Worall H, Keller F. Beck-Depressions-Inventar (BDI). Bern: Verlag Huber; 1994.
- [33] Franke G. Die Symptom-Checkliste von Derogatis—Deutsche Version. Göttingen: Beltz Verlag; 1995.
- [34] Fahrenberg J, Selg H, Hempel R. Das Freiburger Persönlichkeitssinventar FPI. Göttingen: Hogrefe Verlag; 1973.
- [35] Bear DM. Temporal lobe epilepsy—a syndrome of sensory-limbic hyperconnection. *Cortex* 1979;15:357–84.
- [36] Böttcher HR. Der INR Fragebogen. *Probl Ergebn Psychol* 1968;23:41–52.
- [37] Eysenck HJ. Dimensions of personality: the biosocial approach to personality. In: Strelau J, Angleitner A, editors. *Explorations in temperament: international perspectives on theory and measurement*. London: Plenum; 1991. p. 87–103.
- [38] Herzer H, Rabending G, Herzer R. Persönlichkeitsentwicklung und Psychopathologie bei Patienten mit Epilepsie. In: Wolf E, editor. *Das Psychosoziale in Theorie und Praxis*. Tübingen/Hamburg: Verlag Schöppe und Schwarzenbart; 1992. p. 211–325.
- [39] Spreen O. *MMPI Handbuch*. Bern/Stuttgart: Verlag Huber; 1963.
- [40] Janke W, Debus D. Die Eigenschaftswörterliste (EWL). Göttingen/Toronto/Zürich: Verlag Hogrefe; 1978.
- [41] Spielberger CD, Gorsuch RL, Lushene RL. *Manual for the State-Trait Anxiety Inventory*. Paulo Alto: Consulting Psychologists Press; 1970.
- [42] Krampen G. *IPC-Fragebogen zu Kontrollueberzeugungen*. Göttingen/Toronto/Zürich: Verlag für Psychologie; 1981.
- [43] Klauer T, Filipp SH. FEKB—Fragebogen zur Erfassung von Formen der Krankheitsbewältigung: I. Kurzbeschreibung des Verfahrens, Forschungsbericht Nr. 13, Universität Trier; 1987.
- [44] Dahl G. *WIP-Handbuch zum reduzierten Wechsler-Intelligenztest*. Rudolstadt: Hain Verlag; 1986.
- [45] Milner B. Interhemispheric differences in localization of psychological processes in man. *Br Med Bull* 1971;27:272–7.
- [46] Helmstaedter C, Durwen HF. VLMT: Verbaler Lern- und Merkfähigkeitstest. Schweiz Arch Neurol Psychiatry 1990;141(Suppl. 1):21–30.
- [47] Weidlich S, Lamberti G. DCS Diagnosticum für Cerebralschädigung. Bern/Göttingen/Toronto/Seattle: Verlag Huber; 1993.
- [48] Westhoff G. *Handbuch psychosozialer Messinstrumente*. Göttingen: Verlag Hogrefe; 1993.
- [49] Kolb B, Wishaw IQ. *Neuropsychologie*. Heidelberg/Berlin/Oxford: Spektrum Akademischer Verlag; 1996.
- [50] Jirasek J. Application of the “Figure Square Test” in the diagnosis of mild encephalopathies in children. *Cesk Psychiat* 1963;59:9–381.
- [51] Horn W. *Leistungsprüfsystem LPS*. Göttingen: Verlag Hogrefe; 1983.
- [52] Stroop JR. Studies of interference in serial verbal reactions. *J Exp Psychol* 1936;19:643–62.
- [53] Chapuis F. *Der Labyrinth Test*. Bern: Verlag Huber; 1953.
- [54] De Albuquerque M, De Campos CJ. Epilepsy and anxiety. *Arq Neuropsiquiatr* 1993;51(Suppl. 3):313–8.
- [55] Hosakawa J, Fukuma M, Kugoh T, Suwaki H, Hosakawa K. Depressive symptoms in patients with epilepsy. *Jpn J Psychiatry Neurol* 1992;46(Suppl. 2):449–51.

- [56] Bender R, Lange S. Adjusting for multiple testing—when and how?. *J Clin Epidemiol* 2001;54:343–9.
- [57] Strian F, Rabe F. Epileptische Angstaequivalente. *Nervenarzt* 1982;53:246–53.
- [58] Helmstaedter C. Verbaler Lern- und Merkfähigkeitstest. *Schw Arch Neurol Psychiat* 1990;141(Suppl. 1):21–30.
- [59] Helmstaedter C. Visual learning deficits in non resected patients with right temporal lobe epilepsy. *Cortex* 1991;27(Suppl. 4):547–55.
- [60] Elixhauser A, Leidy NK, Meador K, Means E, Willian MK. The relationship between memory performance, perceived cognitive function, and mood in patients with epilepsy. *Epilepsy Res* 1999;37:13–24.
- [61] Quiske A, Helmstaedter C, Lux S, Elger CE. Depression in patients with temporal lobe epilepsy is related to hippocampal sclerosis. *Epilepsy Res* 2000;39:121–5.
- [62] Zentner J, Wolf HK, Helmstaedter C, et al. Clinical relevance of amygdala sclerosis in temporal lobe epilepsy. *J Neurosurg* 1999;91:59–67.
- [63] Laux, I. Glanzmann, P. Schaffner, P. Spielberger, CD. STAI Das State-Trait Angstinventar. Beltz Test; 1981.
- [64] Levenson, H. Distinctions within the concept of internal–external control: development of a new scale. In: *Proceedings of the 80th annual convention of the American Psychological Association*; 1972, vol. 7: p. 261–2.

Systematic, standardized and comprehensive neurological phenotyping of inbred mice strains in the German Mouse Clinic

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Abstract

Neurological and psychiatric disorders are among the most common and most serious health problems in developed countries. Transgenic mouse models mimicking human neurological diseases have provided new insights into development and function of the nervous system. One of the prominent goals of the German National Genome Research Network is the understanding of the *in vivo* function of single genes and the pathophysiological and clinical consequences of respective mutations. The German Mouse Clinic (GMC) offers a high-throughput primary screen of genetically modified mouse models as well as an in-depth analysis in secondary and tertiary screens covering various fields of mouse physiology. Here we describe the phenotyping methods of the Neurological Screen in the GMC, exemplified in the four inbred mouse lines C57BL/6J, C3HeB/FeJ, BALB/cByJ, and 129S2/SvPas. For our primary screen, we generated “standard operating procedures” that were validated between different laboratories. The phenotyping of inbred strains already showed significant differences in various parameters, thus being a prerequisite for the examination of mutant mouse lines.

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Keywords: Neurological phenotyping; Inbred mouse strains; SHIRPA; Grip strength; Rotarod; EEG

1. Introduction

Studying the neurobehavioural phenotype of transgenic mice and their inbred background strains is a powerful tool to understand the neural basis of behaviour and the pathophysiology of neurological and psychiatric disorders. Hundreds of different genes expressed in the central nervous system have been targeted in transgenic and knockout mice (Hafezparast

et al., 2002; Watase and Zoghbi, 2003). Comparison of the mouse and human brain transcriptomes shows a good correlation for highly expressed genes in both transcript identity and abundance (Fougerousse et al., 2000). Therefore, screening of mice with respect to neurological disorders potentially offers an understanding of aetiology and pathogenesis of the human nervous system. For the comparison of neurological phenotyping data, standardized protocols were developed only recently, including a neurodevelopmental screening (Dierssen et al., 2002) and a behavioural phenotyping of mice in pharmacological and toxicological research (Karl et al., 2003). The Mouse Phenome Project (<http://aretha.jax.org/pub-cgi/phenome/mpdcgi?rtn=docs/home>) promotes the quantitative phenotypic characterization of a defined set of inbred mouse

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strains under standardized conditions (Paigen and Eppig, 2000; Bogue, 2003; Bogue and Grubb, 2004; Grubb et al., 2004). Several inbred strain comparisons have been published (Balogh et al., 1999; Tarantino et al., 2000; Volkar et al., 2002). Transgenic and knockout databases with behavioural profiles of mouse mutants are described by Anagnostopoulos et al. (2001).

The German Mouse Clinic (GMC, www.mouseclinic.de) has the goal to develop and optimize a battery of different test parameters in different disciplines. The GMC was established as a part of the German NGFN (National Genome Research Network) and in collaboration with the pan-European Eumorphia consortium (www.eumorphia.org) and offers a systematic, standardized and comprehensive phenotyping of mutant mice to identify and characterize mouse models for human diseases. The GMC comprises thirteen screens covering neurology, behaviour, nociception, dysmorphology, immunology, clinical chemistry, allergy, steroid metabolism, energy metabolism, lung function, expression profiling, cardio-vascular function and pathology (Gailus-Durner et al., 2005). A primary screening of a mutant mouse line (MML) includes all screens; each mouse is tested consecutively in several laboratories.

The neurological screen of the GMC established a standardized primary screening including validation of the data. This comprises the comparison of results of testing on selected inbred mouse strains and/or selected mutants at more than two Eumorphia laboratories (Green et al., 2005). In the primary neurological screening a modified SHIRPA protocol (Rafael et al., 2000; Rogers et al., 1997, 2001) and a grip strength analysis is used that allows for a high-throughput screening of MMLs. Dependant upon results of this primary screen and due to specific questions, additional tests can be carried out for further assessment of neurological functions in a hierarchical way (van der Staay and Steckler, 2001). The secondary screen comprises a rotarod analysis, and the tertiary screen a staircase test and, if applicable, electroencephalography (EEG). We will further broaden this arsenal of methods in the future. Behavioural tests such as the modified hole board test, the open field test and the Morris–Water–Maze test are performed in the complementing Behavioural Screen of the GMC (www.mouseclinic.de). The main aim of the neurological screen is to provide well-characterized mouse models for known neurological diseases with known gene defects (generated by transgenic, knockout and gene trap approaches), to investigate the in vivo consequences of the mutations, and to allow for therapeutic trials. In this paper we present our large spectrum of methods using inbred mouse strains C57BL/6J (C57), C3HeB/FeJ (C3H), BALB/cByJ (BALB), and 129S2/SvPas (129/SvP) as test models. Only the most significant results are presented. The choice of the given inbred strains was based on the frequent use of these mice in transgenic research (Gerlai, 1996; Taketo et al., 1991). In conclusion, we want to highlight the importance of well-established phenotyping protocols and the investigation of baseline data from inbred strains to the diligent phenotype analysis of MMLs. These baseline data facilitate the evaluation of differences found in numerous MMLs analyzed of different or mixed background.

2. Material and methods

2.1. Animals

Four inbred strains of male mice were used: C57BL/6J (C57) from Charles River, Germany, C3HeB/FeJ (C3H) from GSF Munich, Germany, BALB/cByJ (BALB) from Jackson Lab, USA, and 129S2/SvPas (129/SvP) from Charles River, France. All tests of the primary (SHIRPA, grip strength) and secondary (rotarod) neurological screen were performed in 10-week-old mice. The mice were caged in an animal colony maintained on a 12:12 h regular light–dark cycle. All experiments were done according to the German laws on animal protection and with permission from the “Regierung von Oberbayern”.

2.2. Primary screening: SHIRPA protocol

The SHIRPA (Smithkline Beecham, MRC Harwell, Imperial College, the Royal London hospital phenotype assessment) protocol (Irwin, 1968) is a rapid, comprehensive, and semi-quantitative screening method for qualitative analysis of abnormal phenotypes in mice. In the neurological screen within the GMC, it is used in a modified form (Rafael et al., 2000; Rogers et al., 1997, 2001). We carried out 23 test parameters that contribute to an overall assessment of muscle, lower motor neuron, spinocerebellar, sensory and autonomic function (Online supplement Table S I). A “standard operating procedure” (SOP) for the SHIRPA test was generated, tested in the four inbred mouse lines and validated between different laboratories.

2.2.1. Behaviour in the viewing jar

After weighing of the mouse, neurological assessment starts with the observation of the undisturbed animal's behaviour in a glass-viewing jar (\varnothing 11 cm) for 3 min. Items of interest are body position, tremor, palpebral closure, coat appearance, whiskers, and excessive lacrimation or defecation.

2.2.2. Behaviour in the arena

After transfer into an arena (36 cm \times 20 cm), each mouse is tested for transfer arousal, locomotor activity and gait along with any bizarre or stereotyped motor behaviour. For locomotor activity a grid (3 \times 5 squares) on the floor of the arena is used. During 30 s the number of squares are counted that the mouse enters with all four paws. Additionally, tail elevation, touch escape, positional passivity, and skin colour are scored.

2.2.3. Behaviour in or above the arena

Then, each mouse is lifted vertically up at mid-tail for 15 cm and curling of the trunk as well as possible grasping of the hind paws is observed. Pinna and corneal reflexes are tested by approaching the pinna and the eye, respectively, with the tip of a clean cotton swab. For the air-righting reflex, the animals are held horizontally in an inverted position 30 cm above a 10-cm foam bed, and are then released. If the mice show any obvious movement abnormalities before and at the transfer to the arena,

however, the righting reflex is done in the arena by turning the mouse on its back. For the contact-righting reflex, each mouse is placed into a glass cylinder (\varnothing 5 cm) that is turned upside down. Biting and vocalisation are scored during the entire handling.

2.3. Primary screening: grip strength

A grip strength meter (TSE; Bad Homburg, Germany) is used to measure the muscle strength in the forelimbs of the mice. The animals grasp a horizontal metal bar while being pulled by their tail. A sensor allows measurements of up to 600 ponds. Five trials within 1 min are performed for each mouse and their values are used as statistical variables in subsequent analysis. All experimental equipment is thoroughly cleaned with Pursept-A and dried prior to subsequent tests. Again, a SOP was generated for the grip strength analysis, tested in the four inbred mouse lines and validated between different laboratories. The SOP was examined by the Eumorphia administration team for accuracy and consistency and finally approved by a Eumorphia scientist outside the working group (<http://www.eumorphia.org/EMPreSS>).

2.4. Secondary screening: rotarod

A rotarod apparatus (TSE, Bad Homburg, Germany) is used to measure motor coordination, balance and motor learning ability (Bogo et al., 1981; Carter et al., 1999; Crawley, 1999). Rotarod performance requires a high degree of sensorimotor coordination and is especially sensitive to damage in the basal ganglia and the cerebellum (Lalonde et al., 1995, 1996; Mason and Sotelo, 1997). The machine is set up in an environment with minimal stimuli such as noise and movement. The rotarod unit consists of a computer-controlled motor-driven rotating spindle and four lanes for four mice. Infrared beams are used to detect the falling of the mice.

On the first day, the mice are habituated to the apparatus in two 180 s sessions at constant speeds of 12 and 20 rpm. In the motor coordination performance test on the second day, mice exert four trials with accelerating speed from 4 to 40 rpm. The mean latency to fall off the rotarod is recorded. Mice that rotate passively for three times are scored as fallen.

2.5. Tertiary screening: staircase test

The staircase test measures forelimb reaching and grasping abilities in mice but also depends on the tendency of rodents to explore a novel environment. This investigator-independent method measures side-specific deficits in coordinated paw reaching and shows impairments due to contralateral lesions in the motor pathways of the brain, e.g., in motor cortex, striatum, nigrostriatal tract, and subthalamic nucleus (Abrous et al., 1993; Baird et al., 2001; Dunbar et al., 1992; Fricker et al., 1996; Henderson et al., 1999; Montoya et al., 1991; Whishaw et al., 1997). The device (Campden Instruments Ltd.) is a plexiglas box with a removable double staircase. Food pellets (BIOSERV) are placed on both sides of the staircase and present eight stages of reaching difficulty, which provide an objective measure of side

bias, maximum forelimb extension, and grasping skills. Before testing, fasted mice are accustomed to the food pellets in their home cage for 3 days. Then, they are familiarized to the test boxes by placing food pellets on the staircase steps for a further 2 days. On subsequent days, one pellet per step (eight on each side) is placed in the box and the mouse is set in the start compartment. After 15 min training sessions, the number of pellets remaining on the steps and fallen down to the floor are counted. From the raw data, two experimental variables are calculated for each side and used in subsequent statistical analysis: (i) number of pellets grasped by the mouse on each side (i.e., eight minus the number of pellets remaining); (ii) maximum distance reached: the lowest step (numbered 1–8 from the top) with a remaining pellet.

2.6. Tertiary screening: electroencephalography (EEG)

Monitoring of EEG has become increasingly important in the neurological examination of certain mouse models. In our tertiary screening, we offer telemetric EEG of mice. This is a very laborious and time-consuming method and is only applied in selected mouse strains with epileptic seizures. To establish the method and to give a proof of principle, we performed EEG in twenty-six 22–36 weeks old C57 mice. With the DSI PhysioTel[®] telemetry system we can monitor mice while they freely move in their cages. A miniaturized implant transmits the digitized data via radio frequency signals to a receiver. The data are collected with the Dataquest[®] software. For the EEG, the transmitter is placed subcutaneously in the lower lateral trunk with the leads routed subcutaneously to an incision accessing the cranium. Trepanations (1 mm deep in the skull) are done with a microdrill on each side of the midline and 1 mm anterior of the lambda fissure. Microscrews placed in the drill holes lie directly above the dura and act as electrodes for the EEG lead which is wrapped round the screws. The screws are held in place with dental acrylic. EEG recordings are collected with an RPC-1 telemetry receiver (Data Science International), which is placed beneath the mouse's cage at a sampling rate of 250 Hz. Particular stress is laid on the detection of epileptic discharges such as spike-wave complexes and seizure patterns.

2.7. Statistical analysis

2.7.1. SHIRPA results

Values for body weight and locomotor activity are presented as means \pm S.E.M. One-way ANOVA is used to test for strain effects in quantitative parameters. If there is a rough deviation from the normal distribution (checked by inspecting a nor-

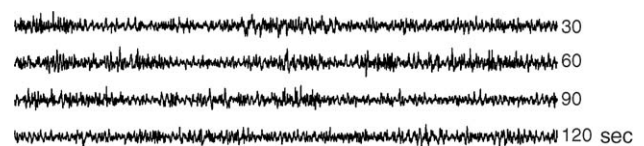


Fig. 1. Two-minute trace of EEG activity filtered by a 1–40 Hz bandpass. Recording of a surface EEG derived from an inbred C57 mouse in vigilance state 'NREM'.

mal probability plot), the nonparametric Kruskal–Wallis test is applied. The χ^2 -test is used for qualitative data.

2.7.2. Grip strength and rotarod test results

The grip strength and rotarod trials produce repeated measurements, which are analyzed by linear mixed effects models (Pinheiro and Bates, 2000). A linear mixed effects model is a modified analysis of variance/covariance (ANOVA/ANCOVA), which allows for the analysis of dependencies in the data. The strain variable and the covariate weight are modelled as fixed effects, mouse-specific intercepts are allowed by including the intercept as random effect. A dependency on the trial number can be checked by including the trial number as fixed and/or random effect. Interaction effects between the independent variables are tested for and excluded if their contribution is not significant. Covariates, which are not involved in an interaction and have no significant effect are also excluded. The statistic of interest is the strain effect in the final model. A significant strain effect in presence of the covariates means evidence of a difference between the strains. In this case, post hoc pairwise comparisons between strains are calculated with the covariates as included in the final model; p -values are not adjusted for multiple testing. Model fitting was performed by the nlme-package in R/SPlus (Project for Statistical Computing, 2004).

2.7.3. Staircase test

The staircase test is evaluated with a likewise analysis of variance with repeated measurements as mentioned above, considering strain effects as well as session length and side preferences on the number of pellets collected and maximum distance reached.

2.7.4. Extended statistical analysis routine phenotyping when both genders are present

In routine phenotyping, mice of both genders will have to be analyzed. In this type of analysis, gender is included as a factor in the ANOVA and mixed-effects models. Interactions involving gender will be tested for. If there is a significant interaction between gender and strain, male and female mice are analyzed separately.

2.7.5. EEG data

Spectral analysis was performed using 24 consecutive 10-s EEG periods derived from each mouse. Each 10-s period was divided into eight segments of 2.56 s duration overlapping each other by 1.28 s. After band-pass filtering (1–40 Hz), elimination of linear trends and tapering, each segment was submitted to Fast Fourier transformation (FFT) resulting in spectral power values [μV^2] with a frequency resolution of 0.488 Hz. The distribution of the power values over the frequency is known as the power spectra. The consecutive spectral evaluation of EEG signals was described by Tirsch et al. (1988). For feature extraction the peak-frequency in Hz and the sharpness of the peak were calculated from each normalised power spectrum and averaged over 24 periods.

3. Results

3.1. SHIRPA

All SHIRPA results are shown in Table 1. Only male mice were used for analysis. Body weight was significantly different ($p < 0.001$). C57 mice had a lower weight as compared to C3H, BALB and 129/SvP mice (Table 1). During observation in the viewing jar, no obvious differences could be found between the strains with the exception of the whiskers presence ($p < 0.01$): in contrast to C3H, BALB, and 129/SvP mice, four C57 mice had no whiskers.

After transfer to the arena, there were significant differences in locomotor activity ($p < 0.0001$). BALB mice showed the highest locomotor activity, followed by C57 mice, while C3H and 129/SvP mice had much lower locomotor activity. 129/SvP and C3H mice had a different tail elevation and touch escape behaviour as compared to C57 and BALB mice.

Behaviour recorded in or above the arena revealed biting and vocal reactions in all 10 C57 mice, but in only one BALB mouse and none C3H or 129/SvP mouse.

3.2. Grip strength

There was a clear effect of strain ($p < 0.0001$) and weight ($p < 0.05$) on grip strength. Trial number had no significant influence, and there was no significant interaction effect between any pair of independent variables. Heavier mice tend to have stronger grip strength. In pairwise comparisons by fitting mixed-effects models with covariable weight for each pair of strains, C3H mice had a significantly higher forelimb strength than C57, BALB, and 129/SvP mice ($p < 0.001$; see Fig. 1). In addition, BALB mice performed significantly better than C57 mice ($p < 0.001$).

3.3. Rotarod

On the accelerating rotarod, strain had a significant effect on the latency ($p < 0.05$). There was a significant interaction effect between weight and trial number ($p < 0.05$) in the way

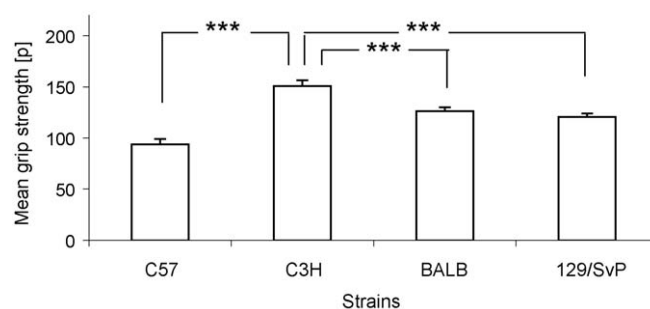


Fig. 2. Grip strength test. Each column represents the mean of the forelimb grip strength [p] taken from four different inbred strains. C3H mice had the significantly highest grip strength as compared to BALB, 129/SvP and C57 mice ($p < 0.001$). Significant differences between the group means are based on ANCOVA with weight as covariable.

Table 1
Results of modified SHIRPA-analysis of four inbred strains

		C57 (<i>n</i> = 10)	C3H (<i>n</i> = 10)	BALB (<i>n</i> = 10)	129/SvP (<i>n</i> = 10)	<i>p</i> -Value
1. Body weight [g]		24.5 ± 0.5	27.2 ± 0.8	26.6 ± 0.4	27.8 ± 0.3	<0.001
2. Body position	Inactive	0	0	0	0	n.s.
	Active	10	10	10	10	
	Excessive active	0	0	0	0	
3. Tremor	Absent	10	10	10	10	n.s.
	Present	0	0	0	0	
4. Palpebral closure	Eyes open	10	10	10	10	n.s.
	Eyes closed	0	0	0	0	
5. Coat appearance	Tidy and well groomed	10	10	9	10	n.s.
	Irregularities	0	0	1	0	
6. Whiskers	Present	6	10	10	10	<0.01
	Absent	4	0	0	0	
7. Lacrimation	Absent	10	10	10	10	n.s.
	Present	0	0	0	0	
8. Defecation	Present	4	5	6	7	n.s.
	Absent	6	5	4	3	
9. Transfer arousal	Extended freeze	0	0	0	2	n.s.
	Brief freeze	7	8	8	8	
	Immediate movement	3	1	2	0	
10. Locomotor activity [number of squares crossed]		23.9 ± 1.7	17.7 ± 2.2	30.7 ± 2.4	8.2 ± 1.9	<0.0001
11. Gait	Fluid movement	10	10	10	9	n.s.
	Lack fluidity	0	0	0	1	
12. Tail elevation	Dragging	0	4	0	3	<0.05
	Horizontal extension	10	6	10	7	
	Elevated tail	0	0	0	0	
13. Touch escape	No response	0	3	0	4	<0.05
	Response to touch	8	7	7	6	
	Flees prior to touch	2	0	3	0	
14. Positional passivity	Struggles when held by tail	10	10	10	10	n.s.
	No struggle	0	0	0	0	
15. Skin colour	Blanched	0	0	0	0	n.s.
	Pink	10	10	10	10	
	Bright, deep red	0	0	0	0	
16. Trunk curl	Absent	8	4	6	8	n.s.
	Present	2	6	4	2	
17. Limb grasping	Absent	10	10	10	10	n.s.
	Present	0	0	0	0	
18. Pinna reflex	Present	10	10	10	10	n.s.
	Absent	0	0	0	0	
19. Corneal reflex	Present	10	10	10	10	n.s.
	Absent	0	0	0	0	
20. Righting reflex	Rights itself	10	10	10	10	n.s.
	Fails to right	0	0	0	0	
21. Contact righting reflex	Present	10	10	10	10	n.s.
	Absent	0	0	0	0	
22. Evidence of biting	Biting in response to handling	0	10	9	10	<0.001
	None	10	0	1	0	
23. Vocalisation	None	0	10	9	10	<0.001
	Vocal	10	0	1	0	

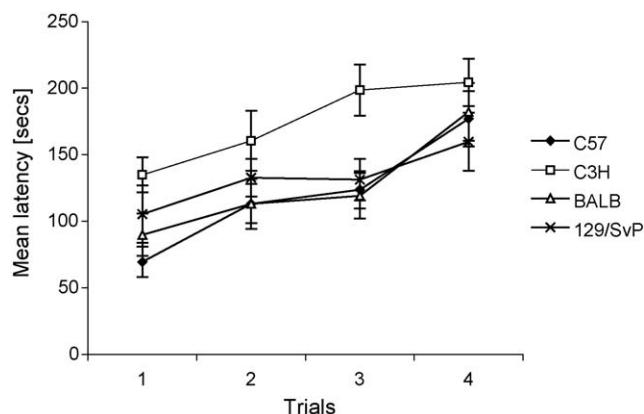


Fig. 3. Rotarod performance test. The data points represent the means over the retention period of the mice on the rotarod in four consecutive trials. C3H mice performed better than C57 and Balb mice ($p < 0.05$).

that the performance improved with the number of trials, but the improvement was less pronounced in heavier animals. The interaction of weight with strain and of trial number with strain was not significant; in fact all groups were able to improve their performance over the training course (Fig. 2). For pairwise comparisons, the strain effect in mixed-effect models with covariables trial number and weight and their interaction was calculated for each combination of strains. C3H

mice performed significantly better than C57 and BALB mice ($p < 0.05$).

3.4. Staircase

There were no significant differences between the inbred strains in the staircase test (Fig. 3). However, C57 mice performed better in the collection of pellets with ongoing time (30 and 60 min) and in the distance reached. All four inbred strains showed altered performance with increasing session duration. Maximal performance was reached after 30 min except for the BALB strain. This line also showed an increase in performance in the last 30 min. There was no significant effect of side preference.

3.5. EEG analysis

An example of an EEG trace is given in Fig. 4. The time course of relative power spectra derived from 24 consecutive periods of the same EEG is shown in Fig. 5. As it can be seen the spectra differ within the whole 4-min EEG-recording and show a clear variance in time. The main peaks of the spectra are mostly located about 3 Hz with a mean peak frequency of 3.6 Hz.

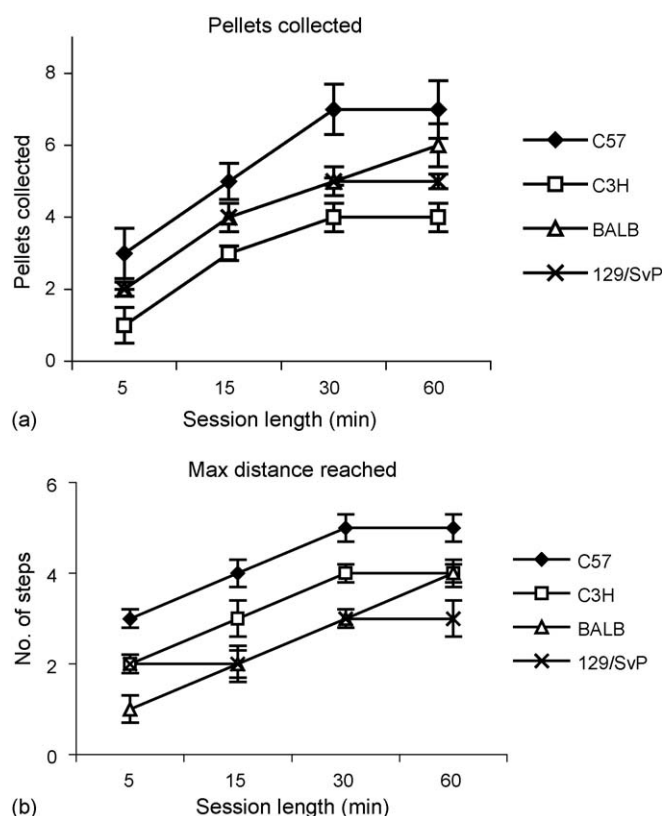


Fig. 4. Performance of inbred mouse strains in the staircase test. Session length, varied between 5 and 60 min. Each mouse performance was analyzed both as the number of pellets collected (a) and as the maximum distance reached (b). Data for the inbred strains are presented separately for each variable; results did not differ between the inbred strains.

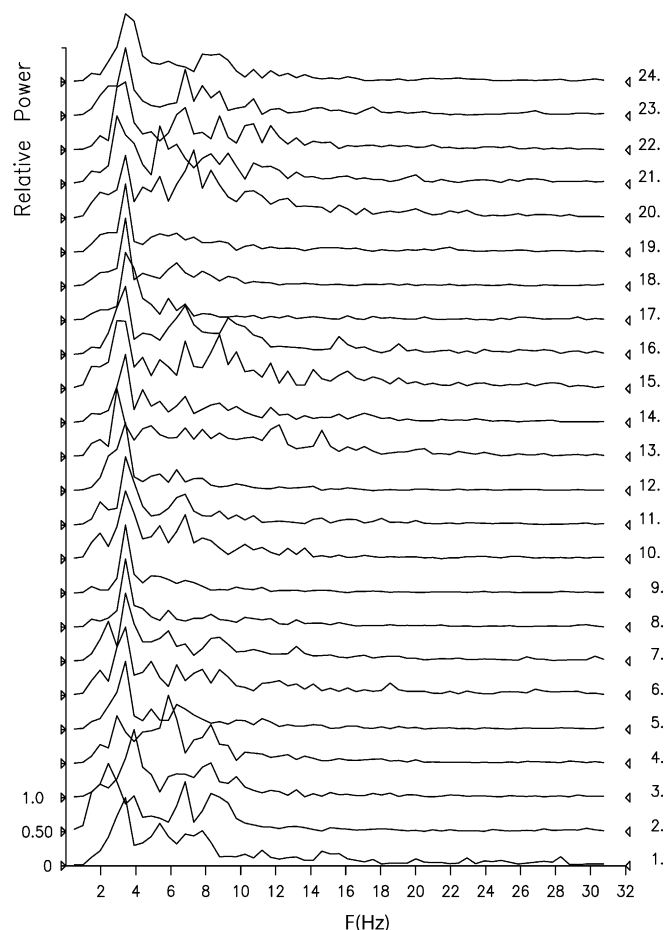


Fig. 5. Time courses of relative power spectra derived from 24 consecutive 10-s epochs of the same EEG as in Fig. 1. The small triangles mark the zero lines.

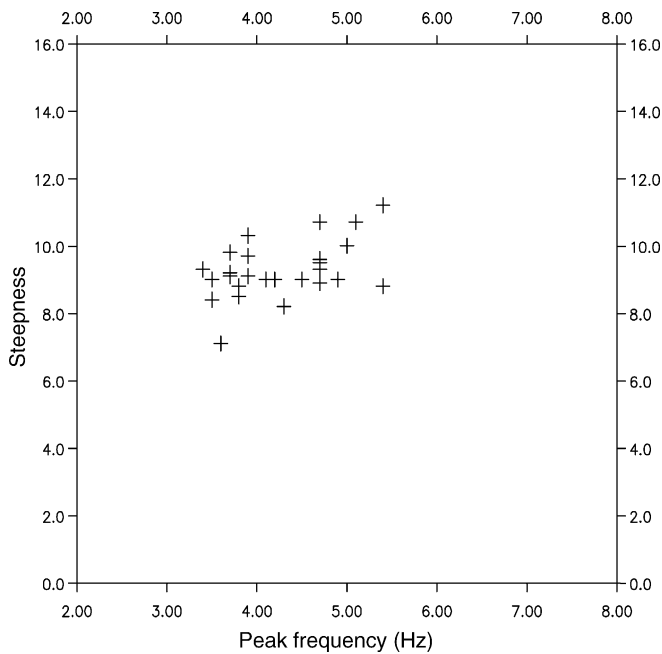


Fig. 6. Scatter diagram of mean spectral peak frequency and steepness of the peak calculated from each 4-min EEGs of $n = 26$ inbred C57-mice.

The main result of the spectral analysis obtained from the sample set of $n = 26$ inbred C57 mice-EEGs is shown in Fig. 6. This scatter diagram illustrates the distribution of mean spectral peak frequency and steepness of the peak in the two-dimensional feature space calculated from each 4-min EEG. Each case is marked by a cross. An intra-individual variance is evident. The range of the spectral peak frequency is between 3.5 and 5.5 Hz, whereas, the complexity ranges from 7.4 to 8.7 corresponding to the relatively broad spectra of high-complex and noisy EEGs in NREM state.

4. Discussion

The neurological performance of four inbred mouse strains was evaluated and compared in a battery of different tests. The tests were standardized for the neurological screen of the GMC and were chosen to gain insight into motor performance, forelimb grip strength, skilled reaching and spatial motor learning. The need for standardization in phenotyping is obvious. As data of behavioural and neurological phenotypes accumulate from large-scale mutagenesis screens (Sayah et al., 2000), there is discussion about the most appropriate neurological tests for evaluating abnormal behaviour (Tarantino et al., 2000). Such tests need to cover a wide range of neuronal and neuromuscular functions as it is shown here. It was shown already that the modified SHIRPA protocol is an adequate method for successful screening of large cohorts of mice (Masuya et al., 2005). In addition, several targeted mouse mutants have been characterized (Burne et al., 2005; Lalonde et al., 2005). Previous studies have shown that inbred mice strains used to generate mutant mice already display marked differences in neurobehavioural tasks (Crawley and Pavlov, 1997; Dierssen et al., 2002). This is confirmed by the marked differences between strains in the present work.

These data emphasize the importance of genetic background of mutant mice in order to evaluate neurological data.

In our primary observational screen, we show that there are marked differences between C57 and C3H mice, in particular regarding body weight, grip strength and locomotor activity. C57 were markedly more aggressive than the other inbred strains. Several genes appear to influence mouse aggression, and strain-related differences are reported (Miczek et al., 2001a,b). Absent whiskers of C57 mice can be explained by the overgrooming of mice that barber the whiskers of their cage mates, a phenomenon often seen in C57 mice but also in other strains (Kalueff et al., 2006; Sarna et al., 2000).

BALB and C57 mice exhibited a higher locomotor activity as C3H and 129/SvP mice. Differences in locomotor activity in mice can be due to differences in the dopaminergic system, which plays an important role in locomotor function and motivational processes (Robbins and Everitt, 1996; Wise, 1996). In contrast to the large difference between BALB and 129/SvP mice, C3H mice may be an intermediate between these strains. C57 and BALB mice were relatively more active than the C3H and 129/SvP mice in the viewing jar in contrast to published data (Rogers et al., 1999). In contrast to 129/SvP, C3H mice have marked visual defects due to retinal degeneration. This may influence locomotor activity in this strain.

Grip strength was highest in C3H as already described (Rogers et al., 2001) and in the range also seen in other laboratories (<http://www.jax.org/phenome>; Bogue and Grubb, 2004; Grubb et al., 2004).

In the rotarod test, C57 mice showed more often than the other inbred strains passive rotation behaviour. This leads to the significantly shorter latency on the rotarod as compared to C3H mice, whereas in other publications it had been described that C57 mice performed rather better than C3H mice (Brooks et al., 2004; McFadyen et al., 2003). In the inbred strains, we tested here, a significant influence of body weight on the improvement of rotarod performance over trials was detected. A similar effect of weight on performance was also described elsewhere (McFadyen et al., 2003).

In conclusion, strain-related differences as we found here with standardized, comprehensive SOPs in the GMC need to be taken into account when performing and interpreting results from genetically modified mice, particularly those of mixed background. Our results clearly demonstrate significant differences between the strains. Therefore, the screening of MMLs in the GMC is performed with wildtype littermates as control mice to minimize the influence of the genetic background.

In addition, the spectrum of neurological tests also includes EEG to detect differences in bioelectrical activity in brains of mutant mice. Benefits of using implanted telemetry monitors are: (i) stress-induced artefacts compared to restrictive monitoring are significantly reduced, (ii) measurements are free from the effect of anaesthesia, and (iii) animal handling is minimized. Differences in the specific rhythmic pattern of the waveforms are indicators of functional disorders in the cerebral cortex. This method is applied for the analysis of paroxysmal neurological disorders and allows the characterisation of mouse models for epilepsy. The facilities of the automatic EEG analysis are shown

in this paper for the C57 mouse strain. These features can be used to disclose differences between genotypes and to complete our neurological examinations of MMLs.

The results presented here could be complemented with an overall examination of a mouse in the GMC with data from behavioural, clinical-chemical, hematological, nociceptive, metabolic (energy, steroids), cardiovascular, immunological, lung function, expression, dysmorphological, and pathological data. Thus, the GMC is capable in performing an overall phenotyping of various MMLs. This leads to the standardized quantification of known phenotypes as well as the detection of new phenotypes in mutant mice covering a wide range of methods in a variety of screening categories. This approach contributes to the understanding of underlying mechanisms that may be affected by a transgene and offers a valuable tool in the expanding field of the generation and analysis of genetically modified mice as models for human diseases.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.jneumeth.2006.04.002](https://doi.org/10.1016/j.jneumeth.2006.04.002).

References

- Abrous DN, Shaltot ARA, Torres EM, Dunnett SB. Dopamine-rich grafts in the neostriatum and/or nucleus accumbens: effects on drug-induced behaviours and skilled paw reaching. *Neuroscience* 1993;53:187–97.
- Anagnostopoulos AV, Mobraaten LE, Sharp JJ, Davisson MT. Transgenic and knockout databases: behavioural profiles of mouse mutants. *Physiol Behav* 2001;73:675–89.
- Baird AL, Meldrum A, Dunnett SB. The staircase test of skilled reaching in mice. *Brain Res Bull* 2001;54:243–50.
- Balogh SA, McDowell CS, Stavnezer AJ, Denenberg VH. A behavioural and neuroanatomical assessment of an inbred substrain 129 mice with behavioural comparison to C57BL/6J mice. *Brain Res* 1999;836:38–48.
- Bogo V, Hill TA, Young RW. Comparison of accelerated and rotarod sensitivity in detecting ethanol- and acrylamide-inducing performance decrement in rats: review of experimental considerations of rotating rod systems. *Neurotoxicology* 1981;2:765–87.
- Bogue M. Mouse phenome project: understanding human biology through mouse genetics and genomics. *J Appl Physiol* 2003;95:1335–7.
- Bogue MA, Grubb SC. The mouse phenome project. *Genetica* 2004;122:71–4.
- Brooks SP, Pask T, Jones L, Dunnett SB. Behavioural profiles of inbred mouse strains used as transgenic backgrounds. I: motor tests. *Genes Brain Behav* 2004;3:206–15.
- Burne TH, McGrath JJ, Eyles DW, Mackay-Sim A. Behavioural characterization of vitamin D receptor knockout mice. *Behav Brain Res* 2005;157:299–308.
- Carter RJ, Lione LA, Humby T, Mangianni L, Mahal A, Bates GP, et al. Characterization of progressive motor deficits in mice transgenic for the human Huntington's disease mutation. *J Neurosci* 1999;19:3248–57.
- Crawley JN. Behavioural phenotyping of transgenic and knockout mice: experimental design and evaluation of general health, sensory functions, motor abilities, and specific behavioural tests. *Brain Res* 1999;835:18–26.
- Crawley JN, Pavlyar R. A proposed test battery and constellations of specific behavioural paradigms to investigate the behavioural phenotype of transgenic and knockout mice. *Horm Behav* 1997;31:197–211.
- Dierrsens M, Fotaki V, Martinez de Lagran M, Gratacos M, Arbones M, Fillat C, et al. Neurobehavioural development of two mouse lines commonly used in transgenic studies. *Pharmacol Biochem Behav* 2002;73:19–25.
- Dunbar JS, Hitchcock K, Latimer M, Rugg EL, Ward N, Winn P. Excitotoxic lesions of the pedunculo-pontine tegmental nucleus of the rat. 2. Examination of eating and drinking, rotation, and reaching and grasping following unilateral ibotenate or quinolinic lesions. *Brain Res* 1992;589:194–206.
- Fougerousse F, Bullen P, Herasse M, Lindsay S, Richard I, Wilson D, et al. Human-mouse differences in the embryonic expression patterns of developmental control genes and disease genes. *Hum Mol Genet* 2000;9:165–73.
- Fricker RA, Annett LE, Torres EM, Dunnett SB. The locus of a striatal ibotenic acid lesion affects the direction of drug-induced rotation and skilled forelimb use. *Brain Res Bull* 1996;41:409–16.
- Gailus-Durner V, Fuchs H, Becker L, Bolle I, Brielmeier M, Calzada-Wack J, et al. Introducing the German Mouse Clinic: open access platform for standardized phenotyping. *Nat Meth* 2005;2:403–4.
- Gerlai R. Gene-targeting studies of mammalian behaviour: is it the mutation or the background genotype? *Trends Neurosci* 1996;19:177–81.
- Green EC, Ghoutos GV, Lad HV, Blake A, Weekes J, Hancock JM. EMPRESS: European mouse phenotyping resource for standardized screens. *Bioinformatics* 2005;21:2930–1.
- Grubb SC, Churchill GA, Bogue MA. A collaborative database of inbred mouse strain characteristics. *Bioinformatics* 2004;20:2857–9.
- Hafezparast M, Ahmad-Annuar A, Wood NW, Tabrizi SJ, Fisher EMC. Mouse models for neurological diseases. *Lancet Neurol* 2002;1:215–24.
- Henderson JM, Annett LE, Ryan LJ, Chiang W, Hidaka S, Torres EM, et al. Subthalamic nucleus lesions induce deficits as well as benefits in the hemiparkinsonian rat. *Eur J Neurosci* 1999;11:2749–57.
- Irwin S. Comprehensive observational assessment: 1a. A systematic, quantitative procedure for assessing the behavioural and physiologic state of the mouse. *Psychopharmacologia* 1968;13:222–57.
- Kalueff AV, Minasyan A, Keisala T, Shah ZH, Tuohimaa P. Hair barbering in mice: implications for neurobehavioural research. *Behav Process* 2006;71:8–15.
- Karl T, von Horsten Pabst. Behavioural phenotyping of mice in pharmacological and toxicological research. *Exp Toxicol Pathol* 2003;55:69–83.
- Lalonde R, Bensoula AN, Filali M. Rotarod sensorimotor learning in cerebellar mutant mice. *Neurosci Res* 1995;22:423–6.
- Lalonde R, Dumont M, Staufienbiel M, Strazielle C. Neurobehavioural characterization of APP23 transgenic mice with the SHIRPA primary screen. *Behav Brain Res* 2005;157:91–8.
- Lalonde R, Filali M, Bensoula AN, Lestienne F. Sensorimotor learning in three cerebellar mutant mice. *Neurobiol Learn Mem* 1996;65:113–20.
- Mason C, Sotelo C, editors. The cerebellum: a model for construction of a cortex. *Perspectives on Developmental Neurobiology Special Issue*, 5, 1997, 1–95.
- Masuya H, Inoue M, Wada Y, Shimizu A, Nagano J, Kawai A, et al. Implementation of the modified-SHIRPA protocol for screening of dominant phenotypes in a large-scale ENU mutagenesis program. *Mamm Genome* 2005;16:829–37.
- McFadyen MP, Kusek G, Bolivar VJ, Flaherty L. Differences among eight inbred strains of mice in motor ability and motor learning on a rotorod. *Genes Brain Behav* 2003;2:214–9.
- Miczek KA, Maxson SC, Fish EW, Faccidomo S. Aggressive behavioural phenotypes in mice. *Behav Brain Res* 2001a;125:167–81.
- Miczek KA, Maxson SC, Fish EW, Faccidomo S. Aggressive behavioural phenotypes in mice. *Behav Brain Res* 2001b;125(1/2):167–81.
- Montoya CP, Campbell-Hope LJ, Pemperton KD, Dunnett SB. The staircase test: a measure of independent forelimb reaching and grasping abilities in rats. *J Neurosci Meth* 1991;36:219–28.
- Paigen K, Eppig JT. A mouse phenome project. *Mamm Genome* 2000;11:715–7.
- Pinheiro JC, Bates DM. Mixed-effects models in S and S-PLUS. New York: Springer; 2000.
- The R Project for Statistical Computing, 2004, <http://www.r-project.org>.
- Rafael JA, Nitta Y, Peters J, Davies KE. Testing of SHIRPA, a mouse phenotypic assessment protocol, on Dmd (mdx) and Dmd (mdx3cv) dystrophin-deficient mice. *Mamm Genome* 2000;11:725–8.

- Robbins TW, Everitt BJ. Neurobehavioural mechanisms of reward and motivation. *Curr Opin Neurobiol* 1996;2:228–36.
- Rogers DC, Peters J, Martin JE, et al. SHIRPA; a protocol for behavioural assessment: validation for longitudinal study of neurological dysfunction in mice. *Neurosci Lett* 2001;306:89–92.
- Rogers DC, Jones DN, Nelson PR, Jones CM, Quilter CA, Robinson TL, Hagan JJ. Use of SHIRPA and discriminant analysis to characterise marked differences in the behavioural phenotype of six inbred mouse strains. *Behav Brain Res* 1999;105:207–17.
- Rogers DC, Fisher EM, Brown SD, Peters J, Hunter AJ, Martin JE. SHIRPA, a proposed protocol for comprehensive phenotype assessment. *Mamm Genome* 1997;8:711–3.
- Sarna JR, Dyck RH, Whishaw IQ. The Dalila effect: C57BL6 mice barber whiskers by plucking. *Behav Brain Res* 2000;108:39–45.
- Sayah DM, Khan AH, Gasperoni TL, Smith DJ. A genetic screen for novel behavioural mutations in mice. *Mol Psychiatr* 2000;5:369–77.
- Taketo M, Schroeder nAC, Mobraaten LE, Gunning KB, Hanten G, Fox RR, et al. FVB/N: an inbred mouse strain preferable for transgenic analyses. *Proc Nat Acad Sci USA* 1991;88:2065–9.
- Tarantino LM, Gould TJ, Druhan JP, Bucan M. Behaviour and mutagenesis screens: the importance of baseline analysis of inbred strains. *Mamm Genome* 2000;11:555–64.
- Tirsch WS, Keidel M, Pöppel SJ. Computer-aided detection of temporal patterns in human CNS dynamics. In: Willems JL, van Bemmelen JH, Michel J, editors. *Progress in computer-assisted function analysis*. Amsterdam: Elsevier; 1988. p. 109–18.
- van der Staay FJ, Steckler T. Behavioural phenotyping of mouse mutants. *Behav Brain Res* 2001;125:3–12.
- Volkmar V, Koks S, Vasar E, Rauvala H. Strain and gender differences in the behaviour of mouse lines commonly used in transgenic studies. *Physiol Behav* 2002;72:271–81.
- Watase K, Zoghbi HY. Modelling brain diseases in mice: the challenges of design and analysis. *Nat Rev Genet* 2003;4:296–307.
- Whishaw IQ, Woodward NC, Miklyaeva E, Pellis SM. Analysis of limb use by control rats and unilateral DA-depleted rats in the Montoya staircase test: movements, impairment and compensatory strategies. *Behav Brain Res* 1997;89:167–77.
- Wise RA. Neurobiology of addiction. *Curr Opin Neurobiol* 1996;2:243–51.

Lateralizing Significance of Quantitative Analysis of Head Movements before Secondary Generalization of Seizures of Patients with Temporal Lobe Epilepsy

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Summary: *Purpose:* To quantitatively evaluate the lateralizing significance of ictal head movements of patients with temporal lobe epilepsy (TLE).

Methods: We investigated EEG-video recorded seizures of patients with TLE, in which the camera position was perpendicular to the head facing the camera in an upright position and bilateral head movement was recorded. Thirty-eight seizures (31 patients) with head movement in both directions were investigated. Ipsilateral and contralateral head movements were defined according to ictal EEG. Head movements were quantified by selecting the movement of the nose in relation to a defined point on the thorax (25/s) in a defined plane facing the camera. The duration of the head version was determined independently of the camera angle. The angle, duration, and angular speed of the head movements were computed and inter and intrasubject analyses were performed (Wilcoxon rank sum).

Results: Ipsilateral movement always preceded contralateral movement. The positive predictive value was 100% for movement in both directions. The duration of contralateral head version was significantly longer than ipsilateral head movement (6.4 ± 4.1 s vs. 3.9 ± 3.1 s, $p < 0.001$). The angular speed of both movements was similar (15.5 ± 12.1 deg/s vs. 17.3 ± 13.0 deg/s).

Conclusion: The quantitative analysis shows the importance of sequence in the seizure's evolution and duration, but not angular speed for correct lateralization of versive head movement. This quantitative method shows the high lateralizing value of ictal lateral head movements in TLE.

Key Words: Versive head movement—Version—Seizure semiology—Lateralization—Temporal lobe epilepsy.

The analysis of seizure semiology is a clinically well-established method in localization of the seizure onset zone of patients undergoing evaluation for resective surgery (Rosenow and Luders, 2001; Noachtar, 2004). Lateralizing seizure phenomena are frequently observed. Seventy-eight percent of patients with temporal lobe epilepsy (TLE) during epileptic seizures, presented with lateralizing signs, which had a positive predictive value (PPV) of 94% (Chee et al., 1993). Some motor phenomena, such as dystonic posturing of the upper limbs show repeatedly to be of high and reliable lateralizing value (PPV 100%) (Kotagal et al., 1989; Steinhoff et al., 1998).

The lateralizing value of versive head movements in TLE, however, has been subject to debate. If defined as forced and involuntary head movement resulting in unnatural positioning (Wyllie et al., 1986a), versive head movement displays a high PPV for localization of a contralateral seizure onset. Although this has been confirmed (Chee et al., 1993; Bleasel et al., 1997; Steinhoff et al., 1998), some have debated its lateralizing value (Robillard et al., 1983; Ochs et al., 1984; Newton et al., 1992). Nonforced head movement is not a lateralizing sign unless ending before generalization (Kernan et al., 1993) or followed by contralateral forced head movement (Wyllie et al., 1986b; Kernan et al., 1993), lateralizing to the ipsilateral side of the seizure onset zone. It is recognized that the qualitative nature of the definition of version may lead to a questionable reliability of the observer (McLachlan, 1987; Jayakar et al., 1992). The different interpretations of versive head movements may explain the presence of contradictory data (Robillard et al., 1983; Ochs et al.,

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1984; Wyllie et al., 1986a; Newton et al., 1992; Chee et al., 1993; Bleasel et al., 1997; Steinhoff et al., 1998). Interobserver reliability has been shown to be poor in qualitative video analysis (Bleasel et al., 1997). In this situation, observer independent quantitative methods may help to resolve the problem. Therefore, we quantitatively analyzed head movements with the application of a proposed method in a typical clinical EMU setting (Cunha et al., 2003) using recently introduced video tracking technology (Li et al., 2002) for clinical application. We chose seizures with bilateral head movements to further quantitatively differentiate ipsi- and contralateral head movement characteristics with regard to correct lateralization. A similar application has proved successful in the differentiation of seizures characterized by motor automatisms (Meier et al., 2004).

METHODS

Patients

Patients were collected from the video archives of the Epilepsy Monitoring Units (EMUs) at the University of Munich (11 patients), Cleveland Clinic Foundation, Ohio (14 patients), and Bethel Epilepsy Monitoring Unit, Bielefeld (6 patients). A database search in each center included the terms [1] TLE, [2] version, [3] versive seizure, and [4] versive head movement. In order to evaluate the significance of the direction of head movements for the lateralization of the seizure onset zone, we focused on seizures, in which bilateral head movement occurred. Thus, for the purpose of this study, all seizures only showing unilateral head version were not further investigated. Randomly, all seizures included in the analysis eventually generalized secondarily. Thirty-eight seizures from 31 patients were included in the study (Table 1) fulfilling the video criteria as described below.

Presurgical evaluation

Presurgical evaluation in all patients included noninvasive video-EEG recordings, magnetic resonance imaging (MRI) and neuropsychological testing. MRI included proton density weighted, T₁- and T₂-weighted images in axial, coronal and sagittal planes (5-mm slices; 1.0 Tesla/Siemens, General Electric, Marconi). If the MRI was normal or surgical planning required additional testing, high resolution (1–3-mm slices) MRI with inversion recovery (IR), 3D fast low angle shot (FLASH) images, fluid attenuated inversion recovery (FLAIR) and magnetization prepared rapid attenuated gradient echo was performed (1.5 Tesla/Siemens) (Jackson et al., 1990; Laxer and Garcia, 1993). Further imaging studies undertaken in selected patients, included interictal [¹⁸F] fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) and ictal ^{99m}Tc-ethyl-cysteinate-dimer single photon emission computerized tomography (ECD-SPECT) following es-

tablished protocols (Arnold et al., 2000; Noachtar et al., 1998).

The TLE and its lateralization was defined in a patient management meeting attended by epileptologists, neuroradiologists, neurosurgeons, and neuropsychologists based on localizing evidence of interictal and ictal EEG patterns, seizure semiology and neuroimaging results (Noachtar et al., 2003).

Continuous noninvasive EEG-video monitoring lasting at least 3 days was performed on all patients. Closely spaced surface electrodes (10–10 system) in combination with 32–64 channel EEG machines (Vanguard, Cleveland, Ohio, U.S.A.) were used. A system previously described elsewhere (Lüders and Noachtar, 2000) was applied when classifying interictal and ictal data. The lateralization of the direction of the ictal head movement (i.e., ipsilateral vs. contralateral) was defined by ictal EEG of a given seizure.

Inclusion and exclusion criteria

The seizures were first analyzed visually by at least two senior epileptologists and classified according to a recently published seizure classification (Lüders et al., 1998; Noachtar, 2001). All patients met the following inclusion criteria:

- (a) Diagnosis of TLE,
- (b) Head turning in both directions lasting at least 1.25 s (31 frames) to evaluate ipsi- and contralateral head movement characteristics quantitatively, and
- (c) Camera position was perpendicular to the head facing the camera in an upright position, complying with geometric model as previously defined (Cunha et al., 2003).

Versive head movement was identified through visual analysis by at least two senior epileptologists and defined as contralateral or ipsilateral according to EEG ictal patterns. We eventually only included seizures which generalized secondarily most likely because the reviewers were more confident to classify contralateral head turning as version if it occurred prior to secondary generalization of a seizure. Previous studies confirm that version has a higher lateralizing significance if occurring prior to secondary generalization (Wyllie et al., 1986b; Kernan et al., 1993). Head movements occurring after secondary generalization were not analyzed.

The following criteria excluded the patients from the study:

- (a) Head movement was possibly in response to external stimuli,
- (b) Head or reference point were hidden for longer than 2 s, and
- (c) Head and trunk left the plane perpendicular to the camera.

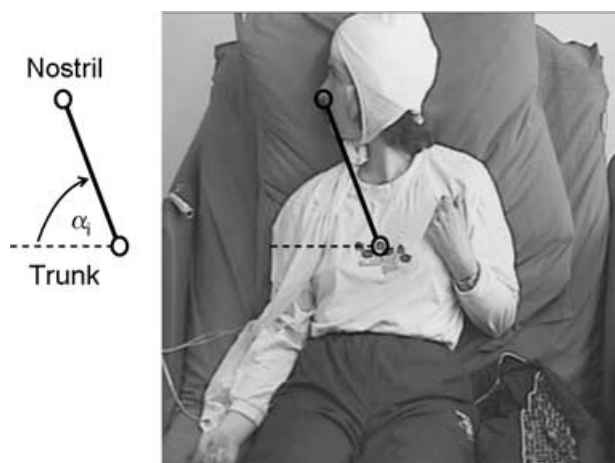


FIG. 1. Measurement of the head version of a patient in a typical EMU setting as defined by two-dimensional geometry. The head movement was tracked at the left nostril in relation to a reference point on the patient's shirt.

Movement analysis

Firstly, two points on the patient were chosen for each seizure, a nostril [Point 1] and an easily identifiable point on the patient's thorax [Point 2], such as a button. Point 1 represented the movement of the head, and Point 2 served as a reference point. We chose the reference point on the patient's thorax to minimize the relative effect of body movements on the head movement (Cunha et al., 2003). This method of movement analysis including the error of the measurements with regard to the reference point (patient's body or external reference) has been published elsewhere in detail (Cunha et al., 2003). Each point was tracked for each video frame (25/s), generating the respective two-dimensional positions (x , y). These positions were then connected and superimposed on the video recording, allowing the movement pattern to be better visualized, as depicted in Fig. 1. Based on the geometric model recently published elsewhere (Cunha et al., 2003), only head movement during which both eyes could be seen was further used for angular analysis. For each frame i , the angle α was computed (α_i) and a movement tracing was generated, as shown in Fig. 2. From these tracings ipsilateral and contralateral angular speed and duration were extracted. In an attempt to reduce further inclusion bias due to the database search, the person who performed the video analysis (RO'D) was blinded to the results of all other investigations.

Duration of head movement

The video and movement tracing were inspected. The frame number at the beginning and at the end of movement in either direction was noted in the video and verified on the tracing, allowing the duration to be calculated. As the duration did not require active tracking of two points, the entire duration of the movement, including movement in which both eyes could not be seen, was measured.

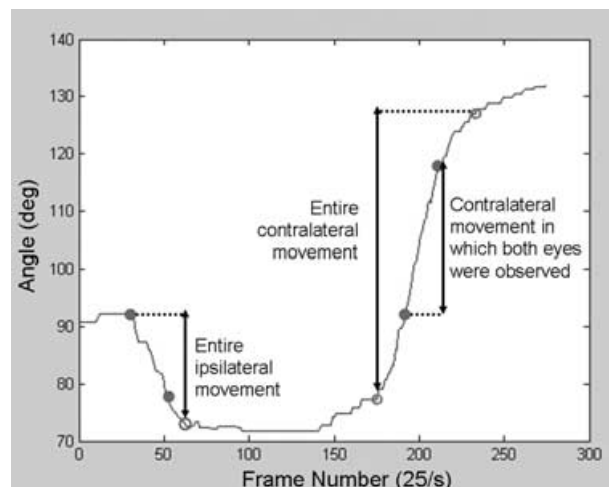


FIG. 2. Tracing displaying the ipsilateral and contralateral head movement over time (25 frames/s) in a patient with temporal lobe epilepsy during a seizure characterized by loss consciousness and manual and oral automatisms (seizure nr. 35). The angle of the head movement was measured at the nostril in relation to a reference point on the thorax 25 times per second, which corresponds to the video time resolution (frames). The seizure later generalized secondarily.

Angular speed of head movement

The movement tracing was inspected and head turning in each direction was identified. The frame numbers at the beginning and end of each head turning (Fig. 2) were noted. These frame numbers were then verified by repeated observation of the video recording. Movement containing artifacts and/or nonfluid in nature (e.g., head extension, rocking of trunk) was identified from the tracing and verified in the video, excluding it from evaluation. The slope of the remaining tracing (as shown in Fig. 2) which depicted head movement in which both eyes could be seen, was used to determine the angular speed.

Statistical analysis

The median, mean and standard deviation were calculated for the desired parameters (Table 2). The angular speed and duration were compared between ipsilateral and contralateral head movements using the Wilcoxon rank sum. A Pearson's product-moment correlation test was performed between the speed and duration in each direction. Differences were considered significant if $p < 0.01$. The PPV was calculated with regard to the ictal EEG and site of TLE in the unilateral TLE patients ($n = 29$). The ictal EEG served as the gold standard for lateralization of a given seizure in the three seizures of the two patients with bilateral TLE (Table 1).

RESULTS

The data of the patients whose ictal videos were included in the study are summarized in Table 1. Fourteen of the 31 included patients were female, the average age

TABLE 1. Patient data including seizure semiology, MRI findings, and surgery outcome

Sz. #	TLE	Age [years] (gender)	Age at onset (years)	MRI findings	Seizure semiology	Ictal EEG	Surgery outcome (Engel et al., 1993)
1	Bilateral	41 (m)	21	nl	Abdominal aura → automotor sz. → GTC sz.	Right temporal	No surgery
2	Right	28 (f)	9	nl	Automotor sz. → GTC sz.	Right temporal	IC
3	Left	39 (m)	5	Post left temporal astrocytoma resection	Aura → automotor sz. → GTC sz.	Left temporal	IC
4	Right	58 (f)	23	nl	Abdominal aura → automotor sz. → GTC sz.	Right temporal	No surgery
5	Left	43 (f)	2	Left mesial temporal sclerosis	Automotor sz. → GTC sz.	Left temporal	ID
6	Left	29 (f)	6	Left mesial temporal sclerosis	Automotor sz. → GTC sz.	Left temporal	IC
7	Right	27 (m)	16	nl	Aura → automotor sz. → GTC sz.	Right temporal	IA
8	Left	34 (m)	1	Bilateral mesial temporal sclerosis	Aura → automotor sz. → GTC sz.	Left temporal	IA
9	Right	42 (m)	21	nl	Abdominal aura → automotor sz. → GTC sz.	Right temporal	IA
10	Right	39 (f)	5	Right mesial temporal sclerosis	Automotor sz. → GTC sz.	Right temporal	IA
11	Right temporal						
12	Bilateral	36 (m)	30	Bilateral parahippocampal edema	Automotor sz. → GTC sz.	Right temporal	No surgery
13					Automotor sz. → GTC sz.	Left temporal	
14	Right	25 (f)	6	Right parahippocampal hamartoma	Automotor sz. → GTC sz.	Right temporal	IB
15	Left	24 (m)	7	Left mesial temporal sclerosis	Aura → automotor sz. → GTC sz.	Left temporal	IA
16	Right	35 (f)	2	Right mesial temporal sclerosis	Aura → automotor sz. → GTC sz.	Right temporal	No surgery
17	Right	34 (m)	30	Right mesial temporal sclerosis	Abdominal aura → automotor sz. → GTC sz.	Right temporal	IB
18	Left	57 (m)	18	Left temporal pole hamartoma	Aura → automotor sz. → GTC sz.	Left temporal	No surgery
19	Right	39 (f)	6	Right mesial temporal sclerosis	Aura → automotor sz. → GTC sz.	Right temporal	IA
20	Left	15 (f)	7	nl	Aura → automotor sz. → GTC sz.	Left temporal	IA
21	Right	27 (m)	20	nl	Automotor sz. → GTC sz.	Right temporal	IIIA
22					Automotor sz. → GTC sz.	Right temporal	
23	Left	42 (m)	29	Left mesial temporal sclerosis	Automotor sz. → GTC sz.	Left temporal	IA
24					Automotor sz. → GTC sz.	Left temporal	
25	Left	10 (m)	1	Left mesial temporal sclerosis	Aura → automotor sz. → GTC sz.	Left temporal	IA
26					Aura → automotor sz. → GTC sz.	Left temporal	
27	Right	52 (m)	21	Right mesial temporal sclerosis	Aura → automotor sz. → GTC sz.	Right temporal	IA
28	Right	21 (m)	4	Right temporoparietal encephalomalacia	Aura → automotor sz. → GTC sz.	Right temporal	IC
29	Right	33 (m)	18	Right amygdala hamartoma	Automotor sz. → GTC sz.	Right temporal	IA
30	Left	11 (f)	3	Left temporal focal cortical dysplasia	Automotor sz. → GTC sz.	Left temporal	IA
31	Right	27 (m)	4	Right mesial temporal sclerosis	Aura → automotor sz. → GTC sz.	Right temporal	IC
32	Left	32 (f)	10	Left mesial temporal sclerosis	Aura → automotor sz. → GTC sz.	Left temporal	IA
33	Left	34 (f)	5	Left mesial temporal sclerosis	Abdominal aura → automotor sz. → GTC sz.	Left temporal	No surgery
34	Right	53 (f)	12	Right mesial temporal sclerosis	Automotor sz. → GTC sz.	Right temporal	IA
35	Left	44 (f)	19	Left mesial temporal sclerosis	Aura → automotor sz. → GTC sz.	Left temporal	IA
36					Aura → automotor sz. → GTC sz.	Left temporal	
37	Right	16 (m)	9	nl	Aura → automotor sz. → GTC sz.	Right temporal	IA
38							

nl = normal; sz. = seizure; GTC = generalized tonic-clonic.

TABLE 2. Movement characteristics of ipsilateral and contralateral head movements

	Angular speed (deg/s)			Duration (s)		
	Ipsilateral	Contralateral		Ipsilateral	Contralateral	
Mean (SD)	15.5 (± 12.1)	17.3 (± 13.0)	n.s.	3.9 (± 3.1)	6.4 (± 4.1)	p < 0.001
Median	13.4	12.3		2.9	5.8	

n.s., no statistical significant difference between ipsilateral and contralateral values.
SD, standard deviation; deg/s, degrees/second.

of the group was 33 ± 12 years and the average duration of epilepsy was 20 ± 11 years. Twenty-nine patients had unilateral TLE and two patients had bilateral TLE (ictal lateralization of head movement direction in each seizure of the latter was defined by the ictal EEG).

Ipsilateral head movement always preceded contralateral head movement. The results of the quantitative analysis of ipsilateral and contralateral head movements are summarized in Table 2. Versive head movement had a 100% high PPV in both directions based on this sequence. Contralateral head movement lasted significantly longer (6.4 ± 4.1 s) than ipsilateral head movement (3.9 ± 3.1 s) ($p < 0.001$), occurring in 32 seizures while 6 seizures presented with a longer ipsilateral movement (Table 2). Ipsilateral and contralateral head movements displayed similar angular speeds (15.5 ± 12.1 deg/s vs. 17.30 ± 13.01 deg/s; Table 2). The angular speeds in both directions correlated to one another. Thus, high angular speed in the ipsilateral direction correlated to a high angular speed in the contralateral direction ($r = 0.595$, $p < 0.001$), likewise for slower speeds (Fig. 3).

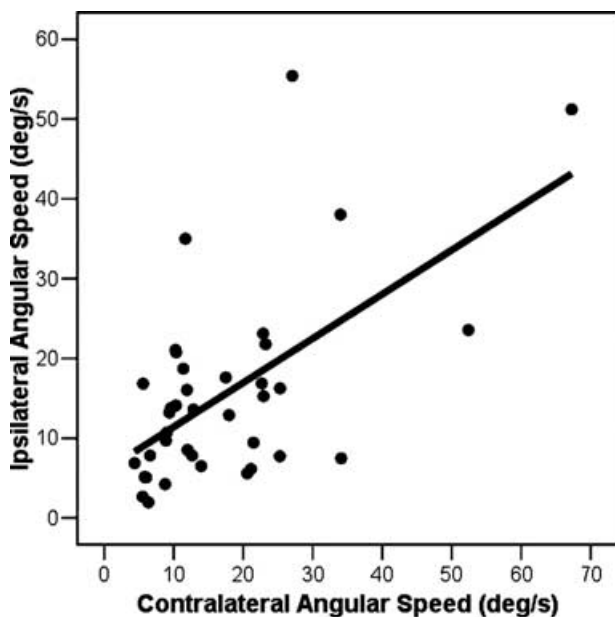


FIG. 3. Scatterplot depicting the significant correlation ($r = 0.595$, $p < 0.001$) between the angular speed (deg/s) of head movement in both the ipsilateral and contralateral directions with regard to the hemisphere of seizure onset.

DISCUSSION

Direction of head movements

This study shows that there are differences in the direction of head movements occurring during seizures in patients with TLE, which is important for the correct lateralization of the seizure onset. In the literature, versive head movements were distinguished from nonversive by qualitative criteria, such as forced, sustained and unnatural contralateral positioning of the head and considered to have a high lateralizing significance (Wyllie et al., 1986a). These contralateral head versions typically occur prior to secondary generalization and thus late in the seizure evolution (Wyllie et al., 1986b). Versive head movements occur significantly earlier in extratemporal than temporal epilepsy patients (Chee et al., 1993). In contrast, nonversive head movement is described as appearing voluntary and “purposeful” in nature and are considered of unreliable lateralizing value (Wyllie et al., 1986a, 1986b; Kernan et al., 1993; Abou Khalil and Fakhoury, 1996). In seizures with secondary generalization, the most common head turning pattern consists of an ipsilateral head turn occurring early in the seizure evolution and before contralateral versive head movement with regard to the hemisphere of seizure onset (Abou Khalil and Fakhoury, 1996). However, other authors found that head movement occurring within the first 10 s of clinical onset was of no lateralizing significance (Kernan et al., 1993). The controversy over the lateralizing significance of head movements may be related to the observation that in many patients in addition to contralateral head version, there is also ipsilateral head turning and no systematic difference has been made as to the sequence of the occurrence and character of the movement (Robillard et al., 1983; Ochs et al., 1984; Chee et al., 1993; Bleasel et al., 1997; Steinhoff et al., 1998). Differences between temporal and extratemporal epilepsy may add to the debate (Robillard et al., 1983; Ochs et al., 1984; Chee et al., 1993; Bleasel et al., 1997; Steinhoff et al., 1998). Our study utilizing a quantitative method of movement analysis shows that ipsilateral head movements followed by contralateral head movements, occurring before secondary generalization have an excellent PPV (100%) for lateralization of the seizure onset.

Quantitative analysis of seizure movements

There is a poor interobserver reliability for versive head movement, although it is more reliable for TLE than for

extra-TLE (Bleasel et al., 1997). To improve interobserver reliability and improve correct lateralization, head movements need to be quantitatively analyzed utilizing an objective method. By studying ictal head movements in both directions with regard seizure evolution certain aspects of head movements could be objectively quantified.

The method used in this study has already been introduced in quantitative movement analysis of seizures (Cunha et al., 2003) and is easily applicable to a typical epilepsy monitoring unit (EMU) environment. The archives of three different epilepsy centers were used without installation of new hardware or further adjustments to the established monitoring setup. There were negligible differences in quantitative results obtained from the three different centers. Careful and constant selection criteria were applied, ensuring that the patient's position during head movements were kept similar in all patients. With the interpretation of movement tracings in conjunction with recorded seizures much additional information about versive head movements can be gained.

It is well known from invasive epilepsy surgery evaluations that electrical stimulation of the frontal eye elicits versive movements of the eyes and head to the opposite side (Godoy et al., 1990). Versive head movements are complex in nature, arising mainly from the contraction of the ipsilateral sternocleidomastoid muscle. Three typical versive head turning patterns have been described: contraversive rotation of face, ipsiversive tilting of the head or a combination of both (Jayakar et al., 1992). Also in this study examination of the movement tracings helped greatly to appreciate these findings but due to two-dimensional constraints they could not be further quantified.

The two-dimensional analysis bears several drawbacks, however. Many seizures were rejected due to the inappropriate positioning of the patient, inappropriate camera angle and head movement that was hidden from camera or which moved largely out of the plane perpendicular to the camera, as such movement could not be accurately measured using two-dimensional geometry. Angular rotational measurements could not be made as another limitation of the two-dimensional movement analysis and angular speed measurements were confined to a defined course in which both eyes could be seen during the head movement (approx. 90°). Future three-dimensional movement analysis could overcome these limitations.

Duration and angular speed of head movements

Our study shows that the duration of contralateral head movement is significantly longer than preceding ipsilateral head movement. Thus, duration of ictal head movement is an additional criterion to serve the correct lateralization of head movements when occurring as a sequence in both directions. Although angular speeds of head movement in either direction were similar for TLE patients, in

the contralateral direction angular speed correlates significantly to the duration of the versive movement. Contralateral versive movements of higher speeds have a shorter duration and slower versive movements have a longer duration, suggesting, with regard to the pathophysiology of the ictal movement, that the rotational distance plays the defining role in the movement and not the speed or duration.

CONCLUSIONS

The sequence of lateral head movement during epileptic seizures characterized by automatisms and secondary generalization in patients with TLE is crucial. Initial ipsilateral movement followed by contralateral head movement has an extremely high lateralizing value (PPV 100%) in TLE. Our study shows that quantitative analysis of seizure movement may help to resolve a controversy based on qualitative criteria. Future studies should utilize three-dimensional technology, allowing further aspects of versive head movement to be quantitatively evaluated.

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REFERENCES

- Abou Khalil B, Fakhoury T. (1996) Significance of head turn sequences in temporal lobe onset seizures. *Epilepsy Research* 23:245–250.
- Arnold S, Berthele A, Drzezga A, Tolle TR, Weis S, Werhahn KJ, Henkel A, Yousry TA, Winkler PA, Bartenstein P, Noachtar S. (2000) Reduction of benzodiazepine receptor binding is related to the seizure onset zone in extratemporal focal cortical dysplasia. *Epilepsia* 41:818–824.
- Bleasel A, Kotagal P, Kankirawatana P, Rybicki L. (1997) Lateralizing value and semiology of ictal limb posturing and version in temporal lobe and extratemporal epilepsy. *Epilepsia* 38:168–174.
- Chee MW, Kotagal P, Van Ness PC, Gragg L, Murphy D, Luders HO. (1993) Lateralizing signs in intractable partial epilepsy: blinded multiple-observer analysis. *Neurology* 43:2519–2525.
- Cunha J, Vollmar C, Li Z, Fernandes J, Feddersen B, Noachtar S. (2003) Movement quantification during epileptic seizures: a new technical contribution to the evaluation of the seizure semiology. In *25th Annual International Conference of the IEEE EMBS*, Cancun, Mexico.
- Engel JJ, Van Ness PC, Rasmussen TB, Ojemann LM. (1993) Outcome with respect to epileptic seizure. In Engel JJ (Ed) *Surgical treatment of the epilepsies*. Raven Press, New York, pp. 609–621.
- Godoy J, Luders H, Dinner DS, Morris HH, Wyllie E. (1990) Versive eye movements elicited by cortical stimulation of the human brain. *Neurology* 40:296–299.
- Jackson G, Berkovic S, Tress B, Kalnins R, Fabinyi G, Bladin P. (1990) Hippocampal sclerosis may be reliably detected by MRI. *Neurology* 40:1869–1875.
- Jayakar P, Duchowny M, Resnick T, Alvarez L. (1992) Ictal head deviation: lateralizing significance of the pattern of head movement. *Neurology* 42:1989–1992.
- Kernan J, Devinsky O, Luciano D, Vazquez B, Perrine K. (1993) Lateralizing significance of head and eye deviation in secondary generalized tonic-clonic seizures. *Neurology* 43:1308–1310.
- Kotagal P, Lüders H, Morris HH, Dinner DS, Wyllie E, Godoy J, Rothner AD. (1989) Dystonic posturing in complex partial seizures of temporal lobe onset: a new lateralizing sign. *Neurology* 39:196–201.

- Laxer KD, and Garcia PA. (1993) Imaging criteria to identify the epileptic focus. Magnetic resonance imaging, magnetic resonance spectroscopy, positron emission tomography scanning, and single photon emission computed tomography. *Neurosurgery Clinics of North America* 4:199–209.
- Li Z, Martins da Silva A, Cunha JP. (2002) Movement quantification in epileptic seizures: a new approach to video-EEG analysis. *IEEE Transactions on Biomedical Engineering* 49:565–573.
- Lüders H, Acharya J, Baumgartner C, Benbadis S, Bleasel A, Burgess R, Dinner DS, Ebner A, Foldvary N, Geller E, Hamer H, Holthausen H, Kotagal P, Morris H, Meencke HJ, Noachtar S, Rosenow F, Sakamoto A, Steinhoff BJ, Tuxhorn I, Wyllie E. (1998) Semiological seizure classification. *Epilepsia* 39:1006–1013.
- Lüders HO, Noachtar S. (2000) *Atlas and classification of electroencephalography*. W.B. Saunders, Philadelphia.
- McLachlan RS. (1987) The significance of head and eye turning in seizures. *Neurology* 37:1617–1619.
- Meier A, Cunha J, Mauerer C, Vollmar C, Noachtar S. (2004) Quantified analysis of wrist and trunk movements differentiates between hypermotor and automotor seizures. *Epilepsia* 45:83–83.
- Newton MR, Berkovic SF, Austin MC, Reutens DC, McKay WJ, Bladin PF. (1992) Dystonia, clinical lateralization, and regional blood flow changes in temporal lobe seizures. *Neurology* 42:371–377.
- Noachtar S, Arnold S, Yousry TA, Bartensfein P, Werhahn KJ, Tatsch K. (1998) Ictal technetium-99m ethyl cysteinate dimer single-photon emission computed tomography findings and propagation of epileptic seizure activity in patients with extratemporal epilepsies. *European Journal of Nuclear Medicine* 25:166–172.
- Noachtar S. (2001) Seizure semiology. In Lüders HO (Ed) *Epilepsy: comprehensive review and case discussions*. Martin Dunitz Publishers, London, pp.127–140.
- Noachtar S. (2004) Video analysis in the definition of the symptomatic zone. In Rosenow F, Lüders HO (Eds) *Pre-surgical assessment of the epilepsies with clinical neurophysiology and functional imaging*. Elsevier, Amsterdam, pp. 187–200.
- Noachtar S, Winkler PA, Lüders HO. (2003) Surgical therapy of epilepsy. In Brandt T, Caplan C, Dichgans J, Kennard C (Eds) *Neurological disorders: course and treatment*. Academic Press, San Diego, pp. 235–244.
- Ochs R, Gloor P, Quesney F, Ives J, Olivier A. (1984) Does head-turning during a seizure have lateralizing or localizing significance? *Neurology* 34:884–890.
- Robillard A, Saint-Hilaire JM, Mercier M, Bouvier G. (1983) The lateralizing and localizing value of aversion in epileptic seizures. *Neurology* 33:1241–1242.
- Rosenow F, Lüders H. (2001) Presurgical evaluation of epilepsy. *Brain* 124:1683–1700.
- Steinhoff BJ, Schindler M, Herrendorf G, Kurth C, Bittermann HJ, Paulus W. (1998) The lateralizing value of ictal clinical symptoms in uniregional temporal lobe epilepsy. 39:72–79.
- Wyllie E, Lüders H, Morris HH, Lesser RP, Dinner DS. (1986a) The lateralizing significance of versive head and eye movements during epileptic seizures. *Neurology* 36:606–611.
- Wyllie E, Lüders H, Morris HH, Lesser RP, Dinner DS, Goldstick L. (1986b) Ipsilateral forced head and eye turning at the end of the generalized tonic-clonic phase of versive seizures. *Neurology* 36:1212–1217.

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Right temporal cerebral dysfunction heralds symptoms of acute mountain sickness

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■ **Abstract** Acute mountain sickness (AMS) can occur during climbs to high altitudes and may seriously disturb the behavioral and intellectual capacities of susceptible subjects. During a Himalayan expedition 32 mountaineers were examined with electroencephalography (EEG) and transcranial doppler sonography (TCD) to assess relative changes of middle cerebral artery velocity in relation to end-expiratory CO₂ (EtCO₂), peripheral saturation (SaO₂), and symptoms of AMS. We tested the hypothesis that O₂ desaturation and EtCO₂ changes precede the development of AMS and result in brain dysfunction and compensatory mechanisms which can be measured by EEG and TCD, respectively. Contrary to our hypothesis, we found that subjects who later developed symptoms of AMS between 3,440 m and 5,050 m altitude exhibited an increase of slow cerebral activity in the right temporal region already at 3,440 m. Cerebral blood flow increased in these mountaineers in the right

middle cerebral artery at 5,050 m. These findings indicate that regional brain dysfunction, which can be documented by EEG, heralds the appearance of clinical symptoms of AMS.

■ **Key words** acute mountain sickness · cerebral blood flow · electroencephalography · high altitude · transcranial doppler sonography

Introduction

Acute mountain sickness (AMS) is characterized by different symptoms that can affect non-acclimatized

travelers shortly after ascending to high altitudes. The most important risk factors for the development of high-altitude illness are rate of ascent, altitude reached (especially the sleeping altitude), and individual susceptibility [3, 8]. Without treatment AMS

Table 1 Differences for non-AMS and AMS mountaineers in measurements at 100 m, 3,440 m, and 5,050 m altitude

Altitude	Lake Louise Score (SD)		SaO ₂ in % (SD)		EtCO ₂ in mmHg (SD)		Mean cerebral blood flow in left MCA in cm/s (SD)		Mean cerebral blood flow in right MCA in cm/s (SD)	
	Non- AMS	AMS	Non- AMS	AMS	Non- AMS	AMS	Non- AMS	AMS	Non- AMS	AMS
100 m	0(0)	0(0)	99(1)	99(1)	32(2)	32(3)	52(15)	59(16)	45(15)	51(12)
3,440 m	1(0,5)	1(0,7)	89(3)	90(3)	31(6)	34(5)	63(12)	63(15)	52(18)	58(20)
5,050 m	0(0,7)	3,5(1,3)	84(3)	86(5)	23(5)	26(3)	42(23)	52(23)	52(13)	71(21)

Summary of the results of the Lake Louise Score, SaO₂, EtCO₂, and TCD findings obtained at each altitude (100 m, 3,440 m and 5,050 m). The Lake Louise Scores refer to differences between the altitudes, i.e., the value at 3,440 m altitude refers to the maximum difference between 100 m and 3,440 m altitude and the value at 5,050 m altitude refers to the difference between 3,440 m and 5,050 m altitude

can evolve into high altitude cerebral edema (HACE), which is defined as a disturbance of consciousness that may progress to deep coma, psychiatric changes of varying degree, confusion, and ataxia of gait [9]. HACE causes significant morbidity and occasionally death in otherwise perfectly healthy persons. There are currently no predictive tests for determining if subjects are prone to develop symptoms of AMS at high altitudes. The aim of our study was to look for predictive markers of AMS before the first symptoms appeared. We tested the hypothesis that O₂ desaturation and EtCO₂ changes precede the development of AMS, which results in brain dysfunction and compensatory mechanisms that can be measured by EEG and TCD, respectively.

Material and methods

Our investigation was conducted during a trek at moderate rates of ascent along a classic and frequently used route in the Khumbu Himal, Nepal. The route began in Lukla (2,860 m) and ended at the Silver Pyramid (5,050 m), which is located near Everest Base Camp. Electroencephalography (EEG) and transcranial doppler sonography (TCD) were always performed the morning after arrival at baseline level (100 m), at Namche Bazaar (3,440 m), and at the Silver Pyramid (5,050 m) by the same investigator. The rates of ascent were as follows: from 2,860 m to 3,440 m in two days and from 3,440 m to 5,050 m in nine days. Peripheral O₂ saturation (SaO₂), end-expiratory CO₂ (EtCO₂), and Lake Louise AMS Score were determined twice daily. All 32 participating mountaineers (mean age: 43.5 years (± 12.2); min-max: 19–66 years; 12 females, 20 males) were neurologically normal. They had no history of neurological or psychiatric disorders, head trauma, or drug abuse. The most recent exposure to high altitude above 2,500 m ended at least 6 months prior to the study.

Digital EEGs (SIGMA Medizintechnik, Thum, Germany) were recorded for 10 min with 24 silver/silver chloride electrodes (<10 kOhms) placed according to the 10–20 system and using a sampling rate of 256 Hz and 16 bit vertical resolution. Data analysis was performed using Fast-Fourier Transformation of 15 \times 4 s artifact-free EEG samples. Constant vigilance during recording was ensured by irregular blinking. TCDs of the middle cerebral artery in 50-mm depths were performed bilaterally using a 2-MHz probe placed over each temporal region (DWL Elektronische Systeme, Sipplingen, Germany). To prevent the well-known interrater vari-

ability in repetitive TCD measurements, all TCD were performed by the same examiner. To obtain the best possible results, the stable signal had to last at least up to one minute before the values were recorded. The study design focused on the assessment of relative changes of the middle cerebral artery velocity. SaO₂ was measured transcutaneously using a clip on the right index finger, and EtCO₂ (Oridion Capnography and Pulsoxymetry Inc., Needham, MA, USA) was measured with a nasal probe. Lake Louise AMS Score was used to quantify symptoms of AMS [14]. This scale has a range of 0 to 29 and includes both self- and external evaluations. Mountaineers with a score ≥ 3 were considered symptomatic. Data were analyzed using SPSS software (release 11.0, SPSS Inc., Chicago IL, USA). Statistical comparisons between symptomatic and asymptomatic mountaineers were made with the Mann-Whitney-U test, between different altitudes in the same group with the Wilcoxon test. The correlation between EtCO₂ and EEG delta activity was calculated with Spearman's correlation coefficient. A p-value of < 0.05 was considered statistically significant. Data are given as mean (\pm SD). Ethics committee approval as well as informed and written consent of all subjects were obtained prior to the study.

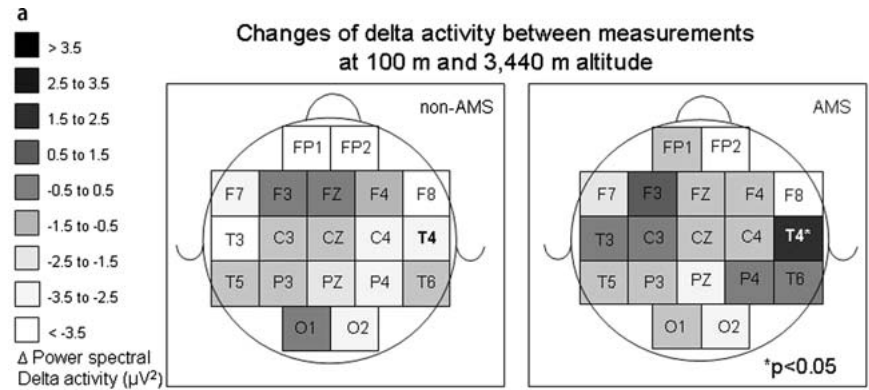
Results

The data of ten mountaineers who developed symptoms of AMS prior to or at 3,440 m altitude (5 subjects), or had excessive artifacts on the EEGs (5 subjects), were not included in the final analysis.

There were no differences in Lake Louise Score between baseline (100 m) and 3,440 m altitude. Twelve of 22 mountaineers developed symptoms of AMS between 3,440 m and 5,050 m altitude, with a mean Lake Louise Score of 3.5 (1.3) compared with 0 (0.7) in the non-AMS group (Table 1). The main AMS symptoms included headache (32%), fatigue/weakness (29%), insomnia (17%), and gastrointestinal symptoms (12%).

Arterial saturation SaO₂ decreased with ascent from sea level to 3440 m altitude: in AMS from 99 (1)% to 89 (3)%, and during further ascent to 5,050 m altitude to 84 (3)% and in non-AMS from 99 (1)% to 90 (3)% and to 86 (5)%. With further ascent from 3,440 to 5050 m altitude, end-expiratory CO₂ fell in AMS from 33 (2) mmHg to 23 (5) mmHg and in non-

Fig. 1 A: This figure shows a significant increase of power spectral delta activity in the right temporal region (electrode T4) at 3,440 m altitude in mountaineers who developed symptoms of AMS at 5,050 m altitude compared with that in non-AMS mountaineers (Mann-Whitney-U test, $p < 0.05$). **B** illustrates the delta power at electrode T4 at baseline (100 m) and at 3,440 m altitude for each individual. Note the interindividual variability



b Right temporal delta activity at 100 m and 3,440 m altitude

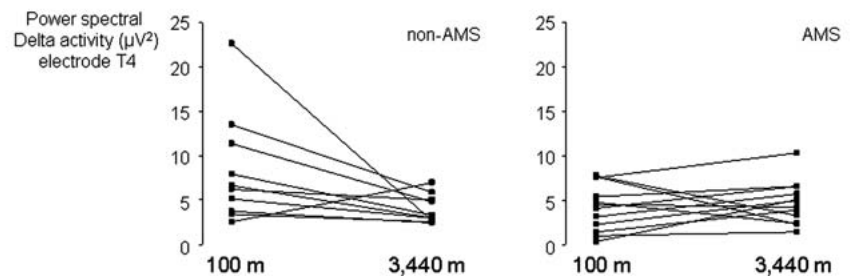
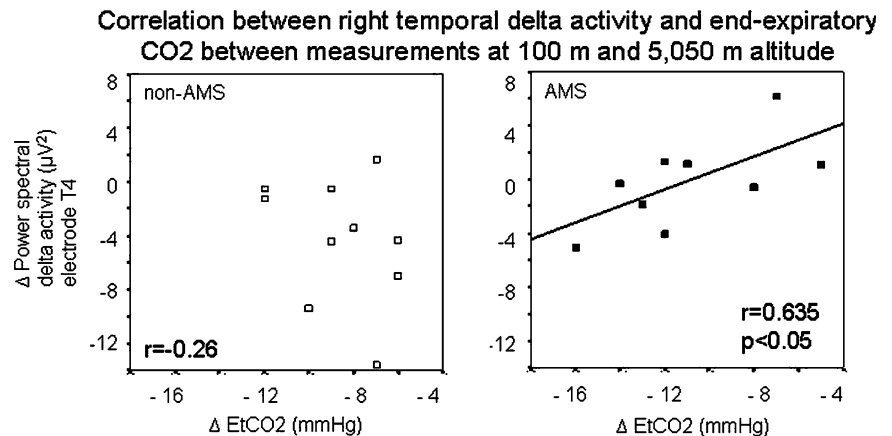


Fig. 2 The EtCO₂ of AMS mountaineers correlated significantly and positively with right temporal delta activity between 100 m to 5,050 m altitude (Spearman's correlation $r = 0.635$, $p < 0.05$) but not in the non-AMS group

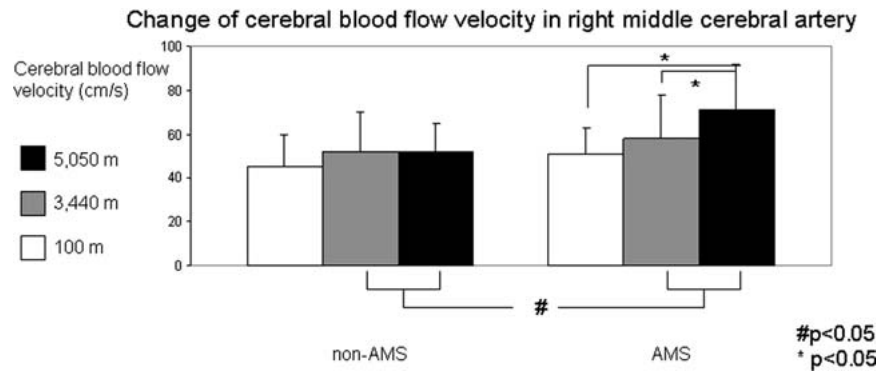


AMS from 33 (2) mmHg to 26(3) mmHg. All changes were significant ($p < 0.05$), according to baseline measurements in each group, but did not differ significantly between AMS and non-AMS mountaineers (Table 1).

All subjects had normal EEG and TCD findings at baseline. There were no differences for all 24 EEG electrodes, and left and right mean cerebral blood flow velocity measurements did not differ between those subjects who developed AMS and those who did not (Table 1). The 12 subjects who developed symptoms of AMS during further ascent at 5,050 m altitude

showed an increase of delta activity in the right temporal region (electrode T4) at 3,440 m altitude compared with measurements at 100 m altitude. In contrast, the ten subjects without AMS showed a decrease of right temporal delta activity [(AMS: non AMS; 1.8 (0.5) μV^2 : -2.9 (-0.9), μV^2 $p < 0.05$)] (Figure 1 A and B). This increase in right temporal delta activity observed in nine AMS subjects who reached 5,050 m (the three other subjects were too ill to continue up to 5,050 m altitude) correlated positively with the decrease of EtCO₂ between measurements at 100 m and 5,050 m altitude (Spearman's

Fig. 3 This figure shows a significant increase of cerebral blood flow velocity in the right middle cerebral artery at 5,050 m altitude in mountaineers who developed symptoms of AMS between 3,440 m and 5,050 m altitude (Wilcoxon test to 100 m $p < 0.05$ and to 3,440 m altitude $p < 0.05$), and as compared to differences in non-AMS mountaineers between 3,440 m and 5,050 m altitude (Mann-Whitney-U-Test $p < 0.05$)



correlation, $r = 0.635$, $p < 0.05$; Figure 2). This suggests that those in the group of AMS-susceptible mountaineers who developed higher EtCO₂ levels due to ineffective hyperventilation exhibited a higher increase of right temporal delta activity.

Cerebral blood flow (CBF) velocity in the right MCA in AMS subjects rose from 51 (12) cm/s at 100 m to 58 (20) at 3,440 m and to 71 (21) at 5,050 m altitude, ($p < 0.05$), while no rise was found on the left in AMS or in non-AMS subjects (Figure 3 and Table 1).

Discussion

Contrary to our hypothesis, the data show for the first time that mountaineers who are affected by AMS exhibit a regional cerebral dysfunction prior to the onset of clinical symptoms of AMS. The increase of delta activity in the non-dominant right temporal lobe preceded the clinical symptoms of AMS. Regional increase of slow delta activity indicates unspecific brain dysfunction. Such EEG changes are typically associated with dysruptions of corticothalamic connections in the white matter, whereas vasogenic edema typically does not cause EEG slowing (delta activity) [12]. This change in cerebral activity could be due to a delayed response to hypoxia, because patients suffering from AMS have a delayed increase of ventilatory response to hypoxia [1]. This might explain why mountaineers with higher EtCO₂ levels in the group who developed symptoms of AMS had higher increases of right temporal delta activity. However, AMS-susceptible subjects seemed to hyperventilate more strongly to compensate for the effects of hypobaric hypoxia when the rate of ascent was moderate, resulting in lower EtCO₂. When this mechanism is exhausted, EtCO₂ increases, resulting in pronounced temporal slow delta activity. Finally, the reduction of oxygen in laboratories at sea level

results in the slowing of delta activity in the EEG, which can be reversed by CO₂-induced hyperventilation [11].

Evidence from animal studies on a cellular level have shown that the hippocampus is especially at risk during hypoxia. This may be transmitted through intracellular Ca⁺⁺ and glutamate increase [6, 7]. Reports of neuropsychological changes during ascent at extreme altitudes underlines the vulnerability of the non-dominant right hemisphere. For instance, the decline of visual long-term memory may reflect a change in right temporal brain function due to hypobaric hypoxia [13]. Transient high-altitude neurological dysfunction such as hallucinations, vestibular disruption, and dressing apraxia may be due to neuronal dysfunction of the right inferior parietal and superior temporal cortex [10]. According to the literature, CBF increases by 20% to 50% 12 to 24 h after arrival at altitudes ranging between 3,475 and 4,559 m [2]. The subsequent rise in cerebral blood flow is a compensating mechanism, which may at least partially restore oxygen delivery to the brain [4]; however, it does not cause AMS [5, 16]. The cerebral vasodilation in hypoxia is still not fully understood, but it seems probable that it is signaled through glia cells connecting neurons to the nearest arteriolar smooth muscle cells. Adenosine, H⁺, K⁺, and NO may serve as vasodilator messengers [15]. The absence of a CBF increase in the healthy mountaineers in our group might have been due to their good acclimatization as a result of a moderate rate of ascent.

In conclusion, an alteration of right temporal brain activity occurs before AMS. It may result from insufficient hyperventilation in mountaineers who are susceptible to develop symptoms of AMS. Our study suggests that EEG-detected regional right temporal cerebral dysfunction may serve as a predictive marker for AMS in mountaineers during high altitude climbing and trekking.

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References

1. Baertsch P, Swenson ER, Paul A, Julg B, Hohenhaus E (2002) Hypoxic ventilatory response, ventilation, gas exchange, and fluid balance in acute mountain sickness. *High Alt Med Biol* 3:361–376
2. Bartsch P, Bailey DM, Berger MM, Knauth M, Baumgartner RW (2004) Acute Mountain Sickness: Controversies and Advances. *High Alt Med Biol* 5:110–124
3. Basnyat B, Murdoch DR (2003) High-altitude illness. *Lancet* 361:1967–1974
4. Baumgartner RW, Spyridopoulos I, Bartsch P, Maggiorini M, Oelz O (1999) Acute mountain sickness is not related to cerebral blood flow: a decompression chamber study. *J Appl Physiol* 86:1578–1582
5. Baumgartner RW, Bartsch P, Maggiorini M, Waber U, Oelz O (1994) Enhanced cerebral blood flow in acute mountain sickness. *Aviat Space Environ Med* 65:726–729
6. Ben-Ari Y (1992) Effects of anoxia and aglycemia on the adult and immature hippocampus. *Biol Neonate* 62:225–230
7. Cervos-Navarro J, Diemer NH (1991) Selective vulnerability in brain hypoxia. *Crit Rev Neurobiol* 6:149–182
8. Hackett PH, Roach RC (2001) High-altitude illness. *N Engl J Med* 345:107–114
9. Hackett PH, Roach RC (2004) High Altitude Cerebral Edema. *High Alt Med Biol* 5:136–146
10. Firth PG, Bolay H (2004) Transient high altitude neurological dysfunction: an origin in the temporoparietal cortex. *High Alt Med Biol* 5:71–75
11. Gibbs FA, Gibbs EL, Lennox WG, Nims LF (1943) The value of carbon dioxide in counteracting the effects of low oxygen. *J Aviat Med* 14:250–261
12. Gloor P, Ball G, Schaul N (1977) Brain lesions that produce delta waves in the EEG. *Neurology* 27:326–333
13. Hornbein TF, Townes BD, Schoene RB, Sutton JR, Houston CS (1989) The cost to the central nervous system of climbing to extremely high altitude. *N Engl J Med* 321:1714–1719
14. Roach RC, Bartsch P, Oelz O, Hackett PH (1993) The Lake Louise acute mountain sickness scoring system. In: Sutton JR, Houston CS, Coates G, (eds) *Hypoxia and molecular medicine*. Charles S. Houston, Burlington, Vt, pp. 272–274
15. Severinghaus JW (2001) Cerebral circulation at altitude. In: Hornbein TF, Schoene RB (eds) *High altitude an exploration of human adaptation*. Marcel Dekker Inc, New York, pp. 343–375
16. Wolff CB (2000) Cerebral blood flow and oxygen delivery at high altitude. *High Alt Med Biol* 1:33–38

Seizures on hearing the alarm clock

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In October, 2006, a 25-year-old trainee graphic designer was referred to us to establish whether her seizures were epileptic or dissociative. For 8 years, she had had seizures triggered by unexpected auditory stimuli, such as the ringing of her telephone or alarm clock. She would become startled and have a “turning feeling in her head”, palpitations, and anxiety. She would then hyperventilate, lose consciousness, and collapse, often with urinary incontinence. These episodes had occurred less frequently when she had avoided stress, not even attending school. However, she was now having seizures, with loss of consciousness, every day. Her electroencephalogram (EEG) and MRI of her head had been normal, as had several electrocardiograms (ECGs). She had no risk factors for epilepsy; she had never received a psychiatric assessment. Nonetheless, she had been diagnosed with complex partial and generalised epilepsy. Trials of antiepileptic drugs (valproic acid, carbamazepine, oxcarbazepine, topiramate, clobazam, and levetiracetam) had been unsuccessful.

During the patient's first night at our EEG-video monitoring unit, she was startled while watching television, and her ECG showed a ventricular ectopic beat that rapidly evolved into torsade de pointes (figure, webvideo). The patient pushed the alarm button before losing consciousness. She started to hyperventilate, then gasp for air; her

EEG showed generalised slowing, then burst suppression. For several seconds, she had a flat trace on the EEG—such as is found in brain death—and was apnoeic, in rapid polymorphic ventricular tachycardia. Her dysrhythmia resolved spontaneously after 165 s, and her breathing, EEG, and level of consciousness subsequently returned to normal. When the patient was at rest, the rate-corrected QT interval on her ECG was 430–480 ms (normal <460 ms). Genetic analysis revealed a hitherto undescribed heterozygous mutation of the *KCNH2* gene (a deletion of two base pairs in exon 6, *c.1275_1276delAC* >*p.Thr425fsX517*) encoding the cardiac potassium channel I_{Kr} , a finding consistent with long-QT syndrome (LQTS). The patient's sister, who had similar, less frequent episodes, and her asymptomatic father are carriers of the mutation. Since starting treatment with metoprolol, potassium, and magnesium, and changing her lifestyle to avoid unexpected noise and excessive stress, the patient has been asymptomatic. After informed discussion, she decided against having an implanted cardioverter-defibrillator, but may be given one in future. She works as a graphic designer, and sleeps early to avoid needing an alarm clock. We avoid contacting her by telephone.

Features widely regarded as typical of epilepsy, like clonic movements, incontinence, and tongue biting, can occur during syncope¹—which can be caused by LQTS. Causes of LQTS include antidysrhythmic, antibiotic, and antipsychotic drugs, electrolyte disturbances, cocaine use, and severe bradycardia.² LQTS can also be congenital, when inheritance is usually autosomal dominant—so there may be a family history of “seizures”. Mutations in at least ten different genes can cause LQTS.³ Mutations either reduce the repolarising potassium current, or increase depolarising sodium or calcium currents. Triggers of dysrhythmia in patients with LQTS include physical exertion, swimming, emotion, auditory stimuli, rest, and sleep; to some extent, people with different mutations are susceptible to different triggers.⁴ We think our patient's gasping for air was caused by adaptation of central oxygen-sensitive neurons to recurrent hypoxia; such an adaptation is found in people who are new to high altitude, or have chronic lung disease.⁵ We suspect this mechanism saved our patient from organ damage.

References

- 1 Lempert T, Bauer M, Schmidt D. Syncope: a videometric analysis of 56 episodes of transient cerebral hypoxia. *Ann Neurol* 1994; **36**: 233–37.
- 2 Khan IA. Clinical and therapeutic aspects of congenital and acquired long QT syndrome. *Am J Med* 2002; **112**: 58–66.
- 3 Lehnart SE, Ackerman MJ, Benson DW, et al. Inherited arrhythmias. *Circulation* 2007; **116**: 2325–45.
- 4 Schwartz PJ, Priori SG, Spazzolini C, et al. Genotype-phenotype correlation in the long-QT syndrome: gene-specific triggers for life-threatening arrhythmias. *Circulation* 2001; **103**: 89–95.
- 5 Neubauer JA, Sunderram J. Oxygen-sensing neurons in the central nervous system. *J Appl Physiol* 2004; **96**: 367–74.

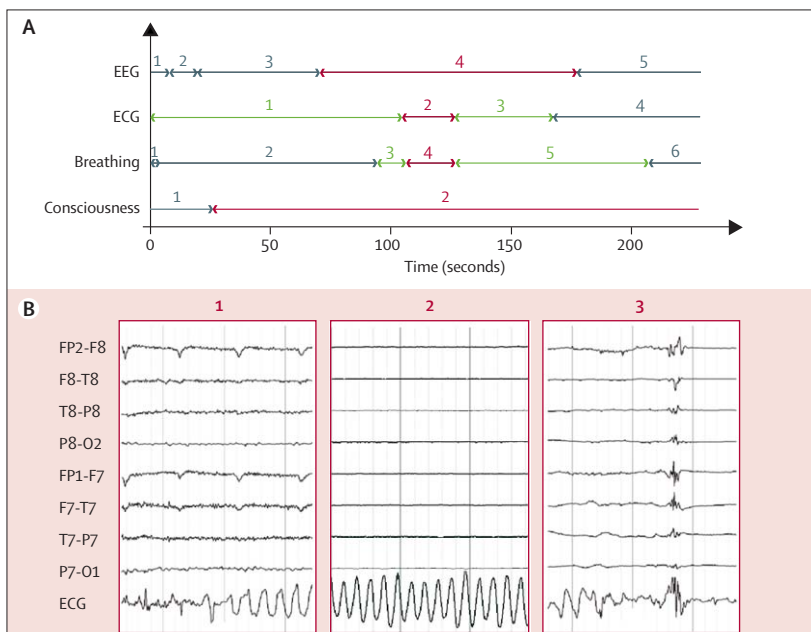


Figure: Hypoxia caused by LQTS

(A) EEG trace showed: (1) α-rhythm, (2) generalised slowing, (3) burst suppression, (4) generalised suppression of brain activity, like that found in brain death, (5) generalised slowing. ECG showed (1) torsade de pointes, (2) ventricular flutter, (3) torsade de pointes, (4) sinus rhythm. Breathing: (1) normal, (2) hyperventilation, (3) gasping, (4) apnoea, (5) gasping, (6) hyperventilation. Consciousness: (1) awake, (2) unconscious. (B) Selections from the EEG and ECG, showing (1) onset of torsade de pointes, (2) ventricular flutter and generalised suppression of brain activity, (3) end of dysrhythmia. The surge in all leads after the end of dysrhythmia is an artifact.

FULL-LENGTH ORIGINAL RESEARCH

Interictal regional polyspikes in noninvasive EEG suggest cortical dysplasia as etiology of focal epilepsies

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SUMMARY

Purpose: To evaluate the clinical significance of interictal regional polyspikes in focal epilepsies secondary to cortical dysplasia.

Methods: We performed a data search for the term “regional polyspikes” in the database of our epilepsy-monitoring unit. Patients with generalized epilepsies including Lennox-Gastaut syndrome were excluded. Regional interictal epileptiform discharges were recorded in 513 patients with noninvasive EEG.

Results: We identified 29 patients with interictal regional polyspikes and focal epilepsies. Another 484 patients showed regional epileptiform discharges other than polyspikes. The etiology of the epilepsy was significantly more frequently cortical dysplasia in the group of patients with regional

polyspikes (35%, 10 of 29 patients) than in the patients with other regional epileptiform discharges (5%, 24 of 484 patients) ($p < 0.01$). The polyspikes were significantly more frequently localized to the extratemporal (72%; $n = 21$) than temporal (28%; $n = 8$) regions ($p < 0.01$). In contrast, regional epileptiform discharges other than polyspikes were significantly more frequently localized to the temporal lobe (75%; $n = 362$) than extratemporal regions (25%; $n = 122$) ($p < 0.01$). Eight of the 10 patients with focal cortical dysplasia had extratemporal polyspikes.

Discussion: Noninvasively recorded regional polyspikes suggest cortical dysplasias as etiology of predominantly extratemporal epilepsies.

KEY WORDS: EEG, Cortical dysplasia, Regional polyspikes, Epilepsy monitoring.

Malformations of cortical development are disorders of cortical formation (proliferation, migration, and differentiation) and are frequently associated with medically refractory epilepsy (Brodtkorb et al., 1998; Hashizume et al., 2000). In selected patients, particularly with focal cortical dysplasia (FCD), resective epilepsy surgery is an option. Results of epilepsy depend on the complete resection of dysplastic cortex (Edwards et al., 2000). Preoperative evaluation includes EEG-video recording, MRI, positron emission tomography (PET) and single photon emission computerized tomography (SPECT) to identify the epileptogenic zone (Rosenow & Luders, 2001). MRI typically underestimates the extent of the pathology, which tends to be larger in histological investigations (Yagishita et al.,

1997; Tassi et al., 2001, 2002). Several authors have indicated that dysplastic cortex has intrinsic epileptogenicity and they have reported this especially with intracranial studies (Palmini et al., 1995; Avoli et al., 1999; Kuruvilla & Flink, 2002). Selected patients, in whom electrocorticography (ECoG) showed polyspikes had also polyspikes in noninvasive EEG recordings (Gambardella et al., 1996).

In the present study, we investigated the frequency of regional interictal polyspikes in noninvasive EEG recordings and identified the relation to FCD in an unselected consecutive sample of patients with different focal epilepsy syndromes who underwent EEG-video monitoring for differential diagnosis of epilepsy and planning of epilepsy surgery.

METHODS

We performed a data search for the term “regional polyspikes” in the database of our epilepsy-monitoring unit

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at the University of Munich between 1994 and 2003. Patients with polyspikes associated with generalized epilepsies including Lennox-Gastaut syndrome were excluded. Regional interictal epileptiform discharges (IEDs) were recorded in 513 patients with noninvasive EEG. The term regional is defined as EEG activity that is limited to a region of the scalp (Noachtar et al., 1999). All patients underwent EEG video monitoring for differential diagnosis or difficult to treat focal epilepsy for planning of epilepsy surgery.

Noninvasive EEG monitoring

All 513 patients underwent between 3 and 14 days of continuous noninvasive EEG-video monitoring with closely spaced surface electrodes using the international 10–10 electrode system with 32–64 channel EEG machines (Vanguard, Cleveland, OH, U.S.A.; XLTEK, Oakville, Ontario, Canada). IEDs were counted in randomly selected EEG periods of 2–10 min samples per hour during wakefulness and sleep. The localizations of all IED were defined and the relative frequency of each focus was calculated for the entire duration of recording. The EEGs were evaluated in daily monitoring conferences and at least two observers agreed on the classification and localization of the EEG findings.

Polyspikes were defined as at least three consecutive spikes with a frequency of at least 10 Hz lasting at least 300 ms. Ictal EEG seizure pattern consisting of polyspikes, which typically lasted more than 4 s were excluded. Thus, we only included regional polyspikes, which were not associated with any ictal clinical change of behavior or sensation.

Imaging studies

All patients underwent cranial MRI evaluation. Each MRI includes axial, coronal, and sagittal planes T₁-weighted, T₂-weighted, proton-weighted and fluid-attenuated inversion recovery (FLAIR) images with a slice thickness of not more than 5 mm. (1.0/1.5 Tesla Impact/Vision/Symphony/Siemens). Additional coronal 3-mm T₁, T₂, and FLAIR images perpendicular to the long axis of the hippocampus were also performed. The acquisition of high-resolution T₁-weighted gradient echo sequence with an in-plane resolution and slice thickness of 1 mm was performed for detection of subtle FCD. FLAIR with 3-mm slice thickness was also performed. Contrast medium was used only if inflammation or tumors was suspected (Vollmar & Noachtar, 2004). Ictal brain perfusion SPECT with a technetium-99m-labeled ethylcysteinate dimer (^{99m}Tc-ECD, Neurolite; BMS Pharma, Brussels, Belgium) and interictal PET with fluorodeoxyglucose (FDG-PET) were performed mainly in selected extratemporal patients. The diagnosis of FCD in this study was based on the MRI results with the exception of one patient (Patient 23, Table 2), in whom histology

of the resected specimen revealed FCD while MRI was normal.

Statistical analysis

Chi-square analysis or Fisher's exact test were used to evaluate the significance of relationship of regional polyspike localization and etiology of epilepsy, assuming significance at $p < 0.05$.

RESULTS

We identified 29 patients with regional polyspikes and focal epilepsies out of 513 patients who underwent noninvasive EEG video monitoring. This comprises 5.7% of the study population ($n = 513$). Another 484 patients showed regional IED other than polyspikes (94.3%) such as spikes, sharp waves, spike-wave complexes (Noachtar et al., 1999). Three of the 29 patients with regional polyspikes showed only polyspikes and did not have any other IEDs. The etiologies of epilepsy of all patients are summarized in Table 1. Table 2 provides all data on the 29 patients with regional polyspikes. The duration of interictal regional polyspikes lasted between 0.5 s and 3 s. Sleep and wake periods had no effect on localization and frequency of the regional polyspikes (Table 2).

Patients with regional polyspikes had significantly more frequently cortical dysplasia (34%, 10 of 29 patients) than the patients with other regional nonpolyspike IEDs (5%, 24 of 484 patients; $p < 0.01$) (Fig. 2). Tumors were more commonly the etiology of epilepsy in patients with nonpolyspike IEDs than in the polyspike group ($n = 3$ of 29 vs. $n = 79$ of 484) (Table 1) ($p < 0.03$). Pure mesial temporal

Table 1. Etiology of epilepsy in patients with regional polyspikes and other regional interictal epileptiform discharges (IEDs)

Etiology	Regional polyspikes $n = 29$ (5.7%)		Other IEDs $n = 484$ (94.3%)		p
	n	(%)	n	(%)	
Unknown	12	(41)	167	(35)	n.s.
Tumor	3	(10)	79	(16)	0.03
Mesial temporal sclerosis	1 ^a	(3)	75	(15)	–
Trauma	–	–	39	(8)	–
Focal cortical dysplasia (FCD)	10	(34)	24	(5)	0.01
Infection	–	–	19	(4)	–
Perinatal lesion	–	–	23	(5)	–
Congenital malformation	–	–	22	(5)	–
Other	4	(14)	36	(7)	–
Total	29	(100)	484	(100)	

The last column shows the statistical significance, with n.s. denoting a not significant result.

^aDual pathology in one patient (mesial temporal sclerosis and ipsilateral frontal FCD); not included in statistical analysis. –, not included in statistical analysis.

Table 2. Data of the 29 patients with FCD^a

Pat.	Age (y), Sex	Age of onset (y)	Localization of the epileptogenic zone	Etiology	MRI	Interictal polyspikes		Other IED		Ictal EEG	Epilepsy surgery outcome class (Engel et al., 1993) ^b
						Localization	%	Localization	%		
1	38 (m)	29	Lt. hemisphere	FCD Lt. hemisphere	FCD Lt. hemisphere	Lt. posterior temporal	20	1. Lt. temporal 2. Rt. temporal	22 58	Rt. frontal	ND
2	22 (f)	14	Rt. temporoparietal	FCD Rt. temporal and temporoparietal	FCD Rt. temporal and temporoparietal	Rt. post. temp.	34	1. Rt. post. temp. 2. Rt. temporal	15 51	1. Rt. post. temp. 2. Rt. central 3. Rt. centroparietal	ND
3	29 (f)	24	Lt. hemisphere	Unknown	Normal	Lt. frontocentral	100	None		Lt. frontocentral	ND
4	33 (m)	19	Lt. frontal	Unknown	Normal	Lt. frontal	13	1. Frontal nonlateralized 2. Lt. frontopolar	57 30	Frontal, nonlateralized	ND
5	42 (m)	34	Rt. frontal	Diffuse gliosis Rt. frontal	Normal	Rt. frontal	3	1. Rt. temporal 2. Rt. frontal	81 16	1. Rt. frontocentral 2. Rt. frontal	1a
6	36 (f)	13	Lt. temporal	Unknown	Normal	Lt. temporooccipital	67	1. Lt. temporooccipital 2. Lt. mesial temporal	27 6	1. Lt. temporal 2. Lt. temporooccipital	ND
7	22 (f)	12	Left paracentral	Unknown	Normal	Lt. central	79	1. Lt. central 2. Rt. central	20 1	1. Lt. central 2. Rt. central 3. Nonlateralized	ND
8	31 (f)	6	Lt. frontal	FCD Lt. frontal	FCD Lt. frontal	Lt. frontal	100	None		Lt. frontal	1a
9	51 (m)	9	Focal	Hypothalamic hamartoma	Hypothalamic hamartoma	1. Lt. temporal 2. Rt. temporal	39 14	1. Lt. temporal 2. Rt. temporal 3. Rt. frontal	38 8 1	Nonlateralized	3
10	9 (f)	6	Rt. parietal	Moderate gliosis Rt. parietal	Normal	Rt. parietal	12	1. Rt. temporal 2. Rt. frontal	67 21	Rt. parietal	3
11	22 (m)	7	Focal	Unknown	Normal	Lt. temporal	8	Lt. temporal	92	Lt. frontal	ND
12	19 (f)	9	Rt. frontal	FCD Rt. frontal	FCD Rt. frontal	Mid central	80	Mid central	20	Mid central	1c
13	22 (m)	1	Bilateral frontal	Calcified lesion Lt. frontocentral	Calcified lesion Lt. frontocentral	Lt. frontocentral	16	1. Lt. frontocentral 2. Rt. frontocentral 3. Lt. temporal	45 29 11	1. Lt. frontocentral 2. Rt. frontocentral	ND
14	30 (m)	11	Focal	Unknown	Normal	Lt. temporo-parietal	75	Lt. temporal	25	Lt. temporal	ND
15	39 (f)	9	Lt. paracentral	Unknown	Normal	Central	100	None		1. Lt. central 2. Nonlateralized	ND
16	39 (f)	11	Focal	Hamartoma Rt. parietal	Hamartoma Rt. parietal	1. Lt. frontal 2. Rt. frontocentral	40 22	1. Lt. frontal 2. Rt. frontocentral	13 25	1. Lt. frontal 2. Rt. frontal 3. Nonlateralized	2
17	34 (f)	8	Rt. frontal	Unknown	Normal	Rt. frontocentral	34	1. Rt. frontocentral 2. Rt. temporo-parietal 3. Lt. temporal 4. Lt. frontal	61 2 1 1	Rt. frontal	ND
18	33 (f)	16	Lt. parietooccipital	FCD Lt. parietooccipital > Rt. parietooccipital	FCD Lt. parietooccipital > Rt. parietooccipital	Rt. temporooccipital	29	1. Rt. temporooccipital 2. Lt. temporal-mesial 3. Rt. temporo-mesial	31 35 5	Rt. temporooccipital	ND

Continued

Table 2. Continued

Pat.	Age (y), Sex	Age of onset (y)	Localization of the epileptogenic zone	Etiology	MRI	Interictal polyspikes		Other IED		Ictal EEG	Epilepsy surgery outcome class (Engel et al., 1993) ^b
						Localization	%	Localization	%		
19	53 (f)	13	Focal	FCD Lt. frontal	FCD Lt. frontal & Lt. hippocampal sclerosis	Lt. frontal	13	1. Rt. temporal mesial 2. Lt. frontal 3. Lt. temporal	49 22 16	1. Rt. frontopolar 2. Lt. frontopolar	ND
20	17 (m)	2	Rt. frontal	FCD Rt. frontal	FCD Rt. frontal	1. Rt. frontal	2	1. Rt. frontal 2. Rt. frontocentral	96 2	Rt. frontal	ND
21	25 (f)	25	Focal	Unknown	Normal	1. Rt. occipital 2. Lt. occipital	13	1. Rt. occipital 2. Lt. occipital 3. Lt. frontal 4. Rt. frontal 5. Lt. temporal 6. Lt. parietal	70 3 2 3 7 2	Lt. temporal	ND
22	20 (m)	13	Focal	Unknown	Normal	Rt. mesial temporal	12	1. Rt. mesial temporal 2. Lt. mesial temporal	59 29	1. Lt. temporal 2. Rt. temp.-occ.	ND
23	32 (m)	17	Rt. frontal	FCD Rt. frontal	Normal	Rt. frontal	72	Rt. frontal	28	1. Rt. frontal 2. Rt. temporal 3. Nonlateralized	2
24	36 (m)	5	Rt. frontal	FCD Rt. mesial frontal	FCD Rt. mesial frontal	Rt. frontal	63	Rt. frontal	37	Rt. frontal	2
25	29 (m)	2	Focal E	Febrile seizures (amygdalo-hippocampectomy) 1983	Status post amygdalo-hippo-campectomy	Rt. parietal	47	1. Rt. parietal 2. Rt. temporal 3. Lt. temporal	49 3 1	1. Rt. frontal 2. Rt. parietal	SUDEP
26	33 (m)	7	Rt. FLE	FCD Rt. frontal	FCD Rt. frontal	Rt. frontal	64	Rt. frontal	36	Rt. frontal	Ia
27	43 (f)	9	Focal E	Cavernoma Lt. frontal and Rt. occipital	Cavernoma Lt. frontal and Rt. occipital	1. Lt. temporal 2. Rt. frontal	28	1. Lt. temporal 2. Rt. frontal 3. Lt. frontal 4. Frontocentral nonlateralized 5. Generalized	39 7 15 4 7	1. Lt. frontocentral 2. Lt. frontal 3. frontocentral nonlateralized 4. Rt. temporal	ND
28	24 (f)	21	Focal E	Unknown	Normal	Rt. frontocentral	40	1. Rt. posterior temporal 2. Rt. frontocentral	47 13	1. Rt. frontal 2. Rt. temporal	ND
29	27 (m)	12	Focal E	Unknown	Normal	Lt. anterior temporal	19	1. Lt. temp.-ant. 2. Lt. posterior temporal 3. Lt. frontopolar 4. Rt. posterior temporal	77 2 1 1	1. Lt. temporal 2. Rt. parietooccipital 3. Lt. parietooccipital	ND

^aValues which are smaller than one have been rounded to one. Lt., left; Rt., right; focal, focal but not further localized; ND, not done; SUDEP, sudden unexpected death in epilepsy.

^bNumbers in this column refer to the Epilepsy Surgery Outcome Classification as proposed by Engel et al., 1993.

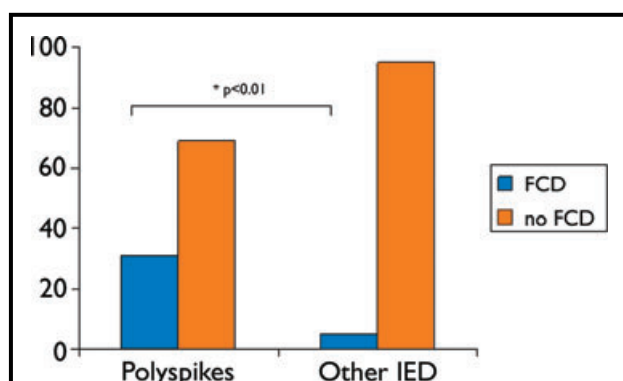


Figure 1.

Focal cortical dysplasia (FCD) is more common in patients with regional polyspikes (10 of 29) than other regional interictal epileptiform discharges (IEDs) (24 of 484).

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sclerosis only occurred in the nonpolyspike IED (Table 1). One patient with frontal polyspikes had a dual pathology with a frontal FCD and an ipsilateral mesial temporal sclerosis (Table 1).

The polyspikes were significantly more frequently localized to extratemporal (72%; $n = 21$) than temporal (28%, $n = 8$) regions ($p < 0.01$) (Table 3). In contrast, regional IEDs other than polyspikes were significantly more frequently localized to the temporal lobes (75%, $n = 362$) than extratemporally (25%, $n = 122$) ($p < 0.01$) (Table 3). Eight of the 10 patients with FCD had extratemporal polyspikes. The localizations of the regional polyspikes and the FCDs were consistent in 9 of 10 patients. In one patient with right frontal FCD the polyspikes were midcentral.

The regional polyspikes had a repetition rate of 10–22 Hz and occurred during wakefulness and sleep in patients with and without FCD. For the purpose of this study, we did not quantify the occurrence of regional polyspikes during sleep or wakefulness. There was no significant difference in the frequency and duration of the regional polyspikes in patients with and without FCD.

DISCUSSION

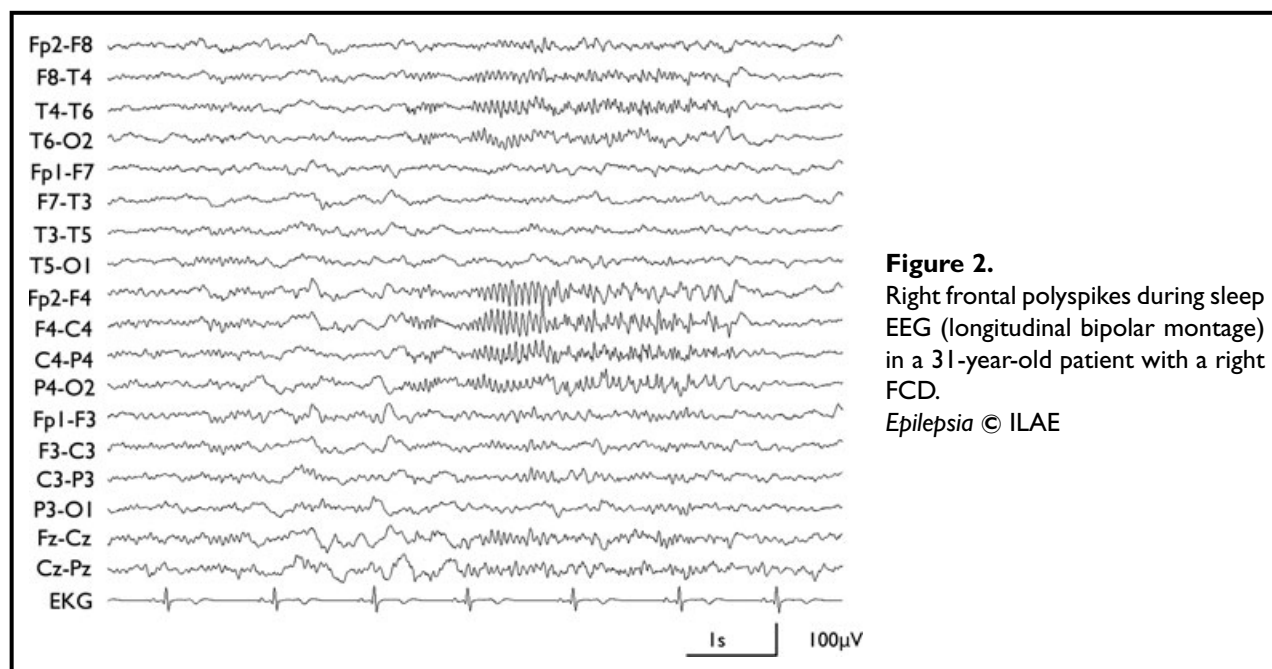
This study shows that scalp-recorded interictal regional polyspikes are more commonly associated with FCD than other epileptiform discharges in epilepsy surgery candidates with poor antiepileptic drug (AED) control. To avoid the selection bias of former studies who primarily look at children with cortical dysplasia (Quirk et al., 1993) or patients who underwent invasive ECoG (Gambardella et al., 1996), we evaluated a series of unselected consecutive patients who all underwent noninvasive EEG-video monitoring. Our patient population was heterogeneous and reflects

Table 3. Frequency of patients with regional polyspikes and other regional interictal epileptiform discharges (IEDs) ($n = 513$) and localization of the IEDs

Localization	Total subjects $n = 513$		Significance
	Regional polyspikes $n = 29$ (5.7%)	Other regional IEDs $n = 484$ (94.3%)	
Temporal	8 (28%)	362 (75%)	$p < 0.01$
Extratemporal	21 (72%)	122 (25%)	$p < 0.01$
Significance	$p < 0.01$	$p < 0.01$	

all patients referred to an epilepsy-monitoring unit for evaluation of possible epilepsy surgery and differential diagnosis of focal epilepsy. Thus, different etiologies of epilepsy are represented.

In invasive recordings (ECoG), FCD was associated with high-frequency spiking (polyspiking), and the prolonged epileptic activity in dysplastic tissue was considered a consequence of impairment of local inhibitory circuits (Palmini et al., 1995). Most common findings were recruiting/derecruiting spikes (48%), high-frequency rhythmic polyspikes (bursting pattern, 30%), and continuous/quasirhythmic rhythmic spiking pattern on intraoperative ECoG recordings (35%). In a retrospective analysis of the surface EEG of these patients, the occurrence of rhythmic epileptiform discharges on the noninvasive EEG and continuous epileptiform discharges on ECoG recordings were compared in patients who underwent resective epilepsy surgery (Gambardella et al., 1996). It was concluded that repetitive spiking/polyspiking was highly specific and a sensitive indicator for focal cortical dysplastic lesions. Autoradiography of surgical specimen of FCD revealed reduced density of GABA-A receptors as visualized preoperatively by flumazenil PET (Arnold et al., 2000). Although continuous spiking was also described in patients with gliosis after traumatic brain injury or brain tumors, it has been suggested that continuous spiking on preresection ECoG can predict the presence of coexisting cortical dysplasia in a high proportion of patients (91%) with a specificity of 96% (Ferrier et al., 2006). These results and our findings support that continuous spiking and regional polyspikes are seen significantly frequent in FCD. However, the specificity of these invasive EEG findings for cortical dysplasia has been questioned by others who found polyspiking in invasive recordings also in other etiologies such as tumors (Rosenow et al., 1998). In electrocorticographic recordings, continuous spiking has been seen in 55% versus 12% of patients with FCD and glioneuronal tumors (GNT), respectively, and the FCDs were more frequently localized extratemporally when compared to GNTs (Ferrier et al., 2006). In concordance with this invasive study, we found that regional extratemporal polyspikes in

**Figure 2.**

Right frontal polyspikes during sleep EEG (longitudinal bipolar montage) in a 31-year-old patient with a right FCD.

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noninvasive EEG are highly associated with cortical dysplasia (80%).

Cortical dysplasias used to be recognized only in the resected tissue during surgical treatment of patients with intractable epilepsy until the development of modern imaging techniques. CT has a low sensitivity for FCD but MRI enabled the recognition and classification of the different types of lesions (Andermann, 2000). High-resolution MRI using special techniques may reveal dysplastic cortex, which was not detected by standard MRI (Hakamada et al., 1979; Quirk et al., 1993; Palmini et al., 1995; Raymond et al., 1995; Raymond & Fish, 1996). However there are medically refractory epilepsy patients with normal MRI (Sisodiya, 2000; Tassi et al., 2002). In some of these patients, postsurgical histological examination helps detecting cortical dysplasia, which was not identified by MRI (Raymond & Fish, 1996; Yagishita et al., 1997; Tassi et al., 2001; Tassi et al., 2002).

Our study shows the diagnostic value of interictal regional polyspikes as a correlate of FCD, which was more significant in extratemporal localizations. We conclude that regional polyspikes, especially in extratemporal location, should lead the clinician to perform advanced MRI studies to detect cortical dysplasia.

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Conflict of interest: We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. The authors report no conflicts of interest.

REFERENCES

- Andermann F. (2000) Cortical dysplasias and epilepsy: a review of the architectonic, clinical, and seizure patterns. *Adv Neurol* 84:479–496.
- Arnold S, Berthele A, Drzezga A, Tolle TR, Weis S, Werhahn KJ, Henkel A, Yousry TA, Winkler PA, Bartenstein P, Noachtar S. (2000) Reduction of benzodiazepine receptor binding is related to the seizure onset zone in extratemporal focal cortical dysplasia. *Epilepsia* 41:818–824.
- Avoli M, Bernasconi A, Mattia D, Oliver A, Hwa GG. (1999) Epileptiform discharges in the human dysplastic neocortex: in vitro physiology and pharmacology. *Ann Neurol* 46:816–826.
- Brodtkorb E, Andersen K, Henriksen O, Myhr G, Skullerud K. (1998) Focal, continuous spikes suggest cortical developmental abnormalities. Clinical, MRI and neuropathological correlates. *Acta Neurol Scand* 98:377–385.
- Edwards JC, Wyllie E, Ruggeri PM, Bingaman W, Luders H, Kotagal P, Dinner DS, Morris HH, Prayson RA, Comair YG. (2000) Seizure outcome after surgery for epilepsy due to malformation of cortical development. *Neurology* 55:1110–1114.
- Ferrier C, Aronica E, Leijten FSS, Spliet WGM, van Huffelen AC, van Rijen PC, Binnie CD. (2006) Electrographic discharge patterns in glioneuronal tumors and focal cortical dysplasia. *Epilepsia* 47:1477–1486.
- Gambardella A, Palmini A, Andermann F, Dubeau F, da Costa JC, Quesney LF, Andermann E, Olivier A. (1996) Usefulness of focal rhythmic discharges on scalp EEG of patients with focal cortical dysplasia and intractable epilepsy. *Electroencephalogr Clin Neurophysiol* 98:243–249.
- Hakamada S, Watanabe K, Hara K, Miyazaki S. (1979) The evolution of electroencephalographic features in lissencephaly syndrome. *Brain Dev* 1:277–283.
- Hashizume K, Kiriya K, Kunimoto M, Maeda T, Tanaka T, Miyamoto A, Miyokawa N, Fukuhara M. (2000) Correlation of EEG, neuroimaging and histopathology in an epilepsy patient with diffuse cortical dysplasia. *Childs Nerv Syst* 16:75–79.
- Kuruvilla A, Flink R. (2002) Focal fast rhythmic epileptiform discharges on scalp EEG in a patient with cortical dysplasia. *Seizure* 11:330–334.
- Noachtar S, Binnie C, Ebersole J, Mauguire F, Sakamoto A, Westmoreland B. (1999) A glossary of terms most commonly used by clinical electroencephalographers and proposal for the report form for the EEG findings. The International Federation of Clinical Neurophysiology. *Electroencephalogr Clin Neurophysiol Suppl* 52:21–41.

- Palmini A, Gambardella A, Andermann F, Dubeau F, da Costa JC, Olivier A, Tampieri D, Gloor P, Quesney F, Andermann E, Paglioli E, Paglioli-Neto E, Coutinho L, Leblanc R, Hyoung-Ihl K. (1995) Intrinsic epileptogenicity of human dysplastic cortex as suggested by corticography and surgical results. *Ann Neurol* 37:476–87.
- Quirk JA, Kendall B, Kingsley DPE, Boyd SG, Pitt MC. (1993) EEG features of cortical dysplasia in children. *Neuropediatrics* 24:193–199.
- Raymond AA, Fish DR, Boyd SG, Smith SJM, Pitt MC, Kendall B. (1995) Cortical dysgenesis: serial EEG findings in children and adults. *Electroencephalogr Clin Neurophysiol* 94:389–397.
- Raymond AA, Fish DR. (1996) EEG features of focal malformations of cortical development. *J Clin Neurophysiol* 13:495–506.
- Rosenow F, Luders HO, Dinner DS, Prayson RA, Mascha E, Wolgast BR, Comair YG, Bennett G. (1998) Histopathological correlates of epileptogenicity as expressed by electrocorticographic spiking and seizure frequency. *Epilepsia* 39:850–856.
- Rosenow F, Luders H. (2001) Presurgical evaluation of epilepsy. *Brain* 124:1683–1700.
- Sisodiya SM. (2000) Surgery for malformations of cortical development causing epilepsy. *Brain* 123:1075–1091.
- Tassi L, Pasquier B, Minotti L, Garbelli R, Kahane P, Benabid AL, Battaglia AL, Munari C, Spreafico R. (2001) Cortical dysplasia: electroclinical, imaging, and neuropathologic study of 13 patients. *Epilepsia* 42:1112–1123.
- Tassi L, Colombo N, Garbelli R, Francione S, Lo RG, Mai R, Cardinale F, Cossu M, Ferrario A, Galli C, Brammerio M, Citterio A, Spreafico R. (2002) Focal cortical dysplasia: neuropathological subtypes, EEG, neuroimaging and surgical outcome. *Brain* 125:1719–1732.
- Vollmar C, Noachtar S. (2004) Neuroimaging in epilepsy. *Turk J Neurol* 10:185–200.
- Yagishita A, Arai N, Maehara T, Shimizu H, Tokumaru AM, Oda M. (1997) Focal cortical dysplasia: appearance on MR images. *Radiology* 203:553–559.