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Effets de la stimulation cérébrale profonde dans l'épilepsie focale motrice

Shivadatta Prabhu

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UNIVERSITÉ DE GRENOBLE

THÈSE

Pour obtenir le grade de

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Présentée par

SHIVADATTA PRABHU

Thèse dirigée par **Stéphan CHABARDES**

préparée au sein de l'**Institut des Neurosciences de Grenoble**
à l'**École Doctorale Ingénierie pour la Santé, la Cognition**

Effets de la stimulation cérébrale profonde dans l'épilepsie focale motrice

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GLOSSARY

Acknowledgements	1
Glossary	2
Figure Glossary	4
Table Glossary	6
Summary	7
Résumé	8
CHAPTER I	12
EPILEPSY	12
1.1 GENERAL INTRODUCTION	12
1.2 SEIZURE AND EPILEPSY	13
1.3 DRUG THERAPY	14
1.4 MOTOR SEIZURES IN HUMANS	17
1.5 PHARMACO RESISTANT EPILEPSY	25
CHAPTER II	31
TREATMENT OF PHARMACO RESISTANT EPILEPSIES	31
2.1 SURGICAL THERAPIES	31
2.2 NEUROSTIMULATION PROCEDURES	39
2.3 NEWER EXPERIMENTAL TECHNIQUES	41
CHAPTER III	45
DEEP BRAIN STIMULATION AND EPILEPSY	45
3.1 INTRODUCTION	45
3.2 RATIONALE IN CHOOSING TARGETS FOR DBS	46
3.3 DBS IN EPILEPSY ANIMAL STUDIES	48
3.4 DBS IN EPILEPSY HUMAN STUDIES	54
CHAPTER IV	63
BASAL GANGLIA AND EPILEPSY	63
4.1 BASAL GANGLIA ANATOMY AND PHYSIOLOGY	63
4.2 CONNECTIVITY AND THE CIRCUITS IN THE BASAL GANGLIA	67
4.3 EVIDENCE OF INVOLVEMENT OF THE BASAL GANGLIA IN EPILEPTIC SEIZURES	72
4.4 EVIDENCE IN HUMAN IMAGING STUDIES	75

CHAPTER V	78
MODEL.....	78
5.1 CHARACTERIZATION OF PENICILLIN-INDUCED FOCAL MOTOR CORTICAL SEIZURES IN PRIMATES.....	78
5.2 MATERIALS AND METHODS.....	79
5.3 RESULTS.....	83
5.4 DISCUSSION	90
5.5 GENERATION OF EPILEPSY BY TETANUS TOXIN IN PRIMATES: TECHNICAL NOTE	92
CHAPTER VI	97
EXPERIMENTAL RESULTS.....	97
6.1 INTRODUCTION	97
6.2 MATERIALS AND METHODS.....	100
6.3 RESULTS.....	112
6.4 RESULT OF PUTAMINAL STIMULATION	123
6.5 RESULT OF HFS STN and LFS PUTAMEN STIMULATION.....	127
6.6 DISCUSSION	129
6. 7 LIMITATIONS OF STUDY.....	138
6.8 CONCLUSION AND GLOBAL PERSPECTIVES	139
ANNEXES I CLASSIFICATION OF SEIZURES AND EPILEPSIES	140
ANNEXES II PUBLICATIONS.....	140
BIBLIOGRAPHY	148

FIGURE GLOSSARY

FIGURE 1: THE BALANCE BETWEEN EXCITATORY AND INHIBITORY EVENTS AT SYNAPTIC LEVEL.....	12
FIGURE 2: THE ANNUAL INCIDENCE OF EPILEPSY AND AGE RELATED VARIATION. (HAUSER ET AL 1991)	13
FIGURE 3: EPILEPTOGENESIS.....	14
FIGURE 4: SITES OF ACTION OF ANTI EPILEPTIC DRUGS (AED)	15
FIGURE 5 : THE SCHEMATIC REPRESENTATION OF ORIGIN OF MOTOR SEIZURES.	17
FIGURE 6 : ALGORITHM FOR DETERMINING A PHARMACO RESISTANT EPILEPSY.....	25
FIGURE 7 : RESPONSE TO ANTI EPILEPTIC THERAPY (REPRODUCED FROM KWAN BRODIE 2000)	26
FIGURE 8 : MOLECULAR HYPOTHESIS OF PHARMACO RESISTANCE (REMY S. AND BECK H. BRAIN 2006)	28
FIGURE 9 : THE FACTORS OPERATING BEHIND SUDEP	30
FIGURE 10 : THE STEPS FOLLOWED DURING PRE SURGICAL EVALUATION OF A CANDIDATE FOR EPILEPSY SURGERY	32
FIGURE 11 : VAGUS NERVE STIMULATION	39
FIGURE 12 : BRAIN CONNECTIVITY.....	45
FIGURE 13 : FUNCTIONAL ANATOMY OF STN (BENARROCH, 2008).....	47
FIGURE 14 : SCHEMATIC CORONAL SECTION OF HUMAN BRAIN.....	63
FIGURE 15 : CONNECTIVITY AND CIRCUITS IN BASAL GANGLIA.	67
FIGURE 16 : SCHEMATIC REPRESENTATION OF INFORMATION PROCESSING IN BASAL GANGLIA	68
FIGURE 17 : BASAL GANGLIA CIRCUITS SHOWING POSSIBLE LOCATIONS IMPLICATED IN EPILEPSY	72
FIGURE 18 : SCHEMATIC REPRESENTATION OF LOCATION OF ELECTRODES FOR ECoG AND CANULAE FOR INJECTION	80
FIGURE 19 : CORONAL SECTIONS OF BRAINS OF MONKEY	82
FIGURE 20 : INTERICTAL SPIKES AND BEGINNING OF A SEIZURE	83
FIGURE 21 : FOCAL MOTOR SEIZURE	84
FIGURE 22 : THE END OF A SEIZURE.	84
FIGURE 23: TIME FREQUENCY ANALYSIS OF FOCAL MOTOR SEIZURE	85
FIGURE 24 : EVOLUTION OF INTERICTAL SPIKES	86
FIGURE 25 : DURATION OF MOTOR SEIZURE IN MONKEY A	87
FIGURE 26 : DURATION OF MOTOR SEIZURE IN MONKEY B	88
FIGURE 27 : INTERSUBJECT VARIABILITY BETWEEN MONKEY A AND B	88
FIGURE 28: EFFECT OF DIAZEPAM ON MOTOR SEIZURES	89
FIGURE 29 : EFFECT OF DIAZEPAM ON INTERICTAL SPIKES	90
FIGURE 30 : TETANUS TOXIN MODEL: PREDOMINANT SPIKES.....	95
FIGURE 31 : TETANUS TOXIN MODEL: PREDOMINANTLY POLYSPIKES.....	95
FIGURE 32 : TETANUS TOXIN MODEL: SPIKES FOLLOWED BY SEIZURES.....	95
FIGURE 33 : TETANUS TOXIN MODEL: A SEIZURE.	96
FIGURE 34 : CHANGES IN MEAN FIRING RATE DURING MOTOR SEIZURE	98
FIGURE 35 : CHANGES OSCILLATORY PATTERN DURING MOTOR SEIZURE	98
FIGURE 36 : FIRING ACTIVITY OF ONE STN NEURON	99
FIGURE 37: FIRING ACTIVITY OF ONE PUTAMEN NEURON	99
FIGURE 38 : TARGETING STN	102
FIGURE 39 : TARGETING STN	102
FIGURE 40 : NEURONAL FIRING PATTERNS DURING TARGETING STN	103
FIGURE 41: SERIAL STEPS FOLLOWED IN IMPLANTATION SURGERY	105
FIGURE 42: TARGETING PUTAMEN.	106
FIGURE 43: TARGETING PUTAMEN.	106
FIGURE 44 : TARGETING STN AND PUTAMEN.....	107
FIGURE 45 : STIMULATION PROTOCOLS	109
FIGURE 46 : ECoG RECORDS DURING STN STIMULATION (CONTROL EXPERIMENT)	110
FIGURE 47 : RECORDS DURING STN STIMULATION (STIMULATION EXPERIMENT)	110
FIGURE 49 : CONFIRMATION OF IMPLANTED DEPTH ELECTRODES	112
FIGURE 50 : CONFIRMATION OF IMPLANTED DEPTH ELECTRODES	112
FIGURE 51 : CONFIRMATION OF IMPLANTED DEPTH ELECTRODES	113
FIGURE 52 : EFFECT OF DBS STN ON NUMBER OF SEIZURES IN SPECIMEN 1	114
FIGURE 53 : EFFECT OF DBS STN ON NUMBER OF SEIZURES IN SPECIMEN 2	115
FIGURE 54 : EFFECT OF DBS STN ON NUMBER OF SEIZURES SPECIMEN 3.....	115
FIGURE 55 : EFFECT OF DBS STN ON TOTAL DURATION OF SEIZURES IN SPECIMEN 1	116
FIGURE 56: EFFECT OF DBS STN ON TOTAL DURATION OF SEIZURES IN SPECIMEN 2	117

FIGURE 57: EFFECT OF DBS STN ON TOTAL DURATION OF SEIZURES IN SPECIMEN 3.....	117
FIGURE 58 : EFFECT OF DBS STN ON AVERAGE DURATION OF SEIZURES IN SPECIMEN 1.....	118
FIGURE 59 : EFFECT OF DBS STN ON AVERAGE DURATION OF SEIZURES IN SPECIMEN 2.....	119
FIGURE 60 : EFFECT OF DBS STN ON AVERAGE DURATION OF SEIZURES IN SPECIMEN 3.....	119
FIGURE 61 : EFFECT OF DBS STN ON NUMBER OF INTERICTAL SPIKES IN SPECIMEN 1.....	120
FIGURE 62 : EFFECT OF DBS STN ON NUMBER OF INTERICTAL SPIKES IN SPECIMEN 2.....	120
FIGURE 63 : EFFECT OF DBS STN ON NUMBER OF INTERICTAL SPIKES IN SPECIMEN 3.....	121
FIGURE 64 : EFFECT OF PREVENTIVE STN DBS ON TOTAL DURATION OF SEIZURES.....	122
FIGURE 65: EFFECT OF PREVENTIVE STN DBS ON AVERAGE DURATION OF SEIZURES.....	122
FIGURE 66: EFFECT ON NUMBER OF SEIZURES LFS PUTAMEN STIMULATION IN SPECIMEN 1.....	124
FIGURE 67: EFFECT ON NUMBER OF SEIZURES LFS PUTAMEN STIMULATION IN SPECIMEN 4.....	124
FIGURE 68: EFFECT ON TOTAL DURATION OF SEIZURES LFS PUTAMEN STIMULATION IN SPECIMEN 1.....	125
FIGURE 69: EFFECT ON TOTAL DURATION OF SEIZURES LFS PUTAMEN STIMULATION IN SPECIMEN 4.....	126
FIGURE 70: EFFECT ON AVERAGE DURATION OF SEIZURES LFS PUTAMEN STIMULATION IN SPECIMEN 1.....	126
FIGURE 71: EFFECT ON AVERAGE DURATION OF SEIZURES LFS PUTAMEN STIMULATION IN SPECIMEN 4.....	127
FIGURE 72 : EFFECT ON NUMBER OF SEIZURES IN SIMULTANEOUS STN + PUTAMEN STIMULATION.....	128
FIGURE 73 : EFFECT ON TOTAL DURATION OF SEIZURES IN SIMULTANEOUS STN +PUTAMEN STIMULATION.....	128
FIGURE 74 : EFFECT ON AVERAGE DURATION OF SEIZURES IN SIMULTANEOUS STN +PUTAMEN STIMULATION.....	129
FIGURE 75 : THE CORTICO BASAL GANGLIONIC CIRCUITS IMPLICATED DURING FOCAL MOTOR SEIZURES IN PRIMATE (MODIFIED FROM NAMBU ET AL 2002).....	131

TABLE GLOSSARY

TABLE 1: COMMONLY USED AED	15
TABLE 2 : DRUG THERAPY FOR COMMON SEIZURE TYPES.....	16
TABLE 3 : CLASSIFICATION OF EPC	19
TABLE 4 : DESCRIPTION OF MALFORMATION OF CORTICAL DEVELOPMENT.....	23
TABLE 5 : THE WHITE MATTER ZONES SACRIFICED HEMISPHERECTOMY	34
TABLE 6 : SEIZURE OUTCOME IN HEMISPHERECTOMY (DE RIBAUPIERRE, DELALANDE, 2008).....	35
TABLE 7 : LONG TERM OUTCOME AFTER CALLOSOTOMY (TANRIVERDI ET AL., 2009).....	36
TABLE 8 : EFFICACY OF VAGUS NERVE STIMULATION FOR CONTROL OF SEIZURES (CONNOR ET AL., 2012).....	41
TABLE 9 : PARAMETERS OF TMS AND EFFECT (THEODORE, 2003)	42
TABLE 10 : EFFICACY OF TMS FOR CONTROL OF SEIZURE (KIMISKIDIS, 2010).....	43
TABLE 11 : ANIMAL STUDIES OF STN STIMULATION FOR EPILEPSY.....	48
TABLE 12 : ANIMAL STUDIES OF SNr STIMULATION FOR EPILEPSY	49
TABLE 13 : ANIMAL STUDIES OF CAUDATE STIMULATION FOR EPILEPSY.....	50
TABLE 14 : ANIMAL STUDIES OF RETICULAR NUCLEUS STIMULATION FOR EPILEPSY	51
TABLE 15 : ANIMAL STUDIES OF RETICULAR NUCLEUS STIMULATION FOR EPILEPSY	51
TABLE 16 : ANIMAL STUDIES OF CEREBELLAR STIMULATION FOR EPILEPSY.....	52
TABLE 17 : ANIMAL STUDIES OF HIPPOCAMPUS - AMYGDALA STIMULATION FOR EPILEPSY	52
TABLE 18 : ANIMAL STUDIES OF STIMULATION OF OTHER TARGETS FOR EPILEPSY	54
TABLE 19 : ANIMAL STUDIES OF NUCLEUS OF TRACTUS SOLITARIUS STIMULATION	54
TABLE 20 : HUMAN STUDIES OF STN STIMULATION FOR EPILEPSY.....	54
TABLE 20 : HUMAN STUDIES OF STN STIMULATION FOR EPILEPSY.....	55
TABLE 21 : HUMAN STUDIES OF ANTERIOR NUCLEUS STIMULATION FOR EPILEPSY	55
TABLE 21 : HUMAN STUDIES OF ANTERIOR NUCLEUS STIMULATION FOR EPILEPSY.....	56
TABLE 22 : HUMAN STUDIES OF CENTRO MEDIAN NUCLEUS STIMULATION FOR EPILEPSY	57
TABLE 23 : HUMAN STUDIES OF CEREBELLAR STIMULATION FOR EPILEPSY.....	57
TABLE 23 : HUMAN STUDIES OF CEREBELLAR STIMULATION FOR EPILEPSY.....	58
TABLE 24 : HUMAN STUDIES OF HIPPOCAMPUS - AMYGDALA STIMULATION FOR EPILEPSY	59
TABLE 24 : HUMAN STUDIES OF HIPPOCAMPUS - AMYGDALA STIMULATION FOR EPILEPSY	60
TABLE 25 : HUMAN STUDIES OF STIMULATION OF OTHER TARGETS FOR EPILEPSY	61
TABLE 26 : ANIMALS EPILEPSY INDUCED WITH TETANUS TOXIN	93
TABLE 27 : DOSE OF TETANUS TOXIN	94
TABLE 28 : RESULTS OF TETANOS TOXIN EXPERIMENTS	96
TABLE 29 : STIMULATION PARAMETERS	108
TABLE 30 : SUMMARY OF SEIZURES IN STN EXPERIMENTS.....	113
TABLE 31 : REDUCTION IN NUMBER OF SEIZURES DURING STN STIMULATION	114
TABLE 32 : REDUCTION IN TOTAL DURATION OF SEIZURES DURING STN STIMULATION	116
TABLE 33 : REDUCTION IN AVERAGE DURATION OF SEIZURES DURING STN STIMULATION	118
TABLE 34 : SUMMARY OF SEIZURES IN PUTAMEN STIMULATION	123
TABLE 35 : REDUCTION IN TOTAL DURATION OF SEIZURES DURING PUTAMEN STIMULATION.	125

SUMMARY

Epileptic seizures arise from pathological synchronization of neuronal ensemble. Seizures originating from primary motor cortex are often pharmacoresistant, and many times unsuitable for respective surgery because of location of epileptic focus in eloquent area. Basal ganglia play important role in seizure propagation. Micro electrode recordings performed during previous studies indicated that input structures of basal ganglia such as GPe, Putamen and Subthalamic nucleus (STN) are strongly modified during seizures. For example the mean firing rate of neurons of the STN and Putamen increased and the percentage of oscillatory neurons synchronized with the ictal EEG was higher during seizures as compared to interictal periods. Pilot studies in humans have shown the possible beneficial effect of chronic DBS applied to STN in treatment of pharmacoresistant motor seizures. Our study was aimed at studying the therapeutic effect of electrical stimulation of input structures of basal ganglia.

We first developed a stable, predictable primate model of focal motor epilepsy by intracortical injection of penicillin and we documented its pharmacoresistance. We then stereotactically implanted DBS electrodes in the STN and Putamen. The stimulator was embedded at the back of the animals. Subthreshold electrical stimulations at 130 Hz were applied to STN. Stimulator was turned ON when penicillin was injected. Sham stimulation at 0 volt was used as a control situation, each monkey being its own control. The time course, number and duration of seizures occurring in each epochs of 1 h were compared during ON and sham stimulation periods. Each experimental session lasted upto 6 hours, we also studied preventive high frequency stimulation of STN and subthreshold low frequency stimulation of Putamen with 5 Hz and 20 Hz in the same model. Finally we studied combined effects of high frequency STN and low frequency Putamen stimulation in one monkey

Results: Data was analysed from 1572 seizures in 30 experiments in three monkeys for chronic STN stimulation, 454 seizures in 10 experiments in one monkey during preventive STN stimulation, 289 seizures from 14 experiments in two monkeys during LFS putamen stimulation and 477 seizures from 10 sessions during combined STN and Putamen stimulation in one monkey.

The best results were observed during chronic STN stimulation. The occurrence of first seizure was significantly delayed as compared to sham situation. Total time spent in focal seizures was significantly reduced by $\geq 69\%$ on an average ($p \leq 0.05$) after STN stimulation, due to a significant decrease in the number of seizures especially so during the first 3 hours after stimulation. The duration of individual seizures reduced moderately. Bipolar and monopolar stimulation modes were equally effective Preventive HFS STN (in one specimen) was not found to be superior to acute stimulation. LFS Putamen alone was effective but mainly in first two hours of stimulation. In a combined HFS STN and LFS Putamen stimulation the effect of stimulation in terms of seizure control was modest and poor compared to HFS STN alone or LFS Putamen alone.

This study provides original data in primates showing the potential therapeutic effect of chronic HFS-STN DBS to treat focal motor seizures. A discussion explaining these results and comparison with STN DBS in human motor seizures as well as future translational perspective in human therapeutics is provided.

RESUME

Les crises d'épilepsie proviennent d'une synchronisation pathologique de réseaux neuronaux du cortex. Les crises motrices, générées à partir du cortex moteur primaire, sont souvent pharmaco-résistantes. La résection neurochirurgicale du foyer épileptique est rarement l'option thérapeutique de choix au regard des risques de déficits moteurs potentiellement induits par la résection. Les ganglions de la base ont un rôle important dans la propagation des crises. Des enregistrements par micro-électrode réalisés dans une précédente étude ont montré que les activités des structures d'entrée des ganglions de la base telles que le Putamen, le noyau caudé et le noyau sous-thalamique (NST) sont fortement modifiées pendant des crises motrices.

Par exemple, le taux de décharge moyen des neurones du NST et du Putamen augmente et le pourcentage de neurones oscillants synchronisés avec l'EEG durant la période ictale est plus élevé durant les crises que pendant la période inter-ictale. Des études pilotes chez l'humain ont montré un effet bénéfique potentiel de la stimulation cérébrale profonde (SCP) chronique du NST pour traiter les crises motrices pharmaco-résistantes. Le but de notre étude est d'évaluer les effets thérapeutiques de la SCP des structures d'entrée des ganglions de la base.

Nous avons dans un premier temps développé un modèle primate de crise d'épilepsie motrice focale stable et reproductible par injection intra-corticale de pénicilline. Nous avons ensuite caractérisé la pharmaco-résistance du modèle. Nous avons implanté stéréotactiquement des électrodes de SCP dans le NST et le Putamen. Le stimulateur a été placé sous la peau dans le dos de l'animal. Un protocole de stimulation à 130 Hz à un voltage inférieur à l'apparition d'effets secondaires a été réalisé dans le NST. Le stimulateur était mis en marche au moment de l'injection de la pénicilline. Un protocole de stimulation à 0 volt a été réalisé comme condition contrôle. Chaque primate étant son propre contrôle. L'apparition des crises, leur nombre et leur durée ont été comparés par période de 1 heure entre la condition stimulée et non stimulée. Chaque session expérimentale a été menée sur une durée de plus de six heures. Nous avons évalué l'effet préventif de la SCP à haute fréquence (130 Hz) du NST sur les crises motrices. Nous avons également étudié l'effet préventif de la SCP à basse fréquence (5-20 Hz) du Putamen sur ce même modèle. Enfin, sur un autre primate, nous avons étudié l'effet combiné de la SCP du NST à haute fréquence et du Putamen à basse fréquence sur les crises motrices.

Résultats :

Les effets de la SCP chronique du NST à haute fréquence ont été analysés à partir de 1572 crises apparues au cours de 30 sessions expérimentales chez 3 primates. Les effets de la SCP préventive du NST ont été évalués sur 454 crises motrices durant 10 sessions expérimentales chez un primate. L'effet de la SCP du Putamen à basse fréquence a été analysé sur 289 crises durant 14 sessions chez 2 primates. Enfin l'effet combiné de la SCP du NST et du Putamen a été évalué sur 477 crises durant 10 sessions. Les meilleurs résultats ont été obtenus par SCP chronique du NST. L'apparition de la première crise était significativement retardée lorsque le primate était stimulé. Le temps total passé en situation de crise motrice était diminué en moyenne d'environ 69 % ($p \leq 0.05$) par rapport à la condition non-stimulé au regard de la diminution significative du nombre de crises particulièrement durant les 3 heures après le début de la stimulation. La durée de chaque crise était modérément réduite. Les modes de stimulation mono-polaire ou bi-polaire avaient une efficacité similaire. La SCP préventive du NST n'a pas eu d'effet supérieur à la stimulation chronique du NST. La SCP chronique du Putamen à basse fréquence avait un effet positif mais principalement durant les deux premières heures de stimulation. L'effet combiné de la SCP du NST et du Putamen était inférieur à la SCP chronique du NST ou du Putamen.

Cette étude montre pour la première fois chez le primate des effets thérapeutiques de la SCP chronique du NST à haute fréquence pour traiter les crises focales motrices. Les résultats obtenus dans cette étude sont discutés au regard de la physiopathologie des ganglions de la base et des hypothèses concernant l'excitabilité et le métabolisme cortical durant les crises d'épilepsie. Finalement, nous discutons nos résultats au regard des résultats préliminaires obtenus chez l'humain. Nous envisageons enfin les perspectives apportées par cette étude pour le développement de stratégies thérapeutiques par SCP chez l'humain pour traiter les épilepsies motrices.

GLOSSARY

AED Anti epileptic drug
ANT Anterior nucleus of thalamus
AVM Arterio venous malformations
BG Basal ganglia
CCM Cavernous malformations
CMT Centromedian nucleus of the thalamus
DBS Deep brain stimulation
DMAZ Dorsal midbrain anticonvulsant zone
ECoG Electrocorticogram
EEG Electroencephalogram
EPC Epilepsia partialis continua
fMRI Functional magnetic resonance imaging
GABA Gamma-aminobutyric acid
GAERS Genetic Absence Epilepsy Rat (from Strasbourg)
GPe Globus pallidus externa
GPi Globus pallidus interna
IGE Idiopathic generalized epilepsy
MCD Malformations of the cortical development
MPTP 1 - méthyle 4 - phényl 1, 2, 3, 6-tétrahydro pyridine
MRI Magnetic resonance imaging
MST Multiple subpial transection
MTLE Mesial temporal lobe epilepsy
NMDA N-methyl-D-aspartate
PET Positron emission tomogram
PUT Putamen
QQL Quality of life
RE Rasmussen's encephalitis
SN Substantia nigra
SNr Substantia nigra pars reticulata
SNc Substantia nigra pars compacta
SPECT Single-photon emission computed tomography
STN Subthalamic nucleus
SUDEP Sudden unexplained death in epilepsy
SVD Spike and wave discharge
TMS Repetitive transcranial magnetic stimulation

CHAPTER I

EPILEPSY

1.1 GENERAL INTRODUCTION

A seizure (from the Latin *scire* to take possession of) is the clinical manifestation of an abnormal, excessive, hypersynchronous discharge of a population of cortical neurons.

Epilepsy is a disorder of the central nervous system characterized by recurrent seizures unprovoked by an acute systemic or neurologic insult. Epileptogenesis is the sequence of events that turns a normal neuronal network into a hyperexcitable network.

Epilepsy represents an imbalance between excitatory and inhibitory membrane properties at synaptic level.

The following figure schematically illustrates this:

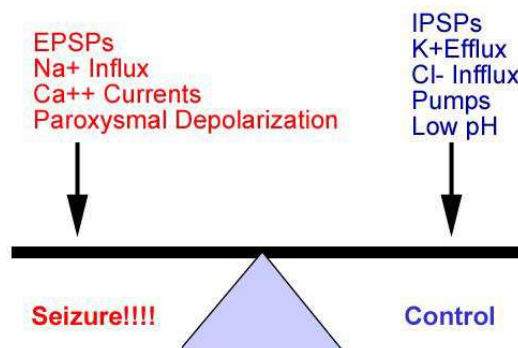


Figure 1: The balance between excitatory and Inhibitory events at synaptic level.

A hyperexcitable state can result from increased excitatory synaptic neurotransmission, decreased inhibitory neurotransmission, an alteration in voltage-gated ion channels, or an alteration of intra or extra-cellular ion concentrations in favor of membrane depolarization. A hyperexcitable state can also result when several synchronous subthreshold excitatory stimuli occur, allowing their temporal summation in the post synaptic neurons.

Epidemiology:

Epilepsy is the second most common neurological disease, the first being cerebrovascular accidents. Incidence of epilepsy is 5-7 per 10,000 persons per year.

This varies with the age,

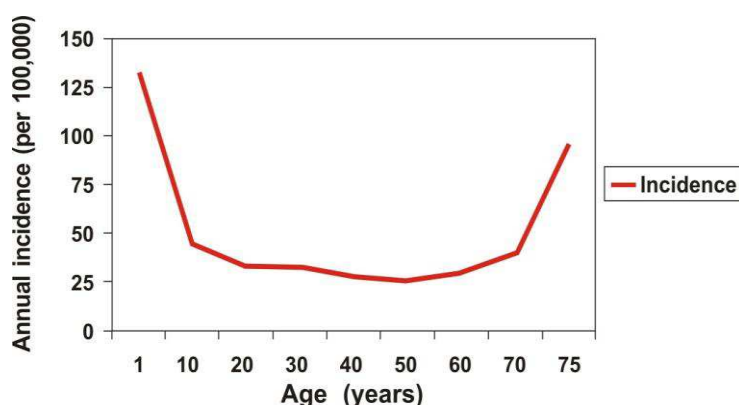


Figure 2: The annual incidence of epilepsy and age related variation. (Hauser et al 1991)

Two peaks are evident. The first at around 2 to 3 years of age, the second around 60 years of age. This is true about generalized epilepsy but focal epilepsy can manifest at any age (Hufnagel and Noachtar, 2003). The causes of epilepsy in infants include developmental malformations, genetic metabolic syndromes and perinatal cerebral injury. Febrile seizures and Temporal lobe epilepsies are major causes for epilepsy between the age of 5-15 years. While traumas, withdrawal of alcohol, infections and neoplasm emerge as leading causes of epilepsy in the adulthood. Stroke is the main etiology of new onset epilepsies after the 60 th year.

The epileptic course can be divided in three phases. An ictal phase characterized by acute systemic changes in neuronal functions called 'seizure'. A post ictal state after the seizures where there is gradual return back to normal functions and an inter ictal phase between two seizure episodes. There are two major categories of seizures. The ones arising from a well circumscribed brain area are called 'partial seizures'. These are propagated by recruitment of surrounding neurons and neuronal circuits related to these neurons. Partial seizures are often related to focal structural abnormality. The other type is primary generalized seizures. Here the seizures propagate because of rapid synchronization of abnormal rhythms in both hemispheres.

1.2 SEIZURE AND EPILEPSY

Following figure schematically represents the events that promote a chronic epilepsy from a single seizure e.g temporal lobe epileptic seizures.

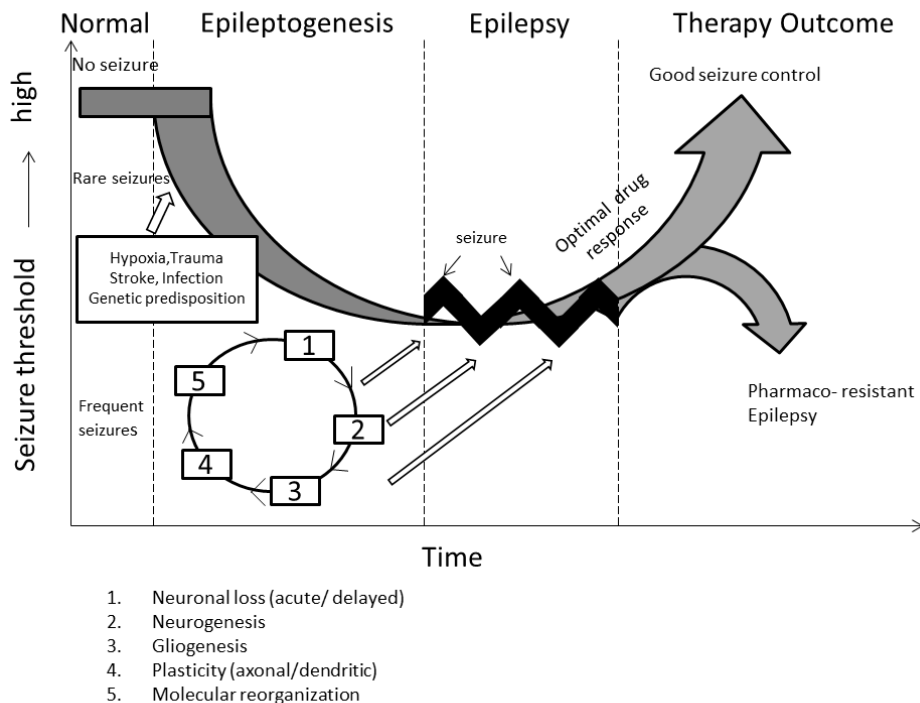


Figure 3: Epileptogenesis.

The process of evolution from a normal state to chronic epilepsy through epileptogenesis. Box indicates the initial event that may lower a normal seizure threshold and produce a clinical seizure. Subsequent epileptogenesis characterized by cellular and synaptic changes represented by a circle. This makes person prone to more seizures and the cycle of cellular events may repeat at each seizure transforming the state to 'Epilepsy'. The likely outcome after drug therapy are also represented

Classification of epileptic disorders and seizures is described separately in annex.

Commentaire [G1]:

1.3 DRUG THERAPY

Pharmaceutical therapy forms the mainstay of treatment for epilepsy. The cellular mechanism operating in seizure can be summarized as imbalance between excitation and inhibition of a synaptic transmission. Excess excitation and decreased inhibition both promote seizures. In an epileptic synapse the excitatory neurotransmitter Glutamate is released under influx of sodium and calcium ions in the presynaptic neuron. Post synaptic Glutamate receptors are of two types. Ionotropic (NMDA, and non NMDA) involved in fast synaptic transmission and Metabotropic receptors related to slow synaptic transmission. GABA is the main inhibitory neurotransmitter. The influx of chloride ions making the membrane hyperpolarised generates the inhibitory post synaptic potential (IPSP) under GABA influence. Anti Epileptic drugs act by one of the several mechanisms influencing one or several processes described above in generation of seizures.

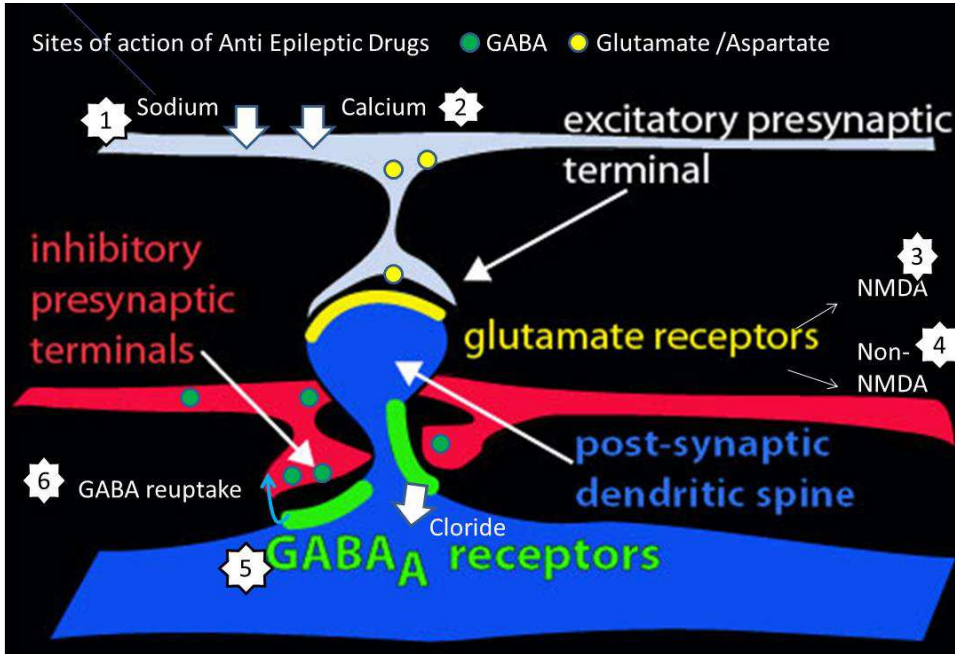


Figure 4: Sites of action of Anti Epileptic Drugs (AED)
 Figure schematically represents a synapse. The possible sites of action of AED are numbered. The table below details commonly used AED corresponding to each site of action.

The commonly used AED and their sites of action (ref figure) are summarized in the table below

Table 1: Commonly used AED

Site of Action	Description	Anti Epileptic Drug
1	Sodium Channel	Standard Phenytoin Carbamazepine Valproate Phenobarbital Newer Lamotrigine Oxcarbazepine Topiramate Zonisamide
2	Calcium Channel	Standard Ethosuximide Newer Zonisamide
3	Glutamate receptor (NMDA)	Felbamate
4	Glutamate receptor (non NMDA)	Standard Phenobarbital Newer Topiramate
5	GABA receptors potentiation Receptor function enhancement Description	Benzodiazepines and barbiturates Topiramate Anti Epileptic Drug
6	GABA re uptake inhibition	Tiagabine
	GABA metabolism (GABA transaminase inhibition)	Vigabatrin

In clinical management of epileptic patients certain drugs are preferred over others in specific types. Following tables summarizes these choices.

Table 2 : Drug therapy for common Seizure types

Seizure type	Seizure pattern	First Line	Second Line
Partial	Simple Complex Partial with secondary generalization	CBZ,VPA	GVG, PHT, LTG CLB, GBP, AXCM FBM, PB
Generalized	Tonic –Clonic Tonic /Clonic	VPA CBZ	PHT, LTG, CLB GVG, PB, AXM FBM
Generalized	Absence	ESM,VPA	LTG CZP AXM
	Atypical Absence Atonic (drop attacks)	VPA	LTG, CLB, CZP AXM, PB, FBM, CBZ,PHT, GBP
Generalized	Myoclonic	VPA	CZP, PCT, PB, AXM
	Infantile Spasm	ACTH	GVG, NZP, CZP

CBZ=carbamazepine,
VPA=valproate,
ESM=ethosuximide,
GVG=vigabatrin,
PHT=phenytoin,
LTG=lamotrigine,

CLB=clobazam,
GBP=gabapentin,
AXM=acetazolamide,
FBM=febamate,
PB=phenobarbitone,
CZP=clonazepam,

PCT=piracetam,
NZP=nitrazepam

Actazolamide (AXM) is an inhibitor of carbonic anhydrase enzyme and is used as an adjuvant to main AED in specific cases. It appears to retard abnormal, paroxysmal, excessive discharge from central nervous system neurons.

1.4 MOTOR SEIZURES IN HUMANS

1.4.1 INTRODUCTION

Epileptic activity arising from frontal lobes frequently manifests clinically as motor epilepsy. Figure below shows the schematic relationships of different motor areas in the frontal lobe which are related to motor epilepsy.

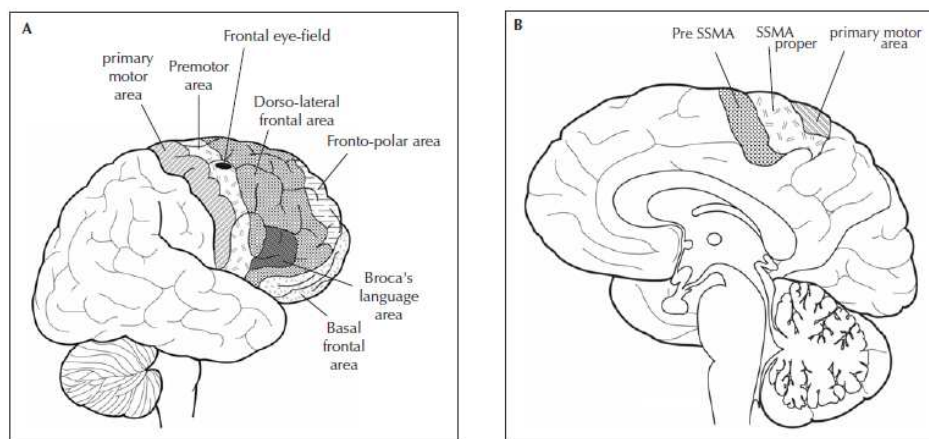


Figure 5 : The schematic representation of origin of motor seizures.

A lateral view of the brain, B medial view of brain

from Kellinghaus C, Lüders HO

The semiological classification of motor seizures

1- Focal clonic seizures

Seizures arising from primary motor cortex or when epileptic activity spreads into the primary motor cortex produce focal clonic motor activity in the contralateral body (Ikeda et al 1999). This manifest as a continuous increase in muscle tone associated with repetitive fast spiking over the precentral gyrus, followed by a regular pattern of synchronous, short contraction of agonistic and antagonistic muscles alternating with muscle relaxation. Consciousness is usually preserved in these types of seizures (Salanova et al 1995).

2- Bilateral asymmetric tonic seizures

Classically, these seizures are of short duration and arise from supplementary motor area. The semiological picture shows asymmetric tonic posturing of both arms but consciousness is preserved. In addition, sometimes patient experience somatosensory aura (Morris et al 1988). Sometimes though the symptomatic zone is SSMA the epileptic discharge might arise from additional frontal lobe areas like frontobasal or mesiofrontal area.

3- Complex motor seizures

Hyper motor seizure: The complex motor seizures are seizures with repeated motor activity which appears as semi purposeful. These activities include motor activity like thrashing of the extremities, body rocking, bicycling leg movements, laughing and shouting (Salanova 1995, Bancaud et al 1992, Holthausen et al 2000, Manford M 1996). The majority (50-90 %) of the patients have auras, these seizures rarely last more than a minute.

There are other seizure types with a motor manifestation for example the versive attacks, or rare forms of seizures where there is inability to initiate movement. But these are not exclusive due to an epileptic focus in motor area and can be observed in other seizure syndromes. Most of the motor seizures are pharmaco resistant. The more severe and progressive partial motor seizure is Epilepsia Partialis Continua (EPC). The features of EPC and its main etiologies i.e inflammatory (Rasmussen's Encephalitis) and developmental (Malformations of cortical development and cerebral vascular malformations) are detailed below in relation to human focal motor seizures.

1.4.2 EPILEPSIA PARTIALIS CONTINUA (EPC)

Introduction

In 1895, Kojewnikoff described a unique type of prolonged focal seizure, which he named epilepsia partialis continua (EPC). In 1927 Omorokow reported 52 cases during an outbreak of Russian spring-summer encephalitis. The clinical entity has been variously labeled as a variation of jacksonian epilepsy, as a jacksonian status epilepticus, as myoclonus epilepsy, or as continuous, localized myoclonia.

In 1985 Obeso et al defined EPC as "Spontaneous regular or irregular clonic twitching of cerebral cortical origin, sometimes aggravated by action or sensory stimuli, confined to one part of the body, and continuing for hours, days or weeks." (Obeso et al 1985) A more generalized definition by Cockerell et al uses "Continuous muscle jerks of cortical origin to define EPC (Cockerell et al., 1996).

Cockerell et al estimated the prevalence of EPC at less than 1 per million, based on 36 cases reported in the United Kingdom over a 1-year period, 10 of the cases being new.

The features of EPC include:

Focal motor clonic seizures without Jacksonian march, localized to a part of the lasting for at least 60 minutes and often for hours, days, weeks, or even longer. Consciousness usually is preserved, but postictal weakness is frequently evident. (Bancaud et al 1982, Gastaut 1968) Antiepileptic drugs, except few, do not seem to significantly alter the course of this condition (Schomer 1993).

Definition

Epilepsia partialis continua is currently defined as a form of partial status epilepticus with simple motor manifestations that are maintained for over 1 hour, with clonic activity restricted to 1 body part and recurring at fairly regular intervals. This clinical presentation of EPC usually has following additional features:

- Motor activity often is modified by sensory stimuli
- Frequency is usually 0.1-6 Hz
- An occurrence of EPC can continue for long periods of time (sometimes years) without spreading, although spread can occur at times
- EPC often is associated with postictal or interictal weakness

Clonic activity in EPC can involve any muscle group but usually frequent in the upper extremities usually confined to a single muscle group in most patients. However in rare cases Jacksonian spread of the seizure or evolution into complex partial or secondarily generalized seizure can be noted. This syndrome also may be accompanied by other neurological and psychopathological symptoms.

Classification

Bancaud et al classified EPC into 2 groups. Both present with similar clinical seizures.

Table 3 : Classification of EPC

Type 1		<ul style="list-style-type: none"> • Usually a fixed lesion • Neurologic deficit • Preceding partial motor seizures • Following myoclonic jerks • Focal abnormalities on electroencephalogram (EEG) • Nonprogressive course • Surgery usually effective
Type 2		
stage 1	Only simple partial motor or complex partial seizures, EPC may occur	<ul style="list-style-type: none"> • Normal development and history until seizure onset • Preceding partial motor seizures • Following myoclonic jerks • Abnormal electroencephalographic background, with focal and diffuse paroxysmal abnormalities • Progressive course
Stage 2	EPC with progressive neurologic deficit and mental deterioration	<ul style="list-style-type: none"> • Chronic encephalitis
Stage 3	Arrest of deterioration and decrease in seizures.	<ul style="list-style-type: none"> • Intractable

The etiological factors of EPS include cerebral neoplastic lesions located in this cortical area, cortical developmental abnormalities, infections, inflammations, metabolic encephalopathies, vascular lesions like AVM and cavernous malformations and trauma. This wide spread etiological origin but unique clinical feature suggests that EPS is related to specific cortical anatomy rather than the physiology.

Explanation of Specific invariable focal status presentation and pharmaco resistance of seizures in EPS:

In case of seizures arising from limbic origin the seizures spread rapidly as limbic system processes functions like memory and emotion, requiring wide spread excitation across many brain regions. In contrast the neocortex process very specific local information in sensory, motor, and cognitive domain and has strong lateral inhibition. This is the mechanism by which though seizures in EPS occur for a long duration their spread to other parts of body is rare. Since surround inhibition might limit seizure spread more effectively in motor neocortex than in any other area because of the tight afferent-efferent relationships, which support the activation of long-loop reflexes, EPC may be a unique expression of cortical organization. This was demonstrated in a monkey model. Injections of aluminum hydroxide in the monkey motor cortex (Chauvel et al., 1978) provided evidence of the long-loop reflexes for the generation of cortical myoclonus. In this study thermocoagulation of the posterior ventrolateralis nucleus of thalamus often caused myoclonic jerks thereby emphasizing that cortical myoclonus as seen in EPC might involve long loops.

The synaptic mechanism of self-sustained status epilepticus has been studied. It is demonstrated that status epilepticus is initiated by failure of GABAergic inhibition but is maintained by widespread potentiation of excitatory (especially N -methyl-D-aspartate [NMDA]) synapses. Therefore, established self-sustaining status epilepticus becomes resistant to all agents except NMDA antagonists (Mazarati et al 1997). Same mechanism might operate in EPC where the epileptic structural focus would have desensitization of GABA receptors, while GABAergic inhibition would be preserved in the surround.

The idiopathic causes of EPC are:

- Rasmussen chronic encephalitis (Biraben et al 1998)
- Autoimmune - Multiple sclerosis, (Spat et al 1995) anti-GluR3 or anti-NMDA-GluR-Epsilon2 antibodies
- Genetic causes like Alpers disease, Kufs disease (Gambardella et al 1998) Leigh syndrome and cytochrome C oxidase deficiency, (Elia et al 1996) nicotinamide adenine dinucleotide (NADH) coenzyme Q reductase deficiency and mitochondrial cytopathies, including mitochondrial encephalopathy with lactic acidosis and stroke (MELAS) (Veggiotti et al 1995).

Diagnosis

Diagnosis of EPS many times requires a multimodal approach. The EEG might not be successful in demonstrating focal cortical abnormal rhythms Evoked-potential techniques, especially somatosensory evoked potentials (SSEP), can be used to examine the physiologic mechanisms and anatomical locations of EPC. Giant SSEPs are seen often and point to cortical hyperexcitability, which may be an essential mechanism of EPC. MRI can point to the structural lesion of the cortex and/or white matter. PET and SPECT scans can be useful when computed tomography (CT) and magnetic resonance imaging (MRI) scans are normal. Combined imaging modalities might show epileptic foci not detected on structural MRI. For example SPECT-MRI fusion has been reported by Matthews to have successfully been used to identify epileptic focus in a patient with EPC (Matthews et al 2006).

Prognosis

The long-term prognosis of EPC depends completely on its underlying cause. Anticonvulsant therapy is not effective for symptomatic control and most of these seizures are pharmaco resistant. In some cases steroids, immunoglobins, antiviral agents have been used depending upon the presumed inflammatory, autoimmune and viral mechanisms in etiology.

Neurosurgical approaches, such as multiple subpial transections (Molyneux et al 1998), and hemispherectomy in refractory cases of Rasmussen encephalitis producing EPC, are also found useful.

1.4.3 RASMUSSEN'S SYNDROME

Introduction

The first description of Rasmussen's syndrome was provided by Rasmussen and co-workers in 1958 when they reported three patients with 'focal seizures due to chronic localized encephalitis' (Rasmussen et al., 1958). It is also called Rasmussen encephalitis (RE) or Rasmussen syndrome. Rasmussen proposed a viral etiology based on lymphocyte infiltration and microglial nodules found in affected brain. Similarity of presentation between Russian spring summer meningoencephalitis, caused by a flavivirus, and RE also supported the viral etiology. But so far no viral agent has been conclusively proved to be the infective agent (Rasmussen, 1978; Farrell et al., 1991; Jay et al., 1995). Hence the pathogenesis of Rasmussen's Encephalitis is thought to be related to autoimmune reaction. Antibodies against subunit 3 of the ionotropic glutamate receptor (GluR3) were found in patients of RE (Rogers et al., 1994). But their specific role in RE is questionable as these are also found in other epilepsy forms in a comparable proportion (Mantegazza et al., 2002). Besides this the role of cytotoxic T lymphocyte (CTL) attack against neurons has been proposed as another immune mechanism since the affected brain tissue is found to contain these cells in large number (Li et al., 1997).

Diagnostic criteria (Bien et al 2005)

Part A:

1. Clinical: Focal seizures (with or without Epilepsia Partialis Continua) and unilateral cortical deficit(s).
2. EEG: Unihemispheric slowing with or without epileptiform activity and Unilateral seizure onset.
3. MRI: Unihemispheric focal cortical atrophy and at least one of the following:
 - Grey or white matter T2/FLAIR hyperintense signal
 - Hyperintense signal or atrophy of the ipsilateral caudate head.

Part B:

1. Clinical: epilepsy partialis continua or Progressive* unilateral cortical deficit(s).
2. MRI: Progressive* unihemispheric focal cortical atrophy.
Histopathology; T cell dominated encephalitis with activated microglial cells (typically, but not necessarily forming nodules) and reactive astrogliosis.

RE can be diagnosed if either all three criteria of Part A or two out of three criteria of Part B are present.

*‘Progressive’ means that at least two sequential clinical examinations or MRI studies are required to meet the respective criteria. To indicate clinical progression, each of these examinations must document a neurological deficit, and this must increase over time. To indicate progressive hemiatrophy, each of these MRIs must show hemiatrophy, and this must increase over time.

Clinical features

The general presentation of RE is childhood epilepsies with progressive neurological deterioration. The disease is conceptualized to be progressive through three stages. Early ‘prodromal stage’ with a relatively low seizure frequency and rare mild hemiparesis; then the ‘acute stage’ of the disease, characterized by frequent seizures, mostly simple partial motor seizures often as *epilepsia partialis continua* (EPC) with neurological deterioration like progressive hemiparesis, hemianopia, cognitive deterioration and, if the language dominant hemisphere is affected, aphasia (Oguni et al., 1991). The last residual stage is characterized by permanent and stable neurological deficits and persistent seizures.

Seizures in RE are often polymorphic depending upon the disease progression. In a study by Oguni and co-workers 77% of seizures were simple partial motor seizures involving one side of the body. Other seizure type included secondarily generalized tonic clonic seizures, complex partial, postural seizures and somatosensory seizures were also noted (21%) (Oguni et al., 1991). EPC has been reported to occur in 56–92% of patients at some time during their disease course (Bien et al., 2002). But the major feature of these seizures is pharmacoresistance. Surgery appears to be the ideal choice of treatment for RE patients. Results of focal resections in RE patients have been reported as disappointing (Olivier, 1991; Honavar et al., 1992) But Hemispherectomy and its variants or the newer disconnective techniques produce seizure freedom rates between 62.5% and 85%. (*Details of the hemispherectomy are described in Chapter 2*).

1.4.4 MALFORMATIONS OF THE CORTICAL DEVELOPMENT (MCD)

Introduction

Malformations of the cortical development are interruptions in the normal process of neuronal migration and establishment of connectivity in a developing brain. These are of interest to epilepsy as often children with MCD present with epilepsies that are pharmacoresistant. With the increased use of better imaging techniques like MRI in management of epilepsies these structural abnormalities are being detected more frequently and are found to be a major cause of partial seizures.

The various types of MCD are described below:

Table 4 : Description of malformation of cortical development

MCD	Brief Description
1 Agyria or Lissencephaly	Absence of normal gyral formation Type 1 : Four layered cortex instead of normal 6 layered
2 Pachygyria	Broad and few number of gyri
3 Polymicrogyria	Narrow and thin gyri
4 Schizencephaly	Cleft of various depth from pial surface to ependymal
5 Subependymal	Ectopic grey matter tissue in the subependymal zone
6 Subcortical Heterotopia	Grey matter nodules below cortical mantle
7 Microdysgenesis	Small number of neurons in the white matter
8 Dysembryogenic	Nodules of pleomorphic cells including dysmorphic neurons
9 Focal cortical Dysplasia	Areas containing large number of dysmorphic neurons in otherwise 'normal' layered and convoluted cortex

The incidence of MCD in patients with refractory epilepsies range from 7% to 12 % (Li et al., 1995, Semah et al., 1998). Even high resolution MRI may not detect the cortical dysplasia at pre operative stage and the presence of cortical dysplasia would be obvious only at post operative histopathology studies. Thus the actual incidence of MCD in pharmaco resistant epilepsy might be higher (Li et al., 1995). The diagnosis of MCD is often made by clinical presentation and EEG abnormalities coupled with imaging studies like CT, MRI.

Epileptic potential of MCD

The epileptic potential of MCD arises from two things. The cortical area affected by maldevelopment is found to be hyperexcitable. The best studied examples of such epileptogenicity are related to focal cortical dysplasia (FCD). In the histological specimen cellular changes that support hyper excitability have been demonstrated previously (Ferrer et al., 1992, Mikuni et al., 1999). Epileptic discharges from human FCD have been reported (Rosenov et al 1998) and the surgically resected human epileptic tissue containing FCD maintained in vitro is shown to generate epileptic activity (Mattia et al., 1995). In case of Periventricular heterotopia invasive recording from the nodules have demonstrated epileptic activity from the region (Debeau et al., 1995, Li et al., 1997). Similarly in a rat model of polymicrogyria the cortex near the vicinity of the lesion was shown to be epileptogenic (Jacobs et al., 1999).

Based on these examples it can be presumed that cortical areas containing the malformations are potentially hyperexcitable. In addition the cellular altered morphology might affect the dendritic connectivity to other neurons. Both these factors (altered excitability and connectivity) might make the zone epileptogenic.

1.4.5 VASCULAR MALFORMATIONS

Introduction

Vascular malformations affect about 2 to 4% of the population. These are abnormal vascular structures. Two main types are found cavernous malformations (CCM) and arterio venous malformations (AVM).

Cerebral cavernous malformations are clusters of dilated sinusoids filled with blood and lined with endothelium without intervening parenchyma. They sometime grow by formation of a vascular cavum due to repeated hemorrhages in them. The CCMs exhibit brittle vascular morphology devoid of mature vessel wall elements.

Diagnosis

Seizures are the main symptomatic manifestation of CCM. MRI are important in diagnosing CCM as due to their small size and often isodense appearance related to subacute hemorrhage or microcalcifications, CCMs are commonly missed or misdiagnosed on CT. Angiographically also these lesions are occult (Robinson et al., 1994).

Epileptogenicity

CCM essentially are malformed blood vessels and do not typically include functioning neural tissue. They are not intrinsically epileptogenic themselves. However they can induce seizures through their effect on the surrounding brain. These effects may include relative ischemia, venous hypertension, gliosis, deposits of blood breakdown products, and cellular and humoral inflammatory responses. These long standing changes in 'occult' non haemorrhagic CCM may make adjacent cortex epileptogenic. Distinct hemorrhage from CCMs may create encephalomalacia and cortical scars that may be additionally epileptogenic (Awad and Jabbour, 2006).

Treatment

The symptomatic drug treatment of seizures related to CCM by anticonvulsants might not be adequate and these seizures are often pharmaco resistant. Resection of structural lesions may be performed in two ways i.e lesionotomy that is resection limited to the lesion alone or lesionotomy and corticotomy where along with resection of the lesion the epileptogenic cortex is also excised. It is reported that the seizure control after lesionotomy alone is inferior to one achieved by lesionotomy and corticotomy. Other therapies like radiotherapy are also useful.

Arterio Venous malformations (AVM) are complex, tangled web of abnormal arteries and veins connected by one or more fistulas. The AVM does not have capillary bed of its own. The AVM permits high-speed, high-flow shunting of blood from the arterial to the venous side of the circulation. This might produce relative ischemia in adjacent cortex and make it prone for epilepsy. AVM can clinically present as epilepsy but cerebral hemorrhage is more often the clinical presentation in this condition. For example arteriovenous malformations

account for approximately one third of primary intracerebral haemorrhage in young adults (Al-Shahi and Warlow, 2001)

1.5 PHARMACO RESISTANT EPILEPSY

Introduction

People with epilepsy experience uncertainty, about getting a seizure and become vulnerable in social situations. Epilepsy patients have stated that uncertainty and fear of having a seizure are the worst things about having epilepsy (Fisher et al., 2000). But this problem assumes grave proportions in medically intractable i.e. pharmaco resistant epilepsies. As apart from the uncertainty the patients face more events like falls, injury, neuropsychiatric problems and even SUDEP (sudden unexplained death in epilepsy). The following text describes the features of pharmaco resistant epilepsies.

The steps followed in initiating drug therapy and arriving at a diagnosis of pharmaco resistant epilepsy are illustrated schematically below

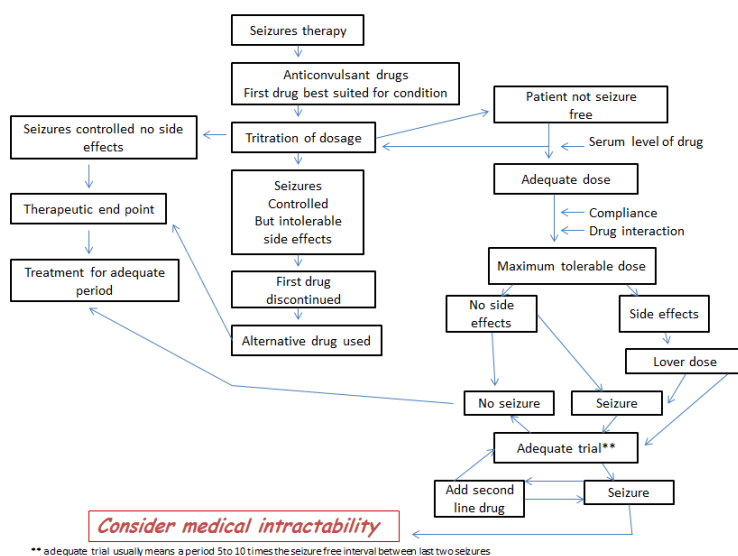


Figure 6 : Algorithm for determining a pharmaco resistant epilepsy

Incidence of pharmaco resistant epilepsy

The mainstay of epilepsy therapy is drugs and about 70 % of epilepsy patients are well controlled on the drug therapy. However 30 % are never controlled despite adequate treatment: and fall in the group of pharmaco resistant epilepsy. A seminal study by Kwan and Brodie illustrates this phenomenon. They studied the treatment and follow up of 523 epilepsy patients over 13 years. The age group ranged from 9 to 93 years and all epilepsy types (generalized, partial, symptomatic as well as idiopathic) were represented in patient population. It showed that 63 % of the patients were treatment responsive and had attained

seizure freedom for at least 1 year. About 50% achieved seizure freedom on first anti epileptic medication. Successive addition of antiepileptic produced minor improvement in this percentage but treatment with three or more anticonvulsant failed to improve this percentage further (Kwan, Brodie, 2000).

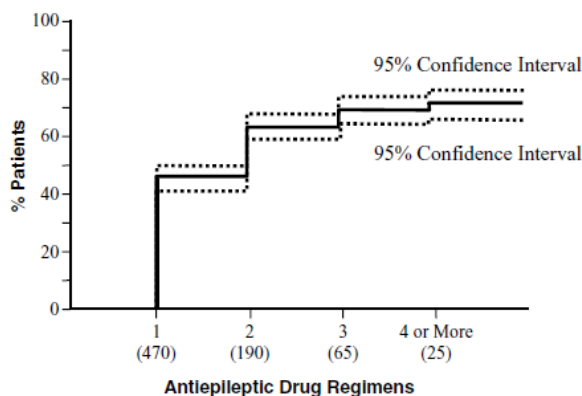


Figure 7 : Response to Anti Epileptic therapy (reproduced from Kwan Brodie 2000)

Nearly 50% of all patients with newly diagnosed epilepsy attained seizure freedom on their first drug. Those who failed their first drug were less and less likely to gain control with each successive drug trial.

Semah and colleagues studied ease of seizure control and final treatment outcome in a sample of 2,200 adult outpatients with epilepsy. In this study it was found that patients with symptomatic or cryptogenic seizures were the least likely (around 26%) to be well controlled on drugs and become seizure free for 1 or more year (Semah et al., 1998). The availability of newer classes of anticonvulsant has not changed the picture of pharmaco resistant epilepsies .Studies show that for patients already considered as suffering from pharmaco resistant epilepsies the newer drugs improves seizure control only marginally. In these patients a further 50% control over seizures was seen in 15% patients with Gabapentine, 15% with lamotrigine 25% with Tigabine 35% with Topiramate, 35% with Oxcarbazine, 32% with Levitiracetam 20% with Zonisamide and 35% with Pregabalin (French, 2007).

1.5.1 FACTORS ASSOCIATED WITH TREATMENT-RESISTANT EPILEPSY INCLUDE

History of early onset of seizures and status epilepticus, long history of poor seizure control, history of multiple seizures high seizure density, (French, 2007) are indicators of pharmaco resistant epilepsy. Symptomatic epilepsies like in patients with a history of brain infection or head trauma are often pharmaco resistant. Certain structural abnormalities like cortical dysplasia, hippocampal sclerosis are associated with pharmaco resistant epilepsy. In a study it was found that for patients with a single identified lesion, TLE with hippocampal sclerosis (HS) had a particularly bad prognosis (11% seizure free) compared with other etiologies (24% with cortical dysplasia seizure free). Patients with Hippocampal sclerosis and another identified pathology (dual pathology) had the worst prognosis (3% seizure free) (Semah,

1998). Developmental delays and other cognitive disability are associated with poor seizure remission rates (Okuma, Kumashiro, 1981).

False pharmaco resistant Epilepsy:

Pharmaco resistant epilepsy means failure to achieve optimum control over seizures by use of anti epileptic medications. Besides the true pharmaco resistance many factors produce suboptimal performance of antiepileptic drugs resulting into false pharmaco resistance. Few of the causes are mentioned below.

Misdiagnosis and misclassification into epileptic syndrome means possible: inappropriate class of anticonvulsant as first choice and poor response.

Drug interactions with other AED and a poor compliance from patient might lead to a false impression of pharmaco resistant epilepsy.

True pharmaco resistant Epilepsy:

What constitutes a definition of pharmaco resistant epilepsy is difficult to decide because various factors like seizure frequency, seizure severity, patient's subjective perception of handicap can influence the meaning of pharmaco resistant epilepsy.

Most epilepsy centers define intractability as failure of at least 2 or 3 first-line antiepileptic medications. However, many physicians define medical intractability differently. They might try numerous antiepileptic drugs (AEDs) before referral for a presurgical evaluation is even considered, (Berg, Kelly, 2006). If the two drug criteria is used then 24% of focal seizures, 9.3% of idiopathic seizures and 66.7% of catastrophic seizures are found to be pharmaco resistant.

The stringent criteria for pharmaco resistant epilepsy as defined by Berg (Berg, 2006) are

- a) failure of two appropriate anticonvulsants
- b) occurrence of an average of one seizure per month for 18 months
- c) no more than 3 months of seizure free interval between these 18 months.

Using these criteria 13.3% of focal epilepsy 3.9% of idiopathic epilepsy and 52.2% of catastrophic epilepsy are found to be pharmaco resistant.

However, this definition is more suitable for epidemiological and research studies in epilepsy. The medical intractability in a particular patient depends upon the natural course of the specific epilepsy and individual's response to anticonvulsant.

Hence a consensus proposal by the Task Force of the International League Against Epilepsy (ILAE) Commission created an operational definition of drug-resistant epilepsy, noting that this definition may change as more empirical evidence becomes available (Kwan et al., 2010). The ILAE defines drug-resistant epilepsy as "a failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom".

Seizure freedom is defined as freedom from seizures for a minimum of 3 times the longest preintervention interseizure interval (determined from seizures occurring within the preceding 12 months) or 12 months, whichever is longer (Kwan et al., 2011).

1.5.2 MOLECULAR HYPOTHESIS OF PHARMACO RESISTANT EPILEPSY

The graphic below schematically illustrates two important hypothesis that explain why a particular epilepsy becomes pharmaco resistant

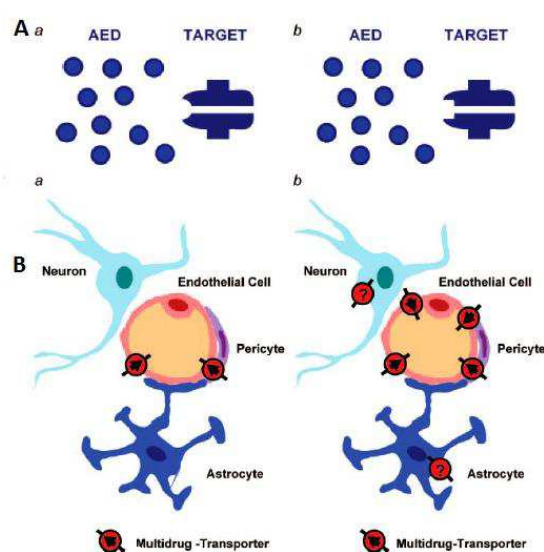


Figure 8 : Molecular hypothesis of pharmaco resistance (Remy S. and Beck H. Brain 2006)

Part A illustrates how a target might be altered.

Part B shows the upregulation of multidrug transporters in epilepsy and subsequent removal of drug in the vascular space.

Target hypothesis (part A):

The Anticonvulsant drug targets are of three types viz. voltage gated ion channels, proteins involved in synaptic inhibition (enhancing GABA neurotransmission) and proteins involved in synaptic excitation (acting on glutamate transmission). These targets can be altered due to altered gene encoding ultimately affecting the pharmacodynamics of AED. Alternatively these targets can have altered sensitivity to AED during the course of epilepsy. Their distribution and density can also become altered. All these mechanisms may contribute to the less seizure control despite adequate therapy.

Multidrug transporter hypothesis (part B):

Inadequate transport to the target neurons may be a cause of pharmaco resistant epilepsy. The drug transport molecules are found upregulated in many types of epilepsy. This could be genetic or 'acquired' as a consequences of repeated seizures. These transporter molecules act as a drug efflux pump proteins and export drug molecules to vascular space at blood brain barrier level. This results in less drug molecules reaching the target neurons.

1.5.3 CONSEQUENCES OF PHARMACO RESISTANT EPILEPSIES

Quality of life

Quality of life (QOL) is a measure of how a person's sense of own wellbeing and degree of functional integration in the society. Health related quality of life is often found affected in chronic diseases like diabetes, hypertension and epilepsy. Recurrent seizures, poor seizure control, multi drug therapy, prolonged treatment period are features of pharmaco resistant epilepsy which augment the negative effects.

The epileptic patients perceive 'loss of control over their lives' and develop anxiety and depression (Ettinger et al 2004, Gilliam et al 2006, Jacoby et al. 1996) studied the impact of epilepsy related variables in an unselected population of people with epilepsy in the UK. Increased seizure activity was significantly related to anxiety and depression. Longer duration of epilepsy and older age of onset were also significantly correlated with depression. In fact, in patients with pharmaco resistant epilepsy, depression was found to be 1 of the 2 independent predictors of poor quality of life. Furthermore, these patients have significantly greater risk of suicidal ideation and suicidal behavior, compared with that in the general population (Jones et al., 2003).

The negative effect on quality of life is more pronounced in intractable epilepsy. Baker and colleagues showed that compared with patients whose seizures were in remission, patients with intractable seizures scored significantly worse across all domains of the Nottingham Health Profile, as well as in relation to sense of mastery and self-esteem (Baker et al 1997). Similarly in a study by Vickrey et al. 340 adults with refractory partial seizures were evaluated presurgically, QOLIE-89 domain scores were considerably lower than those that has been reported for patients with well controlled seizures, (Vickrey et al 2000).

Specific epilepsy syndromes produce cognitive problems in patients with epilepsy and these problems also influence quality of life. MTLE is the most common focal epilepsy syndrome, and is characterized by focal seizures that cause epileptogenic mesial temporal lesions (usually hippocampal sclerosis) which are often resistant to AED therapy. The range of cognitive functions that can be compromised in people with repeated MTLE seizures include intelligence, learning, visuo-spatial functions, problem solving, memory function and academic attainment (Hermann et al., 1997; Hermann and Seidenberg, 2002). Frontal lobe seizures are the second most prevalent type of seizure that are subject to surgical intervention and 15% of refractory epilepsy cases are due to FLE (Helmstaedter, 2001). In such patients improvement in IQ is found after epilepsy surgery (Milner, 1975).

Lastly even employability is found affected in patients experiencing poor control of seizures. In a study (Leidy et al., 1999) studied QOL in 139 adults with active epilepsy, defined as a diagnosis of 1 year minimum and prescribed AEDs, recruited from three U.S. epilepsy centers. It appeared that people with active epilepsy was a disabled group with only 35% reporting being in full-time employment despite a mean age of 38.5 years.

SUDEP

It is known that patients with epilepsy have a mortality rate significantly higher than that of the general population.

The underlying causes of high mortality are summarized below

- Death due to the underlying neurologic disorder in symptomatic epilepsy
- Accidents during epileptic attack (ie, trauma, drowning, burning, choking)
- Status epilepticus
- Suicide
- Treatment-related death
- Sudden unexpected death in epilepsy (SUDEP)

Incidence of SUDEP is considerably higher in patients with chronic epilepsy, 1-2/1,000 person-years, and highest with severe, refractory seizures, 3-9/1,000 (Tomson et al 2005). SUDEP accounts for 8-17% of deaths in people with epilepsy. Sudden unexplained death in epilepsy patients (SUDEP) is 40 times more likely among patients who continue to have seizures than in those who are seizure free (Tomson, 2000).

SUDEP is defined as sudden, unexpected, nontraumatic, nondrowning death in an individual with epilepsy, witnessed or unwitnessed, in which postmortem examination does not reveal an anatomic or toxicological cause for the death.

The possible mechanisms operating in SUDEP are graphically represented below.

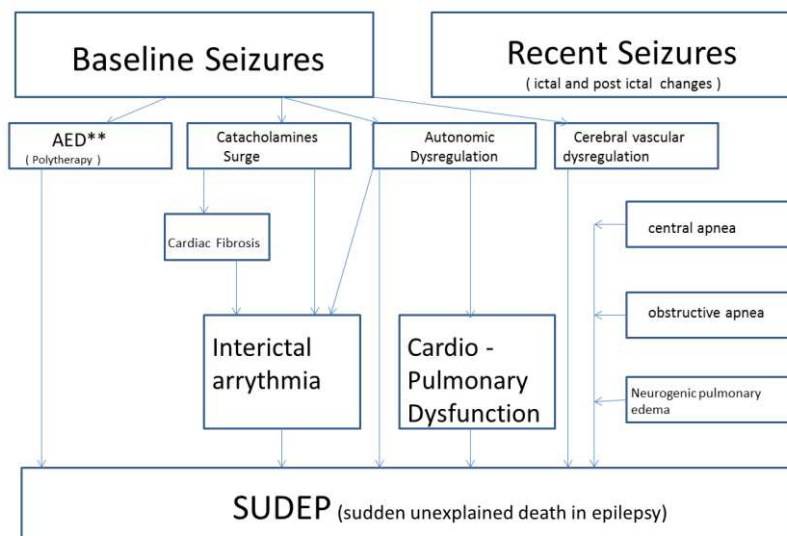


Figure 9 : The factors operating behind SUDEP

Economic burden

In 2000 the annual cost for patients with epilepsy in the United States was estimated to be approximately 12.5 billion dollars (based on a 1995 survey); with pharmaco resistant epilepsy contributing a substantive proportion (Begley et al., 2000, Kwan et al 2011). Another study found that costs correlate with severity of illness and that, those patients who have intractable seizures incur a cost eight times greater than in those whose epilepsy is controlled (Jacoby et al., 1998).

CHAPTER II

TREATMENT OF PHARMACO RESISTANT EPILEPSIES

Treatment of pharmaco resistant epilepsies can be divided into surgical and nonsurgical therapies. Epilepsy surgeries are classified as curative or palliative, depending on the goal. Curative procedures include lobectomy, lesionectomy, and hemispherectomy. Palliative procedures include corpus callosotomy and multiple subpial resections. In addition neuromodulation in terms of vagus nerve stimulation, deep brain stimulation, TMS and radioneurosurgery are non resective-surgical approaches for control of intractable epilepsy. A review of all these therapies except the Deep Brain Stimulation (DBS) is presented in this chapter.

2.1 SURGICAL THERAPIES

Not all patients of refractory epilepsy are good surgical candidates. The decision to offer surgery is based on strict criteria.

2.1.1 SELECTION CRITERIA FOR RESECTIVE SURGERY (NOACHTAR ET AL 2003)

- Confirmed diagnosis of epilepsy.
- Medical intractability.
- Disabling seizures.
- Resectable focus
- Motivated patient.
- No progressive underlying cause (except Rasmussen's encephalitis).
- High probability that better seizure control will improve quality of life.

2.1.2 PRE SURGICAL EVALUATION

When the candidate satisfies the selection criteria, a presurgical evaluation for planning the type and extent of surgery is done. The table describes the evaluation.

These steps are interchangeable and many evaluations are undertaken simultaneously. Not all evaluations are necessary in each patient and the selection of tests depends upon nature of epilepsy and surgery planned. Intra carotid amobarbital is less and less used these days, replaced by functional MRI.

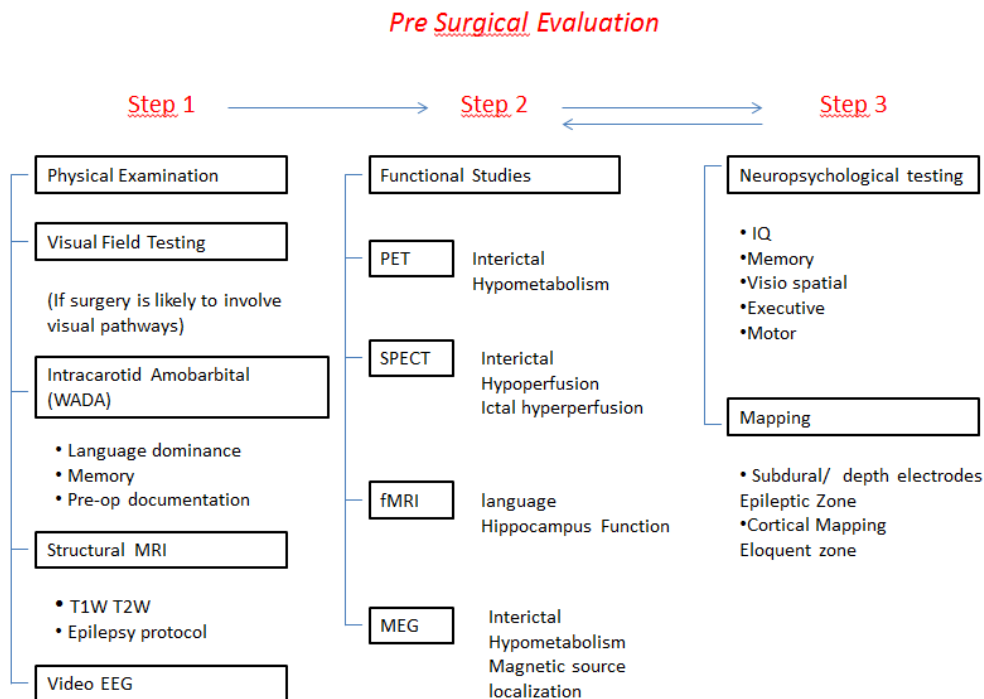


Figure 10 : The steps followed during pre surgical evaluation of a candidate for epilepsy surgery

2.1.3 CURATIVE PROCEDURES:

(Lesionectomy, lobectomy, topectomy,)

Surgical excision of a lesion: gyrectomy (usually performed including a lesion) is rewarding if the ictal onset zone determined by pre surgical evaluation matches the location of a specific lesion (like tumor, dysplasia, sca,r granuloma etc...). Often just excision of the lesion is not sufficient to control seizures and more extensive procedure of lobectomy is necessary as in case of seizures arising from temporal lobes. In addition to lesionectomy, focal excision of the epileptic cortex is also undertaken in specific cases. This procedure is called topectomy.

Neocortical focal resection (topectomy) or gyrectomy

First described by Heath and Poole in 1948(Heath and Poole, 1948) as a treatment for psychoses the technique of topectomy is useful for epilepsy. The technique is more suitable if the cortical epileptic focus is well defined.

Rationale: Resection of the diseased cortex controls possibly the generation of abnormal electric activity.

Technique

The pial surface over the gyrus to be resected is coagulated in the crown of the gyrus roughly in the midline in entire length. Pia is elevated and reflected to expose the grey matter. A gentle subpial aspiration of the cortical matter is performed, avoiding injury to blood vessels running over the gyrus. The depth of aspiration is limited to depth of the gyrus and white matter beyond this level is not breached.

Outcome of gyrectomies

Frontal resections: When unilateral resections are carried out the postoperative cognitive deficits are minimal so that they are not noticeable during routine daily activity of the patient. Resection of the pars opercularis of the inferior frontal gyrus requires careful consideration because of location of language area (Brocas area) in it. Temporal topectomies for epilepsy as such are controversial because standard anterior lobectomy or amygdalohippocampectomy are considered better options. In the central cortex topectomies of face in non dominant side produce temporary deficits. Interference with throat facial muscle functions may produce dysarthria. Care should be taken for preserving hand and limb functions. Mapping of cortex as well as stimulating white matter in the depth of resection is undertaken. It highlights white matter tracts associated with movement and injury to them could be avoided. The parietal lobe topectomies generally are safe with just 0.5% risk of hemiparesis. Visual field deficits in the contra lateral eye are major side effects of some parietal lobe topectomies. Occipital resections are rare and carry the same risks of damaging visual tracts.

Hemispherectomy

Introduction: Hemispherectomy is a surgical removal of one cerebral hemisphere keeping most of the basal ganglionic structures intact. The technique is employed when the pathology is located unilaterally. From large resections of entire hemisphere called as anatomical hemispherectomy in the past, more sophisticated disconnection techniques called 'functional hemispherectomy' and 'hemispherotomy' have emerged recently.

Hemispherotomy was initially described by Dandy in 1928 (Dandy, 1928). He performed it for a malignant glioma. The surgery showed that the survival of patient after such extensive surgery is possible. This led the foundation of using this technique for intractable epilepsy. Kenneth McKenzie (McKenzie, 1938) first used it for intractable partial epilepsy. It became popular till 1970 then the use of anatomical hemispherectomy declined due to awareness of late onset complications related to surgery.

Rationale: Isolating the epileptic focus from other parts of brain by a resection or effectively arresting spread of abnormal electric discharge by disconnection of focus are the basis by which epilepsy can be controlled. There are various methods of achieving this aim. But common to all is interruption of the corpus callosum, the internal capsule and corona radiata, mesial temporal structures and the frontal horizontal fibers.

Techniques

Classical anatomical hemispherectomy:

The classical technique involved ligating the major vessels after the perforant branches then proceeding with the resection of the lobes. This technique left a large vacant space in the skull after the surgery. CSF leakage, hydrocephalus, infections are immediate complications. But more important is ‘superficial hemosiderosis. Due to recurrent hemorrhages in the cavity, a thin film of coagulated blood and its end products form over the brain. This eventually leads to recurrence of seizures and decline in the cognitive performance. Such late complications have made the classical technique less popular. However attempts to minimize these complications were made. The subdural space was reduced by suturing dura to falx tentorium and skull base at the floor of the anterior and middle cranial fossae Plugging of the ipsilateral foramen of Monro with a piece of muscle was also undertaken to avoid communication between ventricle and empty subdural space.

The classical anatomical hemispherectomy is now seldom practiced. There are newer surgical techniques like Functional hemispherectomy (Rasmussen, 1983), Hemidecortication (Carson et al., 1996) and techniques involving extensive disconnection rather than excision called Hemispherotomy (Delalande et al., 2007, Villemure et al., 1995), Hemispherical deafferentation (Schramm et al., 1995).

Regardless of the surgical approach and technique certain connections need to be sacrificed in order to achieve a good seizure control.

The table below describes these.

Table 5 : The white matter zones sacrificed hemispherectomy

White mater fibres	Description	Significance of connection
Corpus callosal fibres	Rostrum and Genu Rostral fibers of the trunk	Frontal lobe Premotor and supplementary motor
	Middle trunk	Precentral fibers
Faciuli	Superior longitudinal bundle	Connects frontal parietal occipital and temporal lobes
	Anterior limb	Connects speech area to frontal eye field
	Posterior limb	Connects secondary visual area to frontal eye field
Uncinate fibers		Temporal lobe and amygdala
Occipito frontal fibers		Association areas

Outcome: seizures

Following table illustrates outcome on seizure control.

Table 6 : Seizure outcome in hemispherectomy (De Ribaupierre, Delalande, 2008)

*Percentage of patients with Engel Class I outcomes in large case series, stratified by underlying pathological condition**

Author & Year	Op	Follow-Up	Cortical Dysplasia	HME	Ras-mussen	Vascular	Sturge-Weber
Carson et al., 1996	hemidecortication	mean 7.4 yrs	35†	35†	73	NA	50
Cats et al., 2007	functional hemispherectomy	mean 3.3 yrs	90	0	50	90	NA
Delalande et al., 2007	hemispherotomy	mean 4.4 yrs	63†	63†	80	73	80
Devlin et al., 2003	functional hemispherectomy, hemispherectomy	>3 yrs	27†	27†	40‡	100	40‡
Di Rocco et al., 2006	hemispherectomy	mean 9.9 yrs	NA	75	NA	NA	NA
Jonas et al., 2004	hemispherotomy, functional hemispherectomy, hemispherectomy	5 yrs	60	33	63	71	NA
Kossoff et al., 2003	hemispherectomy	range 3 mos–22 yrs	57	40	65	81	67
Shimizu, 2005	functional hemispherectomy	NA	31	80	NA	67	NA
Villemure & Daniel, 2006	hemispherotomy	mean 9 yrs	80†	80†	90	93	NA
Vining et al., 1997	hemispherectomy	mean 6.2 yrs	38†	38†	67	50	NA

* HME = hemimegacephaly; NA = data not available.

† The authors did not differentiate between cortical dysplasia and HME in their analyses in these series.

‡ Devlin et al. did not differentiate between Rasmussen syndrome and Sturge-Weber syndrome in their analysis.

Other outcome measures

Hemispherectomy and all its variants are known to improve other functions of brain. Since there is freedom from seizures the cognitive performance is improved as reflected in improved IQ. Other behavioral aspects also improve. The motor deficits that are anticipated after such extensive disruption of the motor tracts may not always be serious. Children who walked before the surgery still are able to walk. Sometimes the paraplegia on the contra lateral side is spastic especially in Rasmussen's encephalitis, and after surgery transmission of weight in spastic limb allows a walk.

2.1.4 PALLIATIVE PROCEDURES.

Corpus callosotomy

There are six midline commissural structures connecting the cerebral hemispheres, including the corpus callosum, anterior commissure, posterior commissure, hippocampal commissures, massa intermedia, and fornix. Of these, the most significant is the corpus callosum. It contains most of the myelinated fibers which are topographically arranged. The rostrum transfers higher cognitive information; the genu and anterior midbody transfer motor information by fibers arising from the premotor, motor, anterior insular, and anterior cingulate areas. The posterior midbody transfers somatosensory information; the isthmus transfers auditory signals; and the splenium transfers visual information (Wong et al., 2006; Funnell et al., 2000).

The first description of corpus callosotomy was by Dandy when the structure was excised during a surgery for pineal tumor. The use of this technique for epilepsy was promoted by Van Wagenen and Herren (Van & Herren, 1940). They observed that tumors of corpus callosum presented clinically as seizures but these seizures decreased as the tumor grew and destroyed more of the corpus callosum. The neurophysiological outcomes were defined by Bogen and Vogel (Bogen & Vogel, 1963). Callosotomy as a replacement for more radical hemispherectomy was advocated in the 1960s.

Rationale

It was noted during experimental epilepsy that epileptic activity in one hemisphere could produce similar activity in other (Crowell & Ajmone, 1972). Thus the interhemispheric connectivity was implicated in bilateral synchrony of abnormal cortical activity and generalized seizures. Since anterior parts of corpus callosum carry motor information sectioning these was considered a palliative measure of controlling tonic clonic seizures and drop attacks.

Outcome

The goal of a callosotomy procedure is to reduce the frequency and severity of seizures by interrupting common seizure spread pathways. Traditionally anterior two third corpus callosotomy has been performed with great success. Different series have reported 50% or more reduction in seizure frequency in 55–100% of patients following this procedure (Wong et al., 2006; Maehara & Shimizu, 2001).

Table 7 : Long term outcome after Callosotomy (Tanriverdi et al., 2009).

Seizure Type	Class A	Class B	FO (%)	Class C	Class D	Class E	UFO (%)	Total
GTCS	42	23	77.3	14	0	5	22.6	84
drop attacks	35	26	77.2	17	1	0	22.7	79
GTS	4	1	71.4	2	0	0	28.5	7
atyp abs	13	10	56.09	14	3	1	43.9	41
CPS	5	6	47.8	10	2	0	52.1	23
SPS	7	3	71.4	4	0	0	28.5	14
myoclonic sz	7	10	65.3	7	1	1	34.6	26

* Except where otherwise indicated, values indicate numbers of patients.

Side effects

A specific syndrome is often described after callosotomy essentially due to disconnection between dominant and non dominant lobes. For example the visual information presented to non language dominant lobe might not be processed by language dominant lobe and patient would not be able to name objects even if he is able to see them. Similarly the non dominant hand might not perform motor acts rapidly if verbal commands are given. This syndrome is more noticed in total callosotomy than the anterior callosotomy. Most of the patients are unaware of the deficits and the severity declines gradually over the postoperative period.

Multiple subpial transection (MST)

Resective procedures in the eloquent cortex leave major postoperative functional deficits. MST was introduced as a surgical tool for addressing medically intractable epilepsy in 1989 by Morrel (Morrel et al 1989). However the concept of MST was formulated in 1960s during animal experiments. Asanuma first concluded that ascending thalamocortical information and descending information to pyramidal cells have an orientation perpendicular to the cortical surface and cutting of horizontal connections does not produce major deficits (Asanuma,

1975). Morrel described in animal model that spread of epileptic discharge could be halted by MST, later it was applied to human patients.

Rationale

As determined by Morrel in his experiments a 'functional cortical unit' is a column of 5mm width. The most important information processing occurs in vertically oriented manner in these columns. The intracortical penetrating vessels also follow a vertical approach. Hence it is possible to control epilepsy if horizontal connections are sacrificed subpially at a distance of about 5 mm. This would not produce damage to a 'functional cortical column'.

Procedure

The pia is opened at the edge of a gyrus by needle or knife blade. A special knife is used for MST. This consists of a stainless still hook with a flattened tip angled at 105° to shaft and a length of 4 mm. This tip is introduced in the pial opening. It is then advanced through arachnoid forwards into the width of the gyrus, keeping the shaft perpendicular to gyral surface directed upwards and sharply brought back. The process is repeated at an interval of 5mm in the entire length of the gyrus. The resultant small red lines of petechial markings are visible through the pia. A MST is considered complete when the intra operative elector corticography indicates disappearance of epileptiform discharges seen before the procedure. Direct cortical stimulation in awake patients or SEEG in anesthetized patients helps in determining the area of cortex that is to be transected.

Outcome

Morel reported findings in 22 patients who had follow up ranging from 5 to 22 years. 55% were seizure free. Others had progressive disorder like Rasmussen's encephalitis. 18 out of 22 patients had immediate cession of epileptiform activity after the procedure.

Blount and colleagues described outcome in 20 pediatric patients in which MST with or without limited cortical resection was performed for intractable epilepsy. Majority of them had invasive subdural grid placement and monitoring prior to surgery 12 (46%) were seizure free (Engel Class I) following surgery. Eleven patients (42%) (Engel Classes II and III) continued to suffer seizures but improvement in seizure control was adequate following surgery (Blount et al., 2004).

A metanalysis of results from six epilepsy centers was performed by Spencer and his group. Fifty-three patients underwent MST without resection. In patients with MST 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 MST 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).

Controversy and current place in therapy

The Morel's hypothesis was based on normal cortex. The variation in the thickness of cortex especially in diseased conditions should be taken into consideration. In an atrophic cortex the technique might transect more white matter and in a thick cortex (example pre central cortex with a thickness of 4 mm) it might not reach the adequate depth. Similarly the rapid spread of epileptic discharges in pathological conditions indicate that the circuits involved are complex and larger than originally hypothesized.

MST was advocated in the period when MRI were not widely available. Intra operative monitoring, that is 'physiology' took precedence over detection of structural abnormality that is 'anatomy' in deciding epilepsy surgery. With advent of MR imaging (both structural and functional MR imaging) resection of epileptic focus is favored over MST as it gives equivalent and even better results. This has led to a decline in the popularity of MST.

However new indications for MST have evolved. MST has been used in temporal lobe epilepsy in dominant temporal area in which pre op MRI shows no atrophy. In such situations resections usually produce major memory deficits. This problem can be addressed by adopting MST to this region (Shimizu, 2008)

2.2 NEUROSTIMULATION PROCEDURES

2.2.1 VAGUS NERVE STIMULATION

Vagus nerve is composed of mainly afferent fibers (upto 80%) coming from gastro intestinal and respiratory tract to the brain. Its extensive connections in the brain and relatively easy accessibility in the neck are attractive features as a target for brain stimulation for control of epilepsy.

Zabara (Zabara, 1992) first demonstrated that experimental epilepsy in dogs could be controlled by Vagus nerve stimulation. Penry (Penry and Dean, 1990) first implanted commercial Vagus stimulator in humans. The European approval for this therapy was provided in 1994 and US FDA approved the Vagus nerve stimulation in 1998. Since then this is an established therapy for control of partial seizures which are medically intractable and not suitable for resective surgeries.

Rationale

The Vagus nerve contains motor, sensory, and preganglionic parasympathetic fibers at the area (mid cervical portion) where clinical nerve stimulation is carried out. The sensory information is conveyed by afferent fibers that terminate on nucleus tractus solitaries, cuneate nucleus and spinal nucleus of trigeminal nerve. From these second order and third order neurons connect to reticular formation, reph nucleus, thalamus. These structures connect extensively to hippocampus, amygdala, septum and eventually cortex. In chronic partial pharmaco resistant epilepsy it is proposed that seizures recur because of lowered seizure threshold as a dysfunction of Benzodiazpine receptors in hippocampus granule and pyramidal cells. Structures like amygdala, orbitofrontal cortex might be modulated by Vagus nerve stimulation and raise the seizure threshold. (Hernando, Pedro, 1993)

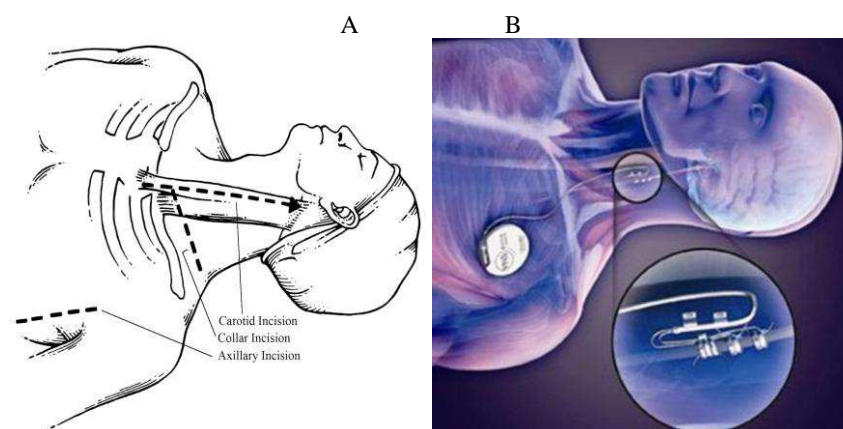


Figure 11 : Vagus Nerve Stimulation

*Part A illustrates the position and incisions for vagus nerve stimulation procedure.
Part B schematically shows the electrodes and stimulator and their placement.*

Procedure

An incision parallel to anterior border of Sternomastoid or a collar incision parallel to clavicle is taken. After cutting the platysma along the direction of its fibers the carotid sheath is opened. The jugular vein is retracted laterally to expose the Vagus trunk in the depth between carotid artery and the jugular vein.

The helical coil shaped electrodes have three segments (Figure 11 part B). The most proximal is a neutral one used as an anchor, the most distal is anode and the middle is cathode. These electrodes are wound over Vagus nerve by using a sting attached to each coil. The remaining portion is secured deep to carotid sheath so as to prevent migration of electrode due to neck movements.

A tunneling instrument is used to create a subcutaneous tunnel from neck to axilla above clavicle. An incision over anterior border of axilla is made to create a subcutaneous pocket to house the stimulator. Impedance of the electrodes and the battery is tested before skin closure.

Stimulation parameters

Stimulation parameters are variable but most beneficial effects are noted with a stimulation frequency of 30 Hz and 30 seconds on and 5 min off cycle.

Side effects

Coughing and hoarseness of voice are side effects of stimulation. These are often transient and settle down with adjustment of the parameters. Like any other implant infection, breakage are also documented with VNS.

Right sided stimulation

Initially VNS was performed exclusively on the left side. There was a concern about the cardiac side effects of right sided Vagus nerve stimulation. However right sided stimulation can also be performed safely and is often undertaken if left sided Vagus nerve stimulation is not possible or fails because of infection, lead migration or local pathology in the neck.

Efficacy

The Vagus nerve stimulation is found useful in both adult and pediatric patients (Elliot et al., 2011). About 40% of patients seem to have a 50% reduction in the seizures (Handforth et al 1998). This effect increases with the time. The number of anticonvulsants needed to control seizures seems to decrease with the time.

Table 8 : Efficacy of vagus nerve stimulation for control of seizures (Connor et al., 2012)

Authors & Year	Evidence Class	No. of Patients	Min FU (mos)	% of Patients	
				Seizure-Free Status	≥50% Reduction
Ben-Menachem et al., 1994	I	67	3.5	—	38.7
Handforth et al., 1998	I	196†	3.0	—	—
George et al., 1994	II	67	16.0	—	—
Ben-Menachem et al., 1995	II	16	9.0	—	—
Salinsky et al., 1996	II	100	24.0	—	18.4
Ben-Menachem et al., 1999	II	64	3.0	—	40.4
Vonck et al., 1999	II	15	12.0	27.0	67.0
Sirven et al., 2000	II	45	3.0	—	67.0
Ardesch et al., 2007	II	19	12.0	—	36.8
Janszky et al., 2005	III	47	12.0	13.0	—
Murphy, 1999	III	60	3.0	—	—
Chavel et al., 2003	III	29	24.0	—	61.0
Murphy et al., 2003	III	96	6.0	—	45.0
Benifla et al., 2006	III	41	6.0	—	3.8
Saneto et al., 2006	III	43	9.0	—	51.0
De Herdt et al., 2007	III	138	12.0	9.0	59.0
Montavont et al., 2007	III	50	21.6	—	—
Ghaemi et al., 2010	III	144	24.0	6.9	61.8
Elliott et al., 2011 ¹⁰	III	436	3.0	—	63.7
Elliott et al., 2011 ¹¹	III	141	3.0	—	64.8

* FU = follow-up; — = not reported.

2.2.2 DEEP BRAIN STIMULATION

Deep brain stimulation is an emerging technique for controlling pharmaco resistant epilepsies. An extensive account of its place in epilepsy therapy is provided in a separate chapter.

2.3 NEWER EXPERIMENTAL TECHNIQUES

2.3.1 TMS: REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION

The TMS technique is a noninvasive method of stimulating brain. It was developed around 1985 by Anthony Barker to stimulate motor cortex. Since then the technique has evolved into many areas of diagnosis, and even therapeutics. It is an attractive method because of its easy to use nature and relative inexpensiveness as well as large safety margin. rTMS (repetitive transcranial magnetic stimulation) reflects neuronal excitability. Different parameters used in TMS represent different events in neuronal functioning and are summarized below:

Table 9 : Parameters of TMS and effect (Theodore, 2003)

Parameter	Measurement	Physiological Significance
Motor threshold	Single pulse: threshold for motor response	Cortical neuronal membrane excitability; corticospinal system threshold
MEP amplitude	Single pulse: averaged maximal amplitude	Excitable proportion of neuronal pool
Cortical silent period	Single pulse: observation of reduced post-MEP background activity during muscle contraction	Cortical inhibitory mechanisms (possibly GABA _B)
Intracortical inhibition	Paired subthreshold conditioning and suprathreshold pulses 2- to 5-ms delay	Possibly GABAergic
Intracortical facilitation	Paired subthreshold conditioning and suprathreshold pulses 7- to 20-ms delay	Uncertain

TMS, transcranial magnetic stimulation; MEP, motor evoked potential; GABA, γ -aminobutyric acid.

Rationale

Though there is very little information about how rTMS may influence human epilepsy the evidence is extrapolated from animal experiments. The application of rTMS as a therapeutic measure stems from its lasting effects even after stopping ongoing stimulation. The low frequency stimulation below 1Hz increases the cortical silent period and decreases excitability while high frequency stimulation promotes cortical excitability.

These effects are similar to long-term depression (LTD) and long term potentiation, two forms of synaptic plasticity elicited in animal models of cortical circuitry by low- and high-frequency electrical stimulation, respectively. So it has been suggested that low-frequency rTMS may exert antiepileptic effects whereas high-frequency stimulation may act as a proconvulsant.

TMS is a relatively new therapy for pharmaco resistant epilepsies. Though it is found useful in human condition as exemplified from the table below many issues need to be addressed. Coil design, best location of coil, best stimulation parameters are few such issues. With advancement in technology and better understanding of its mechanism TMS could become an important tool for treating pharmaco resistant epilepsies in future.

Table 10 : Efficacy of TMS for control of seizure (Kimiskidis, 2010)

1	Authors (first authors)	Study design	Epilepsy syndrome /Numbers	Seizures	Epileptiform discharges
2	Tergau 1999	open-label	TLE=2, ETLE=7	decreasing	NR
3	Menkes 2000	case report	ETLE (parietal CD)	decreasing	decreasing
4	Theodore 2002	randomized, double-blind, sham-controlled	focal (mTLE=10, iTLE=10, ETLE=4)	trend for reduction	NR
5	Tergau 2003	crossover, placebo-controlled	mTLE=2, ETLE=11, multifocal=2, generalized=2	decreasing (at 0.33 Hz only)	NR
6	Daniele 2003	open-label	focal (frontal=2, multifocal=2, due to CD)	decreasing (in patients with a single focus)	NR
7	Rossi 2004	case report	epilepsia partialis continua due to CD	decreasing	decreasing
8	Brasil-Neto 2004	open-label	focal (TLE=2, FLE=3)	decreasing	NR
9	Misawa 2005	case report	epilepsia partialis continua due to CD	decreasing (for 2 months)	NR
10	Kinoshita 2005	open-label	focal (frontal=5, parietal=1, hypothalamic hamartoma=1)	decreasing	NR
11	Fregni 2005	open-label	TLE=3, multifocal=4, ETLE=1, all due to MCD	decreasing (for 1 month)	decreasing (for 1 month)
12	Fregni 2006	randomized, double-blind, sham-controlled	focal (MCD)	decreasing	decreasing
13	Joo 2007	randomized	focal (n=18), multifocal (n=8), non localized (n=9)	trend for reduction (correlation with no. of stimuli)	decreasing
14	Cantello 2007	randomized, double-blind, sham-controlled	focal (mTLE=7, NE=34) generalized=2	no change	decreasing

2.3.2 RADIONEUROSURGERY

Radiosurgery is application of ionizing radiation as a surgical tool. Focused radiation has been used to treat difficult deep seated lesions in brain like tumors, cavernous malformations. Same therapy can be applied to target a non lesional epileptic focus.

Radiation beams are of two types a proton beam and a photon beam. Protons have mass and proton beams scatter less. However the proton accelerators are costly. In contrast photons have no mass but scatter easily. This limitation is overcome by focusing multiple beams to a target. Currently used radiosurgical therapy units use multiple beams focused on a target.

The use of radiosurgery in non lesional epilepsy

The first use of ionizing radiation to treat a non lesional epilepsy was by Talairach and colleagues in mesial temporal epilepsy. They treated 44 epileptic patients with stereotactic implantation of yttrium-90 into the amygdala and the hippocampus. Of the treated patients 88% showed disappearance of epilepsy (Talairach et al., 1974).

First use of current linear accelerators for treatment of epilepsy was done in 1993 in Marseilles. A gamma knife at a low dose of 25Gy was used on 3 patients with medically refractory to perform an entorhinoamygdalohippocampectomy (Régis, 2000b).

The use of radiosurgery in lesional epilepsy

The ameliorating effect on seizures was noted in treatment of cerebral lesions like tumors and cavernous malformations. Initially it was thought that the destruction of lesion leads to control of seizures because the abnormal epileptic activity associated with the lesion gets abolished. However it was noted that seizures associated with AVM treated by radiation ceased even before the AVM was closed and in few cases despite failure of closure. That led to foundation of thought that radiation itself could work as anti epileptic.

Rationale

Ionizing radiation acts by damaging the DNA and generating free radicals. The developed neurons are as such resistant to these effects. Hence the improved control over epilepsy seen after radiosurgery might be not related to destruction of the lesion alone. Perhaps neural plasticity and neurogenesis might be affected by radiation providing a neuromodulatory effect. However MR and MR spectroscopy indicates several changes occurring in the irradiated cerebral tissue. So a combination of structural and functional mechanisms might act together to produce control over the epilepsy.

Outcome

Radiotherapy for epilepsy associated with hypothalamic hamartoma has been explored. Hypothalamic hamartoma are deep seated non malignant lesions difficult to excise surgically because of location and important functions related to the hypothalamus -pituitary complex. About 30% patients were found to be seizure free after radiosurgery (Regis et al., 2000b). However other surgical technique like transcallosal excision has documented better (about 55%) remission rates. No multicentric trial is reported as yet.

Seizure remission rates in RS of arteriovenous malformation range from 55–80%. Although the usefulness of RS in the treatment of cavernous malformation is controversial (mainly from high rates of hemorrhage in some series (Steiner et al., 2010), RS causes remission of seizures in 25–64% of patients with cavernous malformation (Regis et al., 2000b, Kim et al., 2011). In mesial temporal epilepsy the European trial demonstrated a 2-year postoperative seizure remission rate of 62% (Barbaro et al., 2009) An American trial showed a remission rate of 77% in the high-dose group and 59% in the low-dose group. An open label trial radiosurgery versus conventional respective surgery in MSL is ongoing in USA (Quigg et al., 2012).

Safety issues

Radiosurgery for control of lesional and non lesional epilepsy requires that all safety issues with the radiation are addressed. Radiation induced necrosis edema can produced transient symptoms of headache and partial dysfunction of the edematous zone. The control over seizures evolve along the time and patient needs to know this .Some complications like post procedure hemorrhages in the treated area especially cavernous malformations are reported. The dose, treatment protocols are yet to be standardized for epilepsy.

CHAPTER III

DEEP BRAIN STIMULATION AND EPILEPSY

3.1 INTRODUCTION

Stimulating specific brain structures to treat pharmaco resistant epilepsy is a concept gaining ground. Epilepsy occurs due to synchronization of abnormal neuronal activity across regions of the brain. These abnormal circuits could be interrupted by stimulation. The stimulation could be at three sites, ie either at the cortical area where the abnormal rhythm is generated, at the ‘nodes’- the subcortical structures that are involved in seizure propagation and maintenance or at ‘modulatory’ regions which influence the ‘ nodes ‘.

Introduced in 1986, vagus nerve stimulation (VNS) has now become a well established cranial nerve stimulation procedure for treating pharmaco resistant epilepsy. It offers a mean seizure reduction of 28% for patients in whom it is employed with 23% of patients having a greater than 50% reduction in seizure frequency (Class 1 evidence) (DeGiorgio et al., 2000). Rather than stimulating a nerve accessible peripherally and influencing indirectly the brain, direct stimulation of more central structures (deep brain stimulation DBS) appears rational. DBS has advantages like titrability, reversibility, and excellent safety profile, its remarkable success in treating movement disorders like Parkinson's disease (Benabid et al., 2009) has paved the way for exploring its potential application in epilepsy.

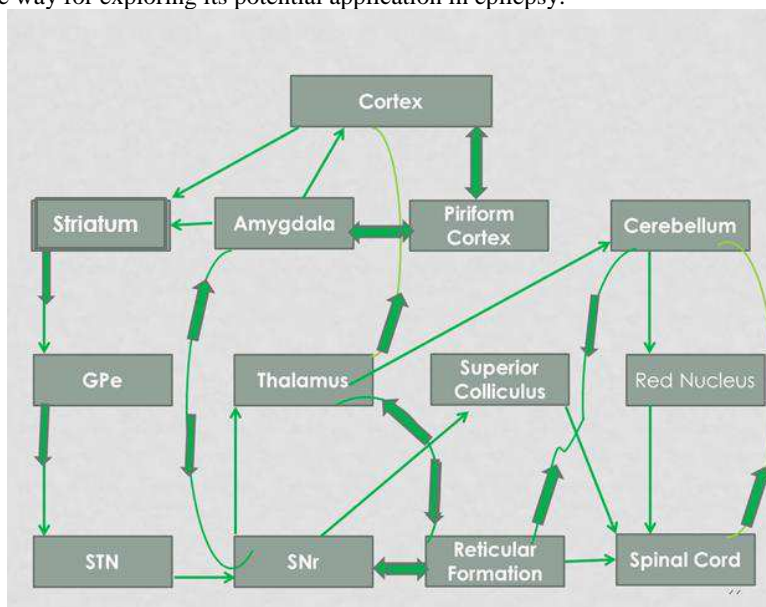


Figure 12 : Brain connectivity

A schematic representation of connectivity in the brain .For reasons of simplicity few of the connections (like recurrent thalamo- cortical relay, hyperdirect cortico STN path are not shown. Any of these structures could be potential targets for DBS in epilepsy.

Circuits implicated in Epilepsy

The classical circuit of Papez links the hippocampus to the thalamus, the cingulate gyrus and entorhinal cortex/parahippocampal gyrus. Fibers from the hippocampus travel via the fornix to the mamillary bodies, which in turn link to the hypothalamus and then the anterior nucleus of the thalamus via the mamillothalamic tract. The anterior thalamic nucleus communicates with the cingulate gyrus, which connects via cingulum to parahippocampal gyrus then to entorhinal cortex. The other circuit is basal ganglia- cortical circuit described in details in next chapter. The third one consists of thalamo cortical loops which allows, forward and back information flow between cortex and thalamus. Though these three circuits appear separate they are interconnected and integrated functionally. Hence different parts in these circuits (nodes) activated by electrical stimulation can modulate and control epilepsy.

3.2 RATIONALE IN CHOOSING TARGETS FOR DBS

Cerebellum

The discovery of the importance of cerebellar Purkinje cells in the generation of widespread inhibitory discharges led the foundation of using this as a target for stimulation in epilepsy. Also it is found that cerebellar input to the ventral lateral thalamic nucleus results in diminished excitatory output to the cortex.

Subthalamic nucleus

The STN is functionally divided into three parts (ref figure below): Medial most portion is related to anterior cingulate cortex and ventral pallidum. The dorsolateral motor portion is connected to motor cortex while ventral portion is related to associative areas with connection to the substantia nigra. Thus STN is connected to limbic areas, motor areas and associative areas of cortex. It is connected to output structure Snr and can perform modulation of the substantia nigra. A nigral control of epilepsy in animals has been well described (Depaulis et al 1994). The substantia nigra receives projections from the subthalamic nucleus (STN), and stimulation of STN is believed to enhance the antiepileptic effect of the substantia nigra pars reticulata (Lim et al., 2007). Moreover, STN has already been well- established as a target for Parkinson's disease (Benabid et al., 2009).

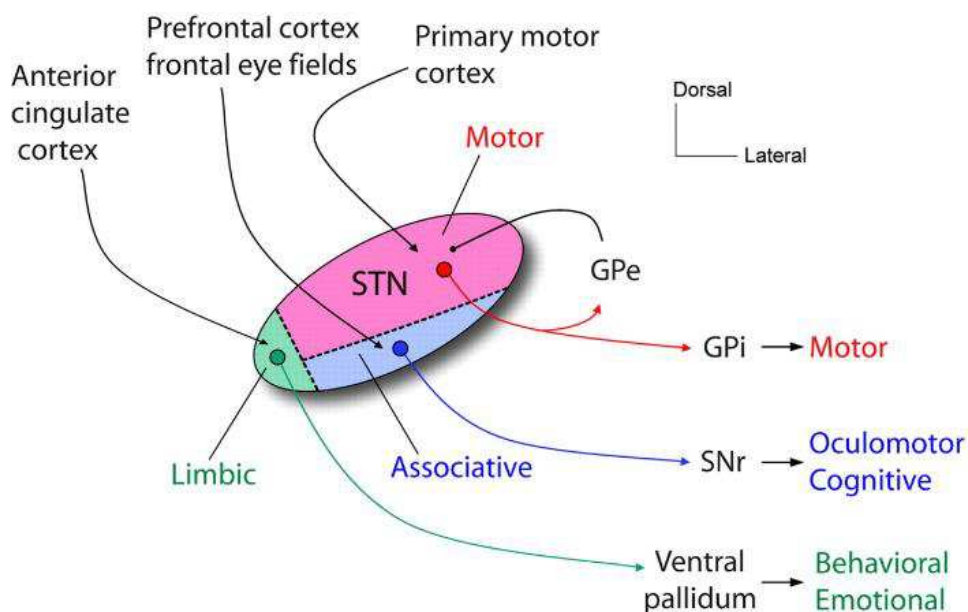


Figure 13 : Functional anatomy of STN (Benarroch, 2008)

Amygdala and Hippocampus

It is known for quite some time that electrographic localization occurs in these areas in cases of Mesial temporal lobe epilepsy. Similarly surgical excision of these structures provides excellent control over seizures. These observations were used to stimulate the hippocampus and amygdala as the areas involved in generation of epilepsy (Velasco et al., 2007).

Thalamic nuclei

1. Anterior nucleus of thalamus (ANT) is a preferred target because it is highly connected with the hippocampus through Papez circuit. Hippocampus is one of the most epilepsy-susceptible areas involved in origin of temporal lobe epilepsy. Moreover the ANT projects largely to the cingulate gyrus, then it further projects to limbic structures and wide regions of neocortex acting as a relay station amplifying and synchronizing seizure activities in these circuits (Takebayashi et al., 2007). ANT is involved in central thalamus and posterior thalamus to amplify and synchronize seizure afterdischarges as noted in metabolic studies. Thus it is important station in intra thalamic pathways (Jones and Leavitt, 1974).
2. The centromedian nucleus of the thalamus (CMT) is an important structure in the reticulo-cortical system, and is thought to mediate cortical excitability (Jasper, 1991).

Striatum (Caudate and Putamen)

The primary motor cortex and the primary somatosensory cortex project mainly to the putamen, but the premotor cortex and supplementary motor areas project to the caudate head.

Frontal lobe projects predominantly to the caudate head and the putamen; the parietal and occipital lobes project to the caudate body; and the temporal lobe projects to the caudate tail. The low-frequency stimulation of caudate is hypothesized to induce cortical hyperpolarization and resultant control over seizures.

3.3 DBS IN EPILEPSY ANIMAL STUDIES

In the following tables experimental evidence in animal models about DBS and epilepsy is summarized.

STN

Table 11 : Animal studies of STN stimulation for epilepsy

Studies (First Authors)	Model /animal	Stimulation parameters	Summary of results
Vercueil 1998	Absence seizures GAERS rats	130 Hz, up to 300 μ A, 60 μ S	Bilateral stimulation effective in suppressing spike wave discharge
Lado 2003	Generalized clonic and tonic-clonic flurothyl seizures. Adult rats	130, 260, 800 Hz, upto 500 μ A, 60 μ S	Bilateral stimulation of at 130 Hz increased the seizure threshold 800Hz was proconvulsive
Usui 2005	Limbic seizures, Kainic acid. Adult rats	130 HZ, 60 μ S	Unilateral stimulation decreased secondary generalization of seizures but time spent in focal seizure unaffected
Shهاب 2006	Tonic Brain stem seizures. Electroshock model; rats	130 260 Hz, upto 300 μ A 30 min before inducing seizures	Tonic hind limb extension (seizure) not affected

Table 12 : Animal studies of SNr stimulation for epilepsy

Studies (First Authors)	Model /animal	Stimulation parameters	Summary of results
Morimo to 1987	Amygdala and pyriform kindled rats	100Hz upto 1.2 μ A 14 days before inducing kindling	After discharges duration decreased, Bilateral prestimulation blocked seizure generalization in some animals, prolonged the latency to bilateral forelimb clonus in others
Velsek 2002	Generalized clonic and tonic-clonic flurothyl seizures. Adult and Young rats	130 Hz, up to 690 μ A for young and 952 μ A for adult rats, 60 μ S	Bilateral stim effective in clonic seizures in adults, effective in both clonic and tonic clonic seizures in young rats
Usui 2005	Limbic seizures, Kainic acid; Adult rats	130 HZ, 60 μ S	No effect
Shi 2006	Amygdala kindling ; rats	130 Hz upto 200 UA, 60 μ S	43.5% rats showed complete blockage of stage six seizures Induced by kindling. There was a protective after effect Subsequent Kindling failed in 60% of rats belonging to this group.
Feddersen 2007	Absence seizures; GAERS rats	5 to 500 Hz ,10 to 100 μ S	60 Hz frequency and th 60 μ S optimal for controlling SWD. But repeated stimulation ineffective and might increase seizure number.
Shehab 2011	Tonic Brain stem seizures. Electroshock model; rats	30 or 260 Hz	fails to suppress tonic seizures
Saillet 2012	Absence seizures; GAERS rats	responsive SNr stimulation and Auditory	Snr bilat stim effective in 97% seizures

Caudate nucleus

Table 13 : Animal studies of caudate stimulation for epilepsy

Studies (First Authors)	Model /animal	Stimulation parameters	Summary of results
Costin (1963)	Hippocampal Stimulation; Rabbits	15, 200, 300 Hz; 2-8 V; 1 ms	Prolongation of after discharge when caudate nucleus was stimulated immediately after the hippocampal stimulation
Mutani (1969)	Cobalt induced rhinencephalic epileptic focus	100 Hz; 5-30 V; 0.6 ms	Decreased excitability of the focus after caudate stimulation
Grutta (1971)	Amygdala stimulation ; Cats	30 Hz; 0.2-1.5 mA; Pulse width 1.5 ms	Preventive stimulation of caudate useful in blocking after discharges
Wagner (1975)	Penicillin induced focal seizures ;cats	400 Hz; 0.3-0.9 mA; Pulse width 0.5 ms	Very active foci driven by stimulation but low activity foci suppressed
Amato (1982)	Amygdala stimulation; rats	30-80 Hz; 4-12 V; 0.1-1 ms	Caudate nucleus stimulation less effective than SNr, Endopeduncular nucleus
Oakley (1982)	Aluminium injection (focal)	10 and 100 Hz; 1-6 mA; Pulse width 1 ms 10 min on/off or continuous	Low frequency stimulation controlled seizure frequency, high frequency increased seizure frequency
Psatta (1983)	Cobalt induced focal seizures ; cats	S5 Hz; 1-5 V; 1 s feedback stimulation by automatic detection of interictal spike pulse width 0.3 ms 30 Hz; 0.2-1 mA; 10-60 s Pulse width 0.5-1 ms	Number of interictal spikes decreased by stimulation
Grutta (1988)	Penicillin induced focal hippocampal seizures; cats	10 or 25 Hz; 0.1-0.5 mA; Pulse width 1 ms	Caudate stimulation decreases number and amplitude if hippocampal spikes

Reticular nucleus

Table 14 : Animal studies of Reticular nucleus stimulation for epilepsy

Studies (First Authors)	Model /animal	Stimulation parameters	Summary of results
Nanobashvili (2003)	Hippocampal Kindling limbic seizures; rats	60 Hz; 150 μ A; pulse width 0.5 ms	Costimulation of caudate during kindling reduced seizure duration and number of seizures

Anterior nucleus of thalamus

Table 15 : Animal studies of Reticular nucleus stimulation for epilepsy

Studies (First Authors)	Model /animal	Stimulation parameters	Summary of results
Mirski (1997)	PTZ; rats	100 Hz and 8 Hz; 350-1000 μ A Pulse width 0.1 ms	high frequency stimulation raised the clonic seizure threshold Low frequency stimulation (8 Hz) was in contrast, proconvulsant
Hamani (2004)	Pilocarpine; adult rats	100 Hz; 800 μ A Pulse width 100 μ s; uni and bilateral	Bilateral thalamic stimulation did not prevent SE (observed in 56% of the animals), but it significantly prolonged the latency to its development
Ziai (2005)	PTZ ;Sprague-Dawley male rats	100 Hz; 150 μ A; Pulse width 0.1 ms; 40 min before and continued during PTZ infusion. bilateral	Bilateral AN stimulation delayed the onset of EEG seizures
Lado (2006)	Systemic Kainic acid producing status and chronic epilepsy; rats	100 Hz; 100-550 μ A; Pulse width 100 μ s; cont./intermitt bilateral	Seizure frequency during stimulation was 2.5 times the baseline. In some cases stimulation triggered seizures
Zhang (2012)	amygdala-kindled seizures ; Wistar rats	15min train of 100 μ s pulses at 150Hz and 450-800 μ A	Bilateral HFS reduced the number, severity of seizures and reduced duration of afterdischarge Preventive stimulation also protected but weaker effect.
Takebayashi (2007)	Kainic Acid in amygdala focal limbic seizure; rats	130 Hz; 140-500 μ A	significantly decreased mean seizure frequency and secondary generalized seizure frequency
Hamani (2008)	Pilocarpine; rats	1000, 500, 200 μ A and 20 Hz or 130 Hz.	stimulation at 500 μ A significantly increased the latency for seizures

Table 16 : Animal studies of Cerebellar stimulation for epilepsy

Studies (First Authors)	Model /animal	Stimulation parameters	Summary of results
Hutton (1972)	Penicillin focal; cats		Cerebellar stimulation inhibits seizure foci
Mutani (1969)	Cobalt focal; cats	100 Hz, 7V Pulse width 0.6 ms Lobus anterior	Decrease or interruption of AD After seizure activity; inhibition ?
Maiti (1975)	Hippocampal electrical Stimulation; cats and monkeys	Cerebellar middle cortex vermis stimulation	After discharges reduced cerebellar cortex can exert inhibitory influence on amygdala and hippocampus
Hablitz (1975)	Aluminium hydroxide gel focal motor seizures ; primate	5-15 Hz and 100 Hz; 1-10 V; 1-30 s Pulse width 1 ms	LFS ineffective HFS proconvulsive
Bantli (1978)	Penicillin focal sensory motor seizures ; cats	10 Hz; 26 mA/cm ² Pulse width 0.1 ms	Duration of seizures significantly reduced
Ebner (1980)	Aluminium hydroxide gel focal motor seizure ;primate	10 Hz; 10 min on/off Pulse width 0.1 ms Vermis	stimulation did not produce any statistically significant effect on excitability at focus
Godlevskii (2004)	Systemic Penicillin Induced seizures ;rats	10-12 Hz and 100-300 Hz; 20% of behavioural threshold Pulse width 0.25-0.5 ms	LFS proconvulsive HFS decreased the frequency and amplitude of spike potentials and decreased total duration of epileptic foci.
Rubio (2004)	Amygdala kindling Rats	100 Hz; 20 µA Superior pedunculus	facilitate the limbic seizures and impede the secondary generalized seizures.
Wang 2008	Amygdala kindling; rats	1 Hz (15-min train of 0.1-ms pulses, 100 µA)immediately after kindling	Ipsilateral Nucleus fastigeus stim significantly inhibitedthe seizure stage and afterdischarge

Hippocampus

Table 17 : Animal studies of Hippocampus - Amygdala stimulation for epilepsy

Studies (First Authors)	Model /animal	Stimulation parameters	Summary of results
Gaito (1980)	Amygdala kindling; Rats	3 Hz; 100-196 µA; 30 s at kindling focus	Suppression of behavioral seizures
Shao (1982)	Amygdala kindling	60 Hz; until 54 µA; 1s at kindling focus	Inhibition

Studies (First Authors)	Model /animal	Stimulation parameters	Summary of results
Ullal (1989)	Amygdala kindling; Rats	Single episode of LFS 4 Hz; 1/2 of AD threshold pulse width 125 ms	After discharge threshold increased
Weiss (1998)	Amygdala kindling; Rats	1 Hz; 5-15 μ A; 15 min Direct Current (DC)	DC produced attenuation of kindling development and an increase in the afterdischarge threshold. This effect persisted in some animals for 1 month after discontinuation
Bragin (2002)	Kainic Acid spontaneous recurrent seizures	1, 50 and 200 Hz; 10 min	Daily 2-h LFS and HFS did not have a long-term effect on the rate of interictal events and spontaneous seizures.
Velsek (2002b)	Amygdala kindling; Immature rats	1 Hz; 280 μ A; 15 min pulse width 200 μ s	LFS suppressed afterdischarge duration and seizure stage
Lopez- Meraz (2004)	Amygdala kindling; rats	1 Hz; 100-400 μ A; 15 min immediately after kindling	The LFS suppressed attainment of stage V kindling) but not the presence of partial seizures in 85.7% of the rats.
Goodman (2005)	Amygdala kindling ; rats	1 Hz; 50 μ A; 30 s	LFS produced significant decrease in AD duration and stage 5 seizures
Wyckhuys (2007)	Alternate Day Rapid Kindling model of temporal lobe epilepsy; rats	130 Hz; 329 \pm 52 μ A;	After discharge threshold increased,duration shortened by high frequency stimulation
Mohammad-Zadeh (2007)	Rapid kindling of Perforant path;rat	1 Hz; 50-150 μ A Pulse width 0,1 ms At Perforant path	LFS of perforant path has a significant antiepileptogenic effec
Urino 2010	Kainic acid in amygdala	10 or 30 Hz, 0.1-0.3 mA.1 msec duration	Seizure frequency was significantly reduced by 10 Hz stimulation of the amygdala thalamus.
Sun 2010	amygdala- kindled seizures ;Sprague-Dawley rats.	LFS (15 min train of 0.1 ms pulses at 1 Hz and 100 μ A)at CA3 region	LFS reduced severity of and susceptibility to evoked seizures,effect weak in Preventive stimulation

Locus coeruleus

Table 18 : Animal studies of stimulation of other targets for epilepsy

Studies (First Authors)	Model /animal	Stimulation parameters	Summary of results
Jimenez-Rivera (1987)	Amygdala kindling	Twenty to thirty minutes of Locus coeruleus stimulation delivered prior to each amygdala kindling session	Stimulated animals spent longer time in stage 1 (inhibitory)
Libet (1977)	Subconvulsive dose pentylenetetrazol; rats	50-200 Hz; 40-100 μ A; 20- 40 min Pulse width 20-200 μ s	A unilateral stimulus suppressed bursts bilaterally.

Nucleus of tractus solitarius (NTS)

Table 19 : Animal studies of nucleus of tractus solitarius stimulation

Studies (First Authors)	Model /animal	Stimulation parameters	Summary of results
Magdaleno-Madrigal (2010)	Amygdala kindling; Cats	1 min on/5 min off, 1 h total /6 days prior to kindling	preemptive NTS electrical stimulation interferes with epileptogenesis
Magdaleno-Madrigal (2002)	Amygdala kindling; cats	30 Hz; 150-300 μ A; 1 min Pulse width 0.5 ms	NTS Significant slower progression towards fully kindled animals

3.4 DBS IN EPILEPSY HUMAN STUDIES

Table 20 : Human studies of STN stimulation for epilepsy

Studies (First Author)	Number of patients / Trail design	Seizure / Epilepsy	Stimulation Parameters	Results
Benabid (2002)	1 cortical dysplasia	Refractory partial seizures		80% reduction in number and severity of seizures. improvement in both motor and cognitive functions
Chabardes (2002)	5	Medically refractory epilepsy one patient of severe myoclonic epilepsy (Dravet	HFS STN	67% to 80% reduction in seizure frequency was observed in three patients. Dravets syndrome responded weekly and no

		syndrome)and one had an autosomal dominant frontal lobe epilepsy		effect on patient with autosomal dominant frontal lobe epilepsy
Shon (2005)	2 already underwent respective surgery on frontal cortex	Bilateral asymmetric tonic seizures (left > right) with rare drop attacks	Chronic HFS	Seizure frequency reduced by 86.7% in patient 1 and by 88.6% in patient 2
Handforth (2006)	2	Partial onset refractory seizures	HFS	One patient had about 50% reduction in seizures other had 33% reduction in frequency but more benefit in seizure severity
Lee (2006)	3			49.1% reduction

Table 21 : Human studies of STN stimulation for epilepsy

Studies (First Author)	Number of patients / Trail design	Seizure / Epilepsy	Stimulation Parameters	Results
Wille (2011)	5-Progressive myoclonic epilepsy syndrome		HFS STN/ SNr + HFS ventral intermediate nucleus (VIM) 4 patients	HFS STN/ SNr Produced 30% to 100% reduction in seizure frequency improved capabilities like free standing, walking ; improved fine motor skills
			VIM stimulation found ineffective, sometimes triggered myoclonia	
Cappecci (2012)	2 patients already undergone anterior collosotomy but no benefit	First patient had Partial motor and tonic clonic seizures Second patient had atonic drops and absence seizures	Bilateral HFS	First patient- had 65% decrease of partial motor seizures and 100% control over tonic- clonic generalized attacks. Second patient -no reduction of fits and an increase atypical absence seizures.

Table 22 : Human studies of Anterior Nucleus stimulation for epilepsy

Studies (First Author)	Number of patients /Trail design	Seizure /Epilepsy	Stimulation Parameters	Results
Upton (1987)	6 open label	Partial onset	60–70 Hz, 300ms pulses, 3.5–3.8V	66% improvement
Hodaie (2002)	5 open label follow up for 15 months	Refractory Secondarily GTC, GTC, CPS, partial motor, atonic drop attack	100 Hz, 10V	mean reduction of 54% In two patients seizure reduction of > or =75%.

Kerrigan (2004)	5 open label follow up from 6 to 15 months	Intractable partial epilepsy. Four of the patients also had secondarily generalized seizures.	100 Hz, pulse width, 90 ms; voltages 1.0 - 10.0 V.	20% reduction
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Table 23 : Human studies of Anterior Nucleus stimulation for epilepsy

Studies (First Author)	Number of patients /Trail design	Seizure /Epilepsy	Stimulation Parameters	Results
Lee (2006)	3	Chronic refractory epilepsy		75.4% reduction in seizure number from stimulation
Osorio (2007)	4 36 months of treatment period	Mesial temporal lobe epilepsy	75 Hz; 4.1 V; 90 μ s; 1 min ON, 5 min OFF)	reduction in seizure frequency was 75.6%
Lim (2007)	4 follow up for 48 months	Generalized seizures, partial seizures and secondary generalization	4-5 V, 90-110 Hz, and 60-90 micros.	35% to 76% seizure reduction.
Fisher (2010) SANTE trial	110 patients Randomised blinded, in first 3 month phase into control and stimulation group	Partial seizures and partial with secondary generalization		By end of blinding phase Stimulated group had a 29% greater reduction in seizures .By end of two years overall reduction was 56%
Oh (2012)	9 follow upto 1 year	Refractory epilepsy		Mean seizure reduction 57.9% (35.6-90.4%). improvements in verbal recall and oral information processing

Centro median nucleus thalamus

Table 24 : Human studies of Centro median Nucleus stimulation for epilepsy

Studies (First Author)	Number of patients /Trail design	Seizure /Epilepsy	Stimulation Parameters	Results
Fisher et al. (1992)	7 double blind cross over blocks of 3 months on / off 3 months washout period	Generalized onset seizures	65 Hz 90-microseconds pulses, 1 min of each 5 min for 2 h/day, with voltage set to half the sensory threshold	tonic- clonic seizure frequency reduced by 30% during stimulation. No effect on number of generalized seizures
Chkhenkeli (2004)	15 open label	Mesio temporal foci	20–130 Hz	desynchronized the EEG and suppressed partial motor seizures
Andrade (2006)	2 open label	GTC, multifocal partial epilepsy with secondarily GTC	100–185 Hz, 1–10V	No benefit
Velasco (2007)	13 open label	Lennox-Gastaut syndrome (LGS)	130 Hz, 0.4–0.6mA	Overall seizure reduction was 80%. Improved quality of life

Table 25 : Human studies of Cerebellar stimulation for epilepsy

Studies (First Author)	Number of patients /Trail design	Seizure /Epilepsy	Stimulation Parameters	Results
Copper (1976)	15 patients open label	Psychomotor, Gen tonic cloinc myoclonic	10 HZ,	66%reduction Apparently no adverse effect
Sramka (1976)	10	Types not described	10–100 Hz, 1 ms, 10 V at bilateral dentate nucleus	100% initial benefit but development of kindling phenomenon
Gillman (1979)	6	Types not described	1 ms 10 HZ	83% had decreased seizures

Table 26 : Human studies of Cerebellar stimulation for epilepsy

Studies (First Author)	Number of patients /Trail design	Seizure/Epilepsy	Stimulation Parameters	Results
Davis (1992)	32 seizures patient implanted 26 followed up for 17 years	Two 'spastic seizures' others variable seizure types	Charge densities were 0.9-2.5 microC/ cm2/ phase delivered at 10-180 pulses/ s to bilateral electrode pads on the superomedial cerebellar cortex. 150 pulses/ s, 1-1.4 mA	5 (31%) continue to be seizure-free, 7 (44%) have a reduction and 4 (25%) have no change or a slight increase
Wright (1984)	12 patients double blind follow up for 6 months	Severe intractable epilepsy		No significant benefit statistically however 11 patients subjectively felt better
Velasco (2005)	Double blind randomized 5 patients	Generalized tonic clonic; motor epilepsy	Post operatively first 3-month double-blind phase-reduction of seizures up to 33% of pre operative phase. Six month follow up reduction to 41% of pre op frequency. Effect persistent for 2 years	
Krauss (2007) (review of many studies)	36 (from different small series of clinical studies)	Various	33.3% seizures free; 91.6% w/ significantly decreased seizures	

Table 27 : Human studies of Hippocampus - Amygdala stimulation for epilepsy

Studies (First Author)	Number of patients / Trial design	Seizure / Epilepsy	Stimulation Parameters	Results
Vonck (2002)	3 follow up 5 months	Complex partial seizures		50% reduction in seizures in all patients
Tellez-Zenteno (2006)	4 double blind, multiple cross-over, randomized controlled	Mesial temporal lobe epilepsy	90 microsec, 190 Hz	Overall reduction in seizure frequency 15% not statistically significant
Boon (2007)	10 follow up 12 to 52 months	Refractory temporal lobe epilepsy		1 patient had 100 % reduction of seizure frequency 1 did not respond 5 patients had 50% reduction
Velasco (2007)	9 follow up 18 months to 7 years	partial complex seizures, some with secondary generalizations		Five non lesional MTI had seizure reduction of >95%, four with hippocampal sclerosis had 50-70% reduction.
McLachlan (2010)	2 double blind, cross-over, randomized controlled	Bilateral mesial temporal epilepsy		Seizure frequency decreased by 33% patients during stimulation and remained lower by 25% for the 3 months after stimulation turned off then returned to baseline

Table 28 : Human studies of Hippocampus - Amygdala stimulation for epilepsy

Studies (First Author)	Number of patients / Trial design	Seizure / Epilepsy	Stimulation Parameters	Results
Tyrand (2012)	6 temporal lobe epilepsy with hippocampal sclerosis (HS) 6 non lesional temporal epilepsy	Temporal lobe epilepsy	130 HZ amygdala-hippocampus area	Interictal epileptic discharge rates significantly reduced in all patients with hippocampal sclerosis but only 2 patients showed this improvement in non lesional group

Other targets

Hypothalamus /Zona inserta

Table 29 : Human studies of stimulation of other targets for epilepsy

Studies (First Author)	Number of patients / Trail design	Seizure / Epilepsy	Stimulation Parameters	Results
Franzini (2008)	4 patients refractory epilepsy	patient 1- multifocal epilepsy, patient 2- refractory partial motor and secondary generalized seizures. Patients 3- focal motor status seizure Patient 4- behavioral multifocalseizure	Patient 1,4- posterior hypothalamus patient 2,3 - caudal zona incerta	All patients showed significant decrease in seizure frequency patient 3 -motor focal reduced by 70%
Khan (2009)	2 hypothalamic hamartoma cases Mamillo thalamic tract		High frequency	one patient seizure free for 10 months post operative period .Other also benefitted
Marras (2011)	1 report follow up 18 months	Left temporal seizures	130 HZ	Number of complex partial seizures decreased but no significant effect overall

Which Target for which epilepsy?

Making a selective recommendation of a particular target for particular form of epilepsy is difficult based on the results of published human data. This is so because except the SANTE trial of Anterior Nucleus of thalamus Stimulation which involved 110 patients, all other reports are based on few case studies or clinical trials on small number of patients. However pooling the robust data of animal studies and considering the circuits mentioned at the beginning of the chapter, some conclusions can be drawn about optimal targets for stimulation based on the seizure onset zone These are described below.

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 PD (Gradinaru et al., 2009). The STN receives a strong input from cortex via hyperdirect pathway as described in details in chapter 4. The substantial benefits of STN stimulation in a case of refractory seizures, due to cortical

dysplasia in motor cortex (Benabid et al., 2002) supports this. Capecchi (Capecchi et al., 2012) reported two patients who had already undergone anterior callosotomy without benefit in which HFS of STN was performed. The best responder had 65% decrease over seizures had tonic clonic motor seizures. Other good responders to STN stimulation appear to be patient suffering from Progressive Myoclonic Epilepsy Syndrome (PME) (ref table 20 above). These patients have often trigger-dependent myoclonic jerks and generalized tonic-clonic seizures with frequent association with additional ataxia and fine motor skills impairment possibly resulting from abnormal sensorimotor integration and hyperexcitability of the sensory and motor cortex (Manganotti et al., 2001). So it can be assumed that pharmaco resistant partial epilepsies and partial with secondary generalization epilepsies arising from frontal lobe would be good candidates for STN stimulation.

The mechanism that generates absence seizures is now believed to involve an alteration in the circuitry between the thalamus and the cerebral cortex (Futatsugi and Riviello, 1998, Kostopoulos, 2001) The animal data (ref table 12 above) suggests that stimulation of Snr would be possibly effective in such cases through the connection of Snr with DMAZ (dorsal midbrain anti epileptic zone).

As mentioned earlier the anterior nucleus of thalamus (ANT) is a component of Papez circuit and is closely associated with hippocampus, limbic structures as well as thalamic nuclei. Hence seizures arising from all these different structures should respond to anterior nucleus stimulation. 92.7 % patients recruited in SANTE trial had complex partial seizures. The best responders with median seizure reduction of 44.2% from baseline had seizure onset in one or both temporal regions. Subjects with multifocal or diffuse seizure origin showed a 35.0% reduction compared to a 14.1% but only in 2 out of 10 such patients. This substantiates the wide spread connectivity of ANT and its possible role in complex partial seizure control.

Direct stimulation of the epileptic focus appears a logical thought as it's the shortest way of action to interrupt ongoing seizure activity. In mesial temporal lobe epilepsy, the most common pathological finding in surgically resected specimens is hippocampal sclerosis (Blumcke et al., 1999, Liu et al 1995). Stimulation of the amygdala, hippocampus seems beneficial in such patients. The strongest evidence is from Vellaso (Vellaso 2007) where non lesional epilepsy patients had a >95% seizure reduction while those of hippocampal sclerosis responded with a 50 to 70% reduction. However double blind cross over trial reported by McLachlan and Tellez-Zenteno (ref table 24 above) seem less spectacular in terms of seizure control. Direct stimulation of an epileptic focus from eloquent cortex (example motor cortex) would produce many stimulation related side effects and it seems possible but not practical. Direct stimulation of malformations like hypothalamic hamartoma is successful but whether a surgical resection of this focus yields better results is a question. Stimulation of the hypothalamic hamartoma would possibly be only therapy when the resection is not possible. Cerebellar outflow is inhibitory and stimulation of cerebellum appeared productive from early studies in 1980s (ref table 23 above) however controlled trials have failed to replicate results of uncontrolled studies (Krauss, Fisher, 1993). Hence recommendation of cerebellum as a target for stimulation for control of seizures is difficult to make.

CHAPTER IV

BASAL GANGLIA AND EPILEPSY

The description of basal ganglia in this chapter is a synthesis of information from articles published earlier. The authors are mentioned at appropriate places.

4.1 BASAL GANGLIA ANATOMY AND PHYSIOLOGY

Basal ganglia are subcortical structures that are connected extensively to the cortex and form a network with other brain structures. They play an important role in integrative functions of the brain. They are involved in processing information related to motor, cognitive and sensory domain arising from the cerebral cortex, thalamus, hippocampus and amygdala. Because of their wide spread connectivity the basal ganglia also control the excitability of brainstem areas, thalamic motor circuits, premotor, prefrontal and limbic circuits of the cerebral cortex. The basal ganglia dysfunction is implicated in many disorders like Parkinson's disease, Dystonias that involve the motor circuits and psychiatric disorders like OCD involving limbic circuits. Treatment options like DBS are found useful for these disorders when specific basal ganglia structures are targeted during electrical stimulation. Their role in patho physiology of seizures essentially a disorder of abnormal synchronization appears interesting. The anatomy, physiology of basal ganglia presented below is a synthesis of various studies on rats, cats and primates.

Basal ganglia comprise the caudate nucleus and putamen (striatum), globus pallidus, subthalamic nucleus and substantia nigra (see figure 14).

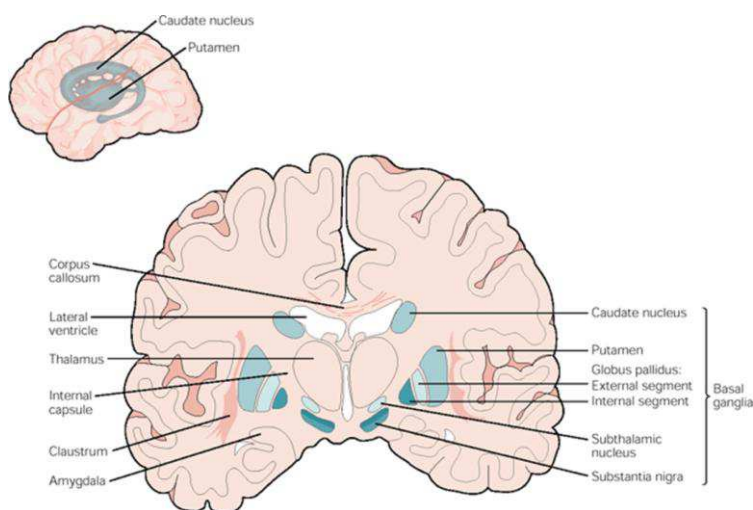


Figure 14 : Schematic coronal section of human brain.
Schema showing the basal ganglia. Inset shows the relationship of caudate and putamen.

Striatum (Caudate and Putamen)

The striatum is by far the largest structure of the basal ganglia. Early neuroanatomists considered the striatum to be a uniform and homogeneous structure. But now we understand that striatum is a complex structure with heterogeneous composition. It has a varied and clustered cytology, and different cytochemistry as evident from its rich neurotransmitter distribution (Graybiel & Ragsdale, 1983).

It is divided into two portions, the caudate nucleus and putamen, separated by fibers of the internal capsule. Despite this division, these nuclei form a single anatomical and functional entity. The head of the caudate nucleus lies rostral to the thalamus and bulges into the anterior horn of the lateral ventricle. Its body extends in a long slender fashion dorsolateral to the thalamus. The putamen lies between the internal capsule and the lateral medullary lamina of the globus pallidus. Rostrally and ventrally, the putamen and the head of the caudate nucleus are continuous, as the internal capsule is absent in this medial region.

Cellular features

Spiny I or medium spiny

The medium spiny neuron has an ovoid cell body of medium size (20-14 μm) giving rise to seven or eight primary dendrites. These dendrites are profusely covered in spines (Groves, 1983). They radiate approximately in a spherical manner and are dense in number so there is a considerable overlap in the dendritic field of each neuron. But very few dendrodendritic synapses exist. The axons of the spiny neurons give many collaterals before the primary branch extends beyond the striatum. These collaterals form axo dendritic synapses. The main neurotransmitter is Gamma Amino Butyric Acid (GABA) (Kita & Kitai, 1988).

Spiny II

These constitute roughly 1% of striatal neurons and are found distributed evenly in striatum. The axon of the spiny II, like the medium spiny, extends beyond the striatum to the major striatal output structures (DiFligia et al., 1976). A number of collaterals have been observed to branch orthogonally near the cell body of origin (Groves, 1983). Together the two types of spiny neurons generate the entire output pathways of the striatum. They fire very infrequently and, are silent for much of the period in normal state.

A number of non spiny types of neurons have also been found in the striatum. They are considered to be interneurons, as their axons (if any) are not traced beyond the structure. But there is evidence that some of these neurons receive afferents from the cortex, thalamus, and globus pallidus).

Neurotransmitter found in these neurons is acetyl choline. However in the cat and primate striatum interneurons also were found to contain neuropeptide somatostatin (Chesselet & Graybiel, 1986).

Activity pattern

Extracellular electrophysiological recordings indicate two striatal populations: Phasically activated striato-pallidal neurons (PAN) also called low firing frequency neurons (LFNs), have with a broad-shaped action potential and a base firing rate of 0.5–1 spikes/s. The other tonically active neurons (TANs), with a base firing rate of 5–15 spikes/s (Kimura et al., 1990, 1996; Apicella et al., 1992). These have since been identified as cholinergic interneurons (Aosaki et al., 1995).

PANs and TANs both respond to movement. It has been shown that that 60% of PANs are correlated to one or more movement parameters and 8% to motor preparation, whereas no TANs respond to sensory stimulus (Kimura et al., 1996). Multi-channel studies allowing cross-correlation analysis have shown that about 60% of TANs fire in a synchronized pattern without oscillation (Raz et al., 2001).

Globus Pallidus

In primates, the globus pallidus is divided into two anatomical segments: internal (GPi) and external (GPe). Although these segments are separated by the medial medullary lamina, the pallidal neurons from each segment are extremely similar, and for the most part morphologically indistinguishable. In non primates the anatomical structures referred to as the pallidum and entopeduncular nucleus corresponds to the external and internal medial segments respectively. In humans the external segment constitutes 70% of the total volume of the globus pallidus. However the mean volume of neurons is higher in the internal segment (Carpenter, 1981). There is a topographical organization of afferents of Globus pallidus with striatum and in between GP externa and interna (Smith et al., 1994).

Cellular features

Two types of pallidal neurons are noted. The majority are large with four to five thick dendrites radiating outwards. The dendrites can extend up to 1000 μm in length. It seems that the dendritic field is so arranged that it's axis lies perpendicular to the incoming striatal afferents. This positions the dendritic fields to intercept maximal numbers of striatal afferents (Park et al., 1982). The large pallidal neurons have thin axons that extend beyond the pallidum. Almost all pallidal output neurons are GABAergic (Parent & Hazrati, 1993). There is also some evidence that neurons in the external segment may coexpress substance P (Parent, 1986).

There are other small interneurons (12-21 μm in diameter) that are observed less frequently. These have few dendrites that extend only up to around 150 μm (Parent, 1986). Occasionally these are identified with short sparsely branching axons. In the macaque monkey medium sized neurons (23–34 μm) have also been found, and may be associated with the pallidal projections to the lateral habenular nucleus.

In monkeys, four types of neurons have been characterized in, and around, the pallidal segments (DeLong, 1971; Bergman et al., 1994; Boraud et al., 1998): (1) GPi neurons that show high frequency firing and respond to passive joint movements (2) GPe neurons with high frequency firing but predominant burst activity and long period of silence responding to passive joint movements (3) GPe neurons showing a low firing rate with bursts, and (4) "border cells", because of their location at the periphery of the pallidal segments and in the internal medullary lamina between the GPe and the GPi.

Activity pattern

GPe neurons present a tonic firing rate with pauses and a frequency of approximately 50–70 spikes/ s (DeLong, 1971, DeLong et al., 1984; Miller and DeLong, 1987). 11% of recorded cells display an oscillatory autocorrelogram in the 5–20 Hz range and fewer than 5% of recorded pairs are correlated (Raz et al., 2000). Ninety-one percent of GPe neurons have been shown to respond to the passive movement of only one joint. GPe neurons respond to movement either by an increase in firing rate for 30% of neurons or a decrease for 70%

(Georgopoulos et al., 1983; Turner and Anderson, 1997). The average onset of response is around 10-15 ms after the onset of movement (Georgopoulos et al., 1983).

A majority of GPi neurons modify their activity not only later than motor cortex neurons (DeLong et al., 1984) but also about 80-100 ms after the onset of muscle activity (Boraud et al., 2000) and even around 10 ms after the onset of movement (Georgopoulos et al., 1983).

The subthalamic nucleus (STN)

It is a major component of the basal ganglia. It is a small lens-shaped nucleus lying on the dorsomedial surface of the internal capsule. STN is a midbrain structure that is included in the basal ganglia because of its close ties with other basal ganglia components. The diversity of STN cytology is still under question.

Cellular features

Early studies revealed a homogeneous structure (Yelnik & Percheron, 1979). Currently, it is considered that there may be up to three principal varieties of neurons in the subthalamic nucleus. Two of these constitute projection neurons, one type is described as having an elongated triangular soma with four to nine dendrites radiating outwards (Afsharpour, 1985; Hammond & Yelnik, 1983). These dendrites are sparsely covered in spines and give rise to tapering branches. The second type of projection neurons are a similar size, yet with polar dendrites. Axons of both of these neuron types are found to emerge from the proximal dendrites or somas and branch into two fibers either inside the STN. A small interneuron has also been observed (Carpenter, 1981). It has only a few long dendrites, with as yet, no clearly identified axon. The neurotransmitter expressed by STN is Glutamergic.

Activity pattern

It has been documented that STN neurons display a tonic activity with a frequency range of 15–25 spikes/s (Georgopoulos et al., 1983; Wichmann et al., 1994) and that more than 50% of STN neurons present bursts (Miller and DeLong, 1987; Wichmann et al., 1994). Very little oscillatory activity has been detected in the normal monkey. In STN from 60 to 90% of STN neurons increase their discharge rate during eye or limb movement (Georgopoulos et al., 1983; DeLong et al., 1984, Wichmann et al., 1994b). For voluntary movement the responding ratio has been reported to range from 20% to 5% (Georgopoulos et al., 1983; Wichmann et al., 1994). A linear correlation has been shown between the timing of STN activity in relation to the onset of movement.

The substantia nigra (SNr)

Substantia nigra is also a midbrain structure, but considered together with basal ganglia as it has extensive relation with the striatum. Classically it has been divided into two components: the pars compacta (SNc), and the pars reticulata (SNr). The pars compacta is a cell-rich region that in humans is composed of large pigmented neurons. The pars reticulata is less rich in cells, and contains morphologically similar neurons deeply entangled in the striatonigral projections. In monkeys the pars compacta contains 85% of the total nigral neuron population.

Cellular features

Cells in both the pars compacta and pars reticulata exhibit a triangular (fusiform) shape and are divided in two types. Small neurons (10-12 μm in diameter) with short axons are considered to be the major nigral interneurons (Parent, 1986). The second type of neuron is larger (15-20 μm in diameter) and constitute the nigral output neurons. The projection neurons are closely grouped in the SNc, yet separated by astrocytic sheaths (Juraska et al., 1977). They display three to five long smooth dendrites orientated in two main directions and with few branches (Juraska et al., 1977). A close similarity has been drawn with the GPI output neurons and STN neurons (Tokuno & Takada, 1993).

It appears that DA neurons are not related to movement itself (DeLong et al., 1983; Schultz et al., 1983), contrary to the other BG projecting neurons, but are sensitive to relevant behavioral stimuli such as reward, the anticipation of a reward and prediction error (Schultz, 1992). These neurons present a typical triphasic action potential of a duration ranging from 2-5 ms (Schultz et al., 1983). Their firing frequency has been reported to be slow (0.5-10 spikes/s; Schultz et al., 1983).

4.2 CONNECTIVITY AND THE CIRCUITS IN THE BASAL GANGLIA

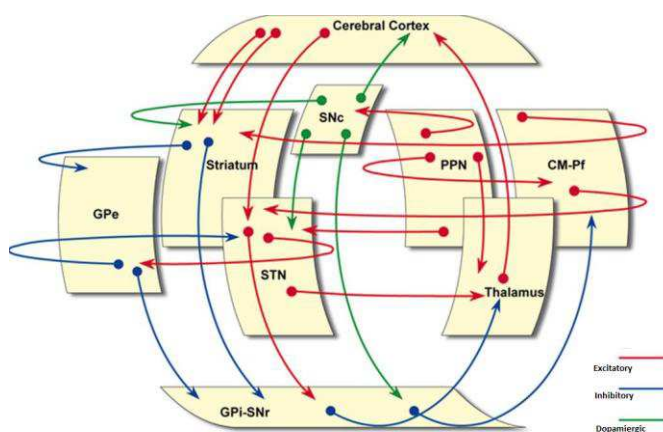


Figure 15 : Connectivity and circuits in basal ganglia.

The 'Box and arrow' type of schematic representation of basal ganglia connectivity. Few of the connections are not shown for simplicity. (Obeso 2011 used with permission)

The individual parts of basal ganglia are connected to each other extensively. These structures can be visualized as two functional entities. The 'input' structures that gather cortical information and also receive information from thalamus the amygdala and the hippocampus. The output structures that relay information to thalamus and CM parafacicular complex, PPN indirectly providing feedback to cortex again.

Circuit level connectivity

The cortical information is transmitted from the input to the output structures via three different pathways:

1. A trans- striatal “direct” pathway, which connects the striatum directly with the output structures. When activated, this direct pathway results in a strong disinhibition of the thalamus and brainstem structures. Cortical glutamatergic excitatory inputs activate the striatal neurons which have inhibitory (GABAergic) projection to the SNr. They suppress the tonic inhibition of the thalamus and brainstem neurons, producing a strong disinhibition of 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. The striatal output is inhibitory (GABAergic) to 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., 1998; Maurice et al., 1998).
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 glutamatergic neurons (Albin et al., 1989, Nambu et al., 2002).

The models of information processing in basal ganglia

After reviewing the anatomy and connectivity within the basal ganglia the models of information processing in the system are described below. These models provide a clue to basal ganglia functions as well as provide substrate for explaining the dysfunctions.

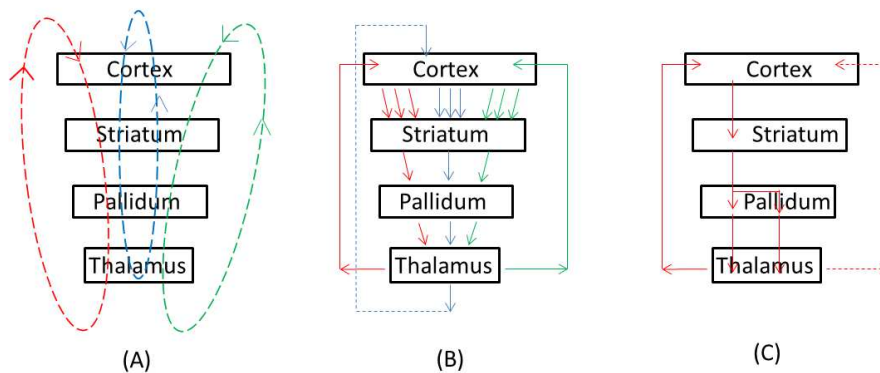


Figure 16 : Schematic representation of information processing in basal ganglia

The different colors represent different sub circuits. For the sake of simplicity only one sub circuit is shown in part C.

A) Segregated loop (Fig.16 part A)

The classical model described by Alexander et al (Alexander, DeLong, 1986) describes the basal ganglia thalamocortical circuits to be arranged in five different parallel loops with both structural and functional separation from each other. Of these two are motor (motor and oculomotor) two associative (dorsolateral prefrontal and lateral orbitofrontal) and one limbic

loop. These loops are conceptualized to arise from separate cortical areas and provide feedback to the same cortical areas. They have a very little interaction between each other during normal physiology.

B) Convergent loops (Fig.16part B)

Parent and Hazarati (1993) proposed that the cortico strial, striato palidal and striatonigral pathways structurally show convergence and thus the loops are not 'parallel'. However Parent et al found that the though there is a high degree of convergence, the motor, associative and limbic areas of cortex project to segregated specific three areas of striatum and same tripartite arrangement is seen in the pallidum.

C) Split Circuit Theory (Fig.16Part C)

Joel and Weiner (1997) proposed the 'split circuit' theory. In this concept the cortico striatal pathway is one but the striato thalamo cortical circuit has two components. One enters and provides feedback to the same cortical area from which it arose and forms a closed loop while other enters different cortical area creating an open loop of information processing.

The strict segregation and parallel circuits as proposed earlier by Alexander et al are not considered valid anymore. Modifications to these connections have been proposed in view of further research. For example the 'direct' pathway from the striatum to the output nuclei has been shown to have branching collateral fibers terminating sparsely in GPe (Wu et al., 2000 Matamales and al., 2008). The exclusive feed forward nature of the 'indirect projection' from the striatum is also doubtful. Because the STN is now recognized as a major input station of the basal ganglia with external afferents from both cortical and subcortical structures (Lanciego et al., 2004; Hartmann-von Monakow et al 1978, Nambu et al 2002, Fger et al., 1994, Coizet et al., 2009). Similarly it is shown that the GPe projects not only to the STN but displays a network of branched collaterals that reaches the GPi, SNr, and to nigrostriatal dopamine neurons (Smith et al., 1998). Reciprocating connectivity between STN and GPe and between the GPe and the striatum has also been documented (Miwa et al., 2001, Shink et al., 1996). Thus though the feed forward nature of information processing in the basal ganglia is still considered relevant, accommodating newer information about connectivity in the model is essential.

These new findings actually support the 'split circuit theory' of information processing in basal ganglia.

Motor activity and basal ganglia pathways

Output from GABAergic GPi and SNr neurons keep targeted structures in the thalamus and brainstem under tonic inhibitory control. The phasic inhibitory signals from direct pathway, as explained above suppresses the thalamic inhibition that is 'disinhibits' thalamocortical neurons and facilitates a movement. The indirect pathway modulates the actions of the direct pathway. Along with the GABAergic system, Dopaminergic input from the substantia nigra pars compacta (SNc) modulates corticostriatal transmission. Dopa has dual effect. Neurons that co-express dopamine D1 receptors, substance P and dynorphin and give rise to the 'direct pathway' are excited by Dopamine. Neurons that co-express D2 receptors and enkephalin, and that give rise to the 'indirect pathway', are inhibited (Gerfen et al., 1996). According to this model, in the normal state, activation of the 'indirect circuits' at the level of the striatum would promote movement inhibition or arrest, whereas activation of the 'direct circuit' would facilitate movement (DeLong et al., 1990).

The subthalamic nucleus neurons that project to the internal globus pallidus and substantia nigra pars reticulata are excitatory. Normally, when the indirect pathway is activated by signals from the cortex, the medium spiny neurons discharge and inhibit the tonically active GABAergic neurons of the external globus pallidus. As a result, the subthalamic neurons become more active and, by virtue of their excitatory synapses with cells of the internal globus pallidus and reticulata, they increase the inhibitory outflow of the basal ganglia.

Dysfunction and basal ganglia models

The functioning of the intricate balance between different structures of basal ganglia can also be interfered from the diseases of the basal ganglia.

Hemiballism is a disorder that is characterized by sudden violent involuntary movements of the limbs. The pathology in this disease is dysfunction of the STN. STN is an important 'node' in indirect pathway. The excitatory influence of STN over the output nodes GPi and SNr becomes less in this disorder. This in turn decreases the inhibitory outflow of basal ganglia affecting the modulation of a motor program.

In patients with Huntington's disease, undesired ballistic and choreoform movements are seen. The pathology is degeneration of the medium spiny neurons of striatum that project to GPe. The reduced inhibitory flow from striatum to GPe makes it more active. The GPe is inhibitory to STN. Thus increased inhibition of STN in this disease leads to decreased excitation of the GPi and SNr. The net result is the inhibitory outflow of the basal ganglia is reduced. Without the restraining influence of the basal ganglia, upper motor neurons can be activated by inappropriate signals, resulting in the hyperkinetic movements like chorea observed in Huntington's disease.

The hypokinetic features of Parkinson's disease can also be interpreted using this paradigm. Parkinsonian features include diminished facial expressions and lack "associated movements" such as arm swinging during walking. Movements are difficult to initiate and, once initiated, they are often difficult to terminate. The pathology in Parkinson's disease is loss of nigrostriatal dopaminergic neurons. As mentioned above, these neurons produce two different effects. The one terminating on the D1 receptors of Striatal spiny cells are excitatory to the cells. These spiny cells project to GPi forming the direct pathway. The nigro strial neurons are inhibitory to the D2 receptors in striatal cells which in turn project to GPe forming the indirect pathway. Both of these dopaminergic effects serve to decrease the inhibitory outflow of the basal ganglia and thus to increase the excitability of the upper motor neurons. In contrast in Parkinson's disease, the inhibitory outflow of the basal ganglia is abnormally high, and thalamic activation of upper motor neurons in the motor cortex is suppressed. This explains the hypokinetic features of Parkinson's disease.

Limitations to old model

The conceptual model of basal ganglia pathophysiology mainly arose from the dysfunctions noted in Parkinson's disease. In animal models of MPTP induced Parkinson's disease it was noted that the GPi neurons fire at a higher rate than the control. The GPi rate theory thus explained the imbalance between direct and indirect pathway as a function of Dopamine depletion, to be the cause of features of Parkinson's disease. This simple feed forward schema of the basal ganglia functioning was proposed earlier. But this model fails to explain other features of Parkinson's disease like cognitive and emotional deficits, language problems.

Many studies have failed to show increased GPi discharge rates at rest in Parkinson's disease as compared to normal controls in patients and animals. Similarly the recent findings of therapeutic DBS of GPi drives the output have also negated the theory.

The 'system oscillator theory': a more generalized model suitable for explaining basal ganglia in epilepsy:

Many of the physiological and pathological processes are mediated by neuronal synchrony and oscillations. Basal ganglia also exhibit oscillatory discharges. The single spike mode of neuronal activity represents information transfer or processing. But basal ganglia neurons also fire in burst mode. These bursts indicate functional changes in the system. (Ivry, 1996, Steriade, 1997) Such oscillatory discharges have been recorded in corticostriatal neurons, (Plenz & Kitai, 1996) tonically active striatal interneurons (Aosaki et al., 1995, Raz et al., 1996), the substantia nigra pars compacta (SNc) (Li et al., 1996), both pallidal segments and the STN (Beurrier et al., 1999).

The system oscillatory theory (Montgomery 2007)

Earlier models explaining the basal ganglia functions were based on a unidirectional flow of information from input to output. The circuit level models explained basal ganglia functioning in terms of parallel or converging circuits. Extrapolating the circuits to a system level, the system oscillatory theory was developed. It maintains that basal ganglia and connections of thalamus to cortex comprises of dynamically coupled, nonlinear, reentrant, polysynaptic oscillators representing a wide range frequencies. And the main oscillator is the very high frequency (140Hz) Vento lateral nucleus of thalamus. Activity of the system is conceptualized to be modulated by lower frequency oscillators comprising the BG nuclei. Just as the system oscillators participate in the normal functioning of the basal ganglia, their dysfunction can be explained as the pathological basis of diseases. In fact pathological oscillatory synchrony has been used to explain features of Parkinson's disease (Hutchison et al., 2004), epilepsy (Timofeev, Steriade 2004, Traub, 2003) schizophrenia (Stelt et al., 2004), dementia (Jeong, 2004).

4.3 EVIDENCE OF INVOLVEMENT OF THE BASAL GANGLIA IN EPILEPTIC SEIZURES

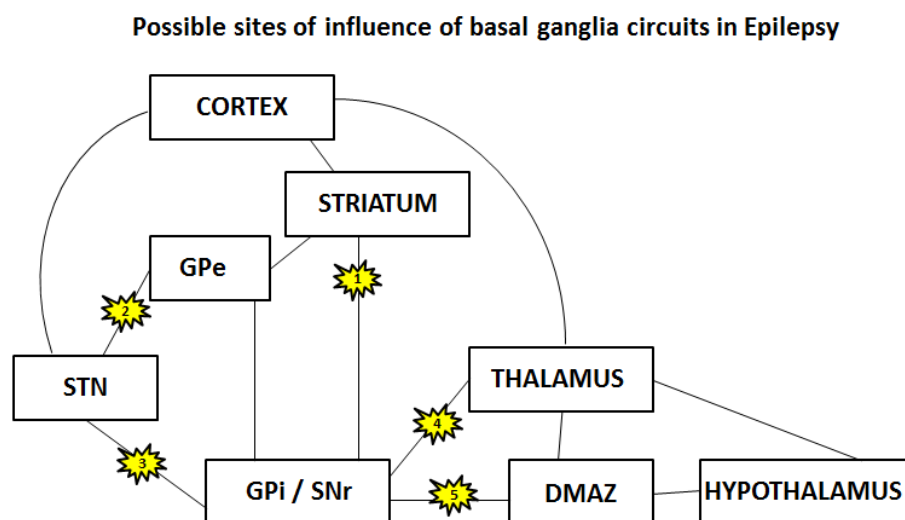


Figure 17 : Basal ganglia circuits showing possible locations implicated in epilepsy
1-Dopaminergic modulation 2-Excitatory influence over STN 3-Excitation of output structure 4-Inhibition of thalamic nuclei indirectly influencing the thalamo cortical connections 5- Influence of SNr over DMAZ (Dorsal Midbrain Antiepileptic Zone).

In the earlier text the intricate networking among the basal ganglia structures and models of information processing in them were mentioned. These circuits might influence the epileptic seizure by various mechanisms (see fig 17). A review of evidences of involvement of basal ganglia is presented below.

4.3.1 PHARMACOLOGICAL STUDIES IN ANIMALS

Striatum

Dopamine acts differently on two receptors D1 and D2. Acting on D1 receptors, it activates the direct inhibitory GABAergic striato- nigral pathway. Acting on D2 receptors it reduces the activity in the indirect pathway by an inhibition of the subthalamo- nigral excitatory projection. The net effect of both mechanisms is suppression of the SNr. Injections of D2 agonists into the dorsal striatum have been shown to block seizures in pilocarpine induced seizures in rats (Al tazir et al., 1991, Wahnschaffe, 1991). Apomorphine, a Dopamine agonist, has been shown to be anticonvulsant when applied in striatum (caudate-putamen, nucleus accumbens) in pilocarpine induced seizures in rats. Halopridol, a Dopamine antagonist used systematically or applied into caudate, putamen bilaterally has been shown to lower the seizure threshold in the same model (Turski et al., 1988) but intrastriatal injection of a D1 agonist failed to suppress clonic seizures in the pilocarpine model. NMDA (N-methyl-D-aspartate) is an excitatory amino acid and is a proconvulsant if injected intracortically. But bilateral microinjections of NMDA into the caudate-putamen, however, protected against limbic seizures induced by pilocarpine. Further lesioning the caudate- putamen by bilateral

microinjection of the excitotoxin ibotenate converted subconvulsant doses of pilocarpine into convulsant ones (Turski et al., 1987). Similarly the application of NMDA intrastriately was shown to be protective in amygdala kindled rats (Cavalheiro et al., 1986).

In a genetic model of absence seizures GAERS, it was observed that activation of striatal neurons by NMDA or by a D1 receptor agonist, significantly suppressed absence- seizures especially so when injection sites were located in the core of the nucleus accumbens. Conversely, blockade of the D1 receptors in the nucleus accumbens or of the GABA receptors in the SNr increased the occurrence of absence-seizures in GAERS (Deransart, Depaulis, 2002).

Pallidum

Involvement of pallidum in epilepsy has been studied in few species using pharmacological manipulation. In GAERS, disinhibition of the globus pallidus or the ventral pallidum by injection of a GABA antagonist has been shown to suppress absence seizures. This effect was found correlated with a decrease in glutamate levels in the SNr as measured by microdialysis, indicating a possible involvement of STN: that is indirect path (Deransart et al., 1999). The preferential involvement of the ventral aspects of the pallidum was also documented in amygdala kindling. In this model, disinhibition of the ventral pallidum by local injection of a GABA antagonist reduced both the behavioral expression of seizures and the duration of the after discharge' (Deransart, Depaulis, 2002). In a pentylenetetrazol (PTZ) induced tonic seizures pretreatment with bilateral intrapallidal microinjection of tiagabine a GABA uptake blocker suppressed the incidence of tonic seizures by 67.7 % and reduced the mortality rate to 16.7 %. GABA-B receptor agonist (baclofen) completely suppressed PTZ- induced tonic seizures but this effect was largely abolished by co-injection of the GABA-B receptor antagonist CGP55845 (Chen et al., 2004).

In rats, behavioural and electrographic signs of limbic seizures following pilocarpine (380 mg/kg) were suppressed by the focal microinjection into the entopeduncular nucleus of the NMDA antagonist, 2-amino-7-phosphonoheptanoate or the kainate antagonist, gamma-D-glutamylamino-methylsulphonate (40 nmol) (Patel et al., 1988).

STN

The STN sends glutaminergic output to the substantia nigra. Inhibition of the subthalamic projection by bilateral injections of a GABAergic agonist in the STN was found to suppress absence seizures in the GAERS (Deransart et al., 1996), flurothyl seizures (Velskov et al., 1996) and amygdala-kindled seizures (Deransart et al., 1998). 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 (Dybdal and Gale, 2000).

SNr

Substantia nigra (SN) is the output structure of basal ganglia. Because of its connection to various nuclei of thalamus; the substantia nigra modulates thalamo cortical rhythms. Similarly a dorsal midbrain anticonvulsant zone (DMAZ) has been proposed in rats. (Shehab et al., 1995, Redgrave et al., 1992) SN connections to superior colliculus and nearby structures seem interesting in this regard. Hence its role in dynamics of seizure has been investigated in the past. Iadarola and Gale showed that elevation of GABA in the ventral midbrain tegmentum

would lead to blockade of tonic hind limb extension in the maximal electroshock model. It also produced blockade of tonic and clonic seizures produced by pentylenetetrazole and bicuculline. Thus they concluded that substantia nigra to be the site of anticonvulsant activity (Iadarola, Gale, 1982). In a maximal electroshock seizure model introduction of gamma-vinyl GABA, an inhibitor of GABA transaminase, within the SN suppressed seizures (Miller et al., 1987; Platt et al., 1987) and in Flurothyl seizure model (Xu et al., 1991). Bilateral intranigral injection of muscimol was shown to suppress EEG recorded spike and wave discharge in wistar rats that show spontaneous 0 Hz SVD (Depaulis, 1988). In amygdala kindled model of motor and limbic seizures bilateral micorinjections of muscimol in SN was shown to suppress seizures (McNamarra, 1984). However such suppression of seizures by inhibition of the SNr was not found to be universal. In a model of audiogenic seizures Lesions of the SC markedly attenuated audiogenic seizure (AGS) severity by abolishing all behavioral components (Merril, 2003) but these seizures were not suppressed by bilateral activation of GABAergic transmission within the SNr (Depaulis et al., 1990). This suggests that the so-called “nigral control of epilepsy” may be dependent on the different circuits involved in seizures.

4.3.2 ELECTROPHYSIOLOGICAL STUDIES IN ANIMALS

Striatum

In a GAERS model it was shown that corticostriatal neurons display suprathreshold rhythmic depolarizations in-phase with local EEG spikes. Consistent with this synchronized firing in their excitatory cortical afferents, striatal output neurons also exhibited, during SWDs, large-amplitude rhythmic synaptic depolarizations. During spike and wave discharge (Slaght, 2004). Similarly in amygdala kindled rats the ictal discharges in amygdala were found synchronized with cortex, STN and SNr during the course of the seizure. But the temporal evolution of ictal discharges from amygdala arrived first at cortex then SNr and then STN (Shi et al., 2006).

Subthalamic nucleus

Electrical stimulation of the motor cortex (Kitai and Deniau, 1981) has been used to document bursting patterns in STN. Paz et al have shown in GAERS that cortical paroxysms generate bursting patterns in the STN which in turn may produce phasic synaptic excitation of the basal ganglia output nuclei (Paz et al., 2005).

In a primate model of focal motor seizures, our group at Grenoble showed dynamic changes that occur in basal ganglia structures during a seizure (Devergnas et al., 2012). These findings are described in details in chapter 6.

Substantia nigra

It was shown that the SNr controls the thalamus and superior colliculus neuronal activity especially during the motor activity (Chevalier and Deniau, 1990). These connections can be postulated to participate in the epileptic process. In a study by Bonhousse et al in amygdala kindled seizures in rats the relationship of amygdala, cortex and subcortical structures (STN, SNr) was documented by using the EEG and behavioral (clonic motor) expression in both immobilized and unrestrained animals. The principal finding was that in both immobilized

and unrestrained animals the SNr neurons of kindled, but not control, animals were recruited (Bonhouise et al., 1991). Kaniff et al demonstrated involvement of substantia nigra in focal cortical epilepsy. In this study single unit activity was recorded in the substantia nigra during focal cortical epileptiform discharges induced by topical application of penicillin to the cortical surface in urethane anesthetized rats. Eighty percent of SN units responded during the cortical interictal spike discharge (Kaniff et al., 1983). In a genetic model of absence epilepsy (GAERS), It was shown that pharmacological blockade of glutamatergic transmission in the SNr increased the rate of discharge in VM thalamic cells and produced an irregular tonic firing pattern matched with an interruption of cortical SWDs. Thus the disinhibition of VM nucleus by SNr could be conceptualized to produce cortical desynchronization leading to control over spike wave discharges (Paz et al., 2007).

Other techniques: Few representative studies using other techniques implicating basal ganglia in epilepsy are presented below.

4.3.3 METABOLIC STUDIES IN ANIMALS

Measurement of glucose uptake is a reflection of brain metabolism. An increase in glucose uptake as sign of increased activation was seen in different models of epilepsy. In amygdala kindled rats, 14C-2-deoxyglucose (DG) autoradiographic technique showed increased uptake increased in the substantia nigra, specific and nonspecific thalamic nuclei, globus pallidus, and neocortex. After the appearance of generalized motor seizures (Engel et al., 1978). Using same technique Fernandes et al showed that in status epilepticus, evoked by pilocarpine injection in rats; a rise of glucose metabolism was noted in the caudate (Fernandes et al., 1999).

4.3.4 EXPERIMENTAL CELL TRANSPLANTATIONS

In an amygdala kindled model of temporal lobe epilepsy, transplant of GABA producing immortalized embryonic rat cells were shown to be anticonvulsant (Nolte et al., 2008) Similarly in a kainic acid induced seizures in rats, it was shown that dose of kainic acid required to induce seizures increased and the severity of motor seizure decreased in the group that received intranigral GABAergic cells (Castillo et al., 2008).

4.4 EVIDENCE IN HUMAN IMAGING STUDIES

The evidence of basal ganglia involvement in various types of epilepsies in humans has been documented by different imaging techniques. These include volumetric measurements on structural MRI, SPECT and PET studies, and fMRI and EEG coregistered with fMRI. Few studies representing each technique are mentioned below.

Structural MRI

Pulsipher (2007) and colleagues studied 48 patients with unilateral temporal lobe epilepsy and compared the volumes of subcortical structures with 29 healthy controls. The greatest volume loss was noted in ipsilateral hippocampus, corpus callosum, thalami bilaterally. The putamen also showed the next highest volume reduction. Du et al., (2011) made MRI comparison of

volumes of subcortical structures in 14 male patients of IGE with 28 age and sex matched controls. It showed significant regional atrophy in the left thalamus, left putamen and bilateral globus pallidus in patients with IGE than control fourteen male patients with IGE. While MRI morphometric analysis of patients with temporal lobe epilepsy showed smaller thalamic and striatal volume in both hemisphere (Dreifuss et al., 2001) In another volumetric MRI study, patients, with tonic clonic seizures, exhibited 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).

Functional MRI

In patients with partial seizures getting secondarily generalized Group analysis during generalization revealed that the cerebral blood flow (CBF) increased in the superior medial cerebellum, thalamus and basal ganglia. Post-ictally, there was also marked progressive CBF increase in the midbrain and basal ganglia. (Blumenfeld et al., 2009)

The altered connectivity of subcortical structures including the basal ganglia has been demonstrated. In fMRI study of resting state network in patients of idiopathic generalized epilepsy characterized by tonic-clonic seizures MRI imaging signal correlations and diffusion tensor image tractography showed altered nodal characteristics and functional connectivity was altered in patients with epilepsy than healthy controls (Zhang et al., 2011).

Functional connectivity of basal ganglia at resting state was studied in IGE patients. It demonstrated there was significantly more integration within the basal ganglia structures in IGE patients than control groups. Furthermore the increased functional connectivity was found in bilateral caudate nucleus and the putamen in patients of IGE with interictal discharges than patient without evidence of interictal discharges (Luo et al., 2012).

EEG coregistered with fMRI

In typical absence seizures in children a simultaneous registration of EEG and fMRI showed that six out of eight patients had decrease BOLD signals in basal ganglia during the typical spike wave discharge (Berman et al., 2010). A similar study of EEG and fMRI in absence seizures showed deactivation of the caudate nuclei in 59% of the patients during the seizures (Moeller et al., 2010).

PET and SPECT studies

In Ring chromosome 20 syndrome epilepsy is a major clinical symptom. Seizures are often complex partial and reported as episodes of altered consciousness with staring, oral automatisms, unspecified automatic behavior, focal motor symptoms and/or head turning. These seizures are often pharmaco resistant. An [18F] fluoro-L-dihydroxyphenylalanine ([18F] fluoro- L-DOPA) PET study showed that uptake was significantly decreased bilaterally in putamen and caudate nucleus of patients with ring chromosome 20 epilepsy, compared with controls (Biraben et al., 2004) The authors suggested that dysfunction of striatal dopaminergic neurotransmission might impair mechanisms that interrupt seizures.

SPECT study with (99m) Tc-hexamethyl-propylene-amine-oxime (HMPAO) was performed in tonic seizures with different semiology presentation like versive, bilateral symmetric and

hypermotor seizures. It was found that in versive seizures prominent hyperperfusion was present in the frontal eye field opposite to the direction of head version along with caudate .In bilateral asymmetric seizure group hyperperfusion in ipsilateral supplementary sensorimotor area alongwith bilateral basal ganglia was noted. The hypermotor seizure subgroup also demonstrated hyperperfusion in caudate and basal ganglia (Wong et al., 2010).

CHAPTER V

MODEL

5.1 CHARACTERIZATION OF PENICILLIN-INDUCED FOCAL MOTOR CORTICAL SEIZURES IN PRIMATES

5.1.1. INTRODUCTION

The pre-clinical testing of the effectiveness of novel therapeutic modalities requires well-characterized animal models mimicking various epilepsy types (Chabardes, et al., 2008, Pallud et al., 2008). In rodents, acute and chronic models of generalized, multifocal, or limbic epilepsy have been previously described (Chevassus-Au-Louis et al., 1999, De Deyn 1999, Fisher, 1989). Previous studies also reported focal neocortical seizures in rats produced by local injection of kainic acid (Hashizume and Tanaka, 1998, Yamamoto et al., 1995), 4 amino pyridine (Yamamoto et al., 1995, Yang et al., 2003), iron (Willmore et al., 1978) or bicuculline (Eder et al., 1997,). However, few models are available in big mammals and in particular, models of focal neocortical epilepsy in non human primate are uncommon and have not been well characterized.

5.1.2 MECHANISM OF ACTION OF PENICILLIN

The proconvulsant effect of penicillin topically applied to cerebral cortex is known since 1946 (Johnson and Walker, 1946). Penicillin acts as a gamma amino butyric acid (GABA) blocker. PNC is a blocker of the cortical gamma- aminobutyric acid (GABA)-dependent interneurons (Elger and Speckmann, 1983; Gloor, 1969; Gloor, et al., 1977).

Penicillin leads to suppression of lateral inhibition and the facilitation of the horizontal cortical activation. The neurons in the area where penicillin is injected show paroxysmal depolarizing shift (Matsumoto and Ajmonemarsan, 1964) mimicking epileptic neurons in an epileptic focus. Previous studies suggested that intra-cortical injection of penicillin creates a suppression of the activity of the surrounding inhibitory interneurons that limit the spread of spikes at seizure onset (Gloor, 1969; Gloor et al., 1977; Meyer and Prince, 1973; Noebels, and Prince, 1977). Intracellular recording studies (Elger and Speckmann, 1983) showed that penicillin induces epileptic activities in the superficial layer of the cortex and there is a vertical inhibition of the spread of spikes due to hyperpolarization of neurons in deeper layers of cortex.

5.1.3 PENICILLIN AMONG OTHER EPILEPTIC AGENTS

In rats, acute focal neocortical epilepsy using kayanic acid, (Hashizume and Tanaka, 1998; Yamamoto et al., 1995), using intracortical 4-amino-pyridine (4-AP) 37 are documented. Use of local epidural bicuculline, another proconvulsant drug that also acts as a GABA- blocker has been described in the past (Anschel et al., 2004), Campbell and Holmes (1984), Eder et al., 1997). Focal seizures in rats can also be induced by focal electrical stimulation (Ajmone-Marsan, 1972; Hiroshi et al., 2002).

All these models have limitations that make them difficult to be used in primates. For example, the 4-AP model requires repeated injections to maintain status epilepticus. Bicuculline can lead to extremely violent seizures and high mortality. Such difficulty in administering proconvulsant and high mortality precludes use of these agents in primates. The seizures induced by electric stimulation often get generalized, are acute and do not generate themselves spontaneously.

Considering the mechanism of seizure induction by Penicillin and limitations of use of other proconvulsants, we choose intracortical injection of Penicillin to generate focal motor status epilepticus. We also tested effect of Diazepam on the seizures in this model. Diazepam was specifically selected as anti epileptic drug in our experiments because of its allosteric modulation of GABA receptors. In this study we present electrophysiologic and clinical characteristics of seizures induced by acute focal intracortical injection of PNC in the motor cortex of NHP.

5.2 MATERIALS AND METHODS

5.2.1 ANIMALS

Study was performed on two *Macaca fascicularis* (CRP, Port Louis, Mauritius), one 7 years old weighing 6.9 kg (Monkey A) and the other 7.5 yrs old weighing 7.8 kg (Monkey B). These 2 monkeys were included in two distinct experimental protocols that are not described in the present study, but in those protocols spontaneous seizures were recorded under similar conditions.

5.2.2 SURGERY

The animals were kept fasting 10 hours before surgery. The surgery was performed under general anesthesia with intra muscular injection of Ketamine (Imalgene, Merial laboratory, France). 0.4 mg at induction followed by 0.2 mg per hour) and Xylazine (Rompun, Bayer Healthcare AG, Germany) 2%, 0.2 ml at induction followed by 0.1 ml per hour. Additional local scalp anesthesia was provided with subcutaneous injection of Lidocaine with 1% Adrenalin. Prophylactic antibiotics, analgesics and anti-inflammatory drugs were delivered during peri operative period.

Surgery was performed with a stereotactic frame (David Kopf Instruments, Tujunga California USA) under intraoperative tele- radiographic control. The motor strip was first localized using bi-commissural landmarks obtained by a ventriculography performed by injecting 2 ml water soluble iodine contrast medium (Bracco Imaging, France). Motor responses were induced by epidural cortical stimulation delivered by an external stimulator (Grass Technologies Astromed Inc USA) and were used to confirm the location of the motor strip through a small craniotomy. Two canulae were screwed in the skull above the hand area of the right motor cortex to enable further injections of penicillin. Four stainless steel screws (radius of the head 2.25 mm length 20 mm, Safix, Echirolles, France) were implanted bilaterally over the cranium and one additional screw was implanted close to the canulae. The

screws were secured with their heads in contact with the dura (see Figure 18). Finally, a head holder (Crist Instrument Company, Hagerstown, USA) was positioned and secured with dental cement. Antero-posterior and lateral tele Xray were used whenever necessary to check the position of the screws.

Animals were allowed to recover and monitored in the post operative period. Food and water was provided ad libitum. Experimental induction of seizures was performed after 10 days of recovery period.

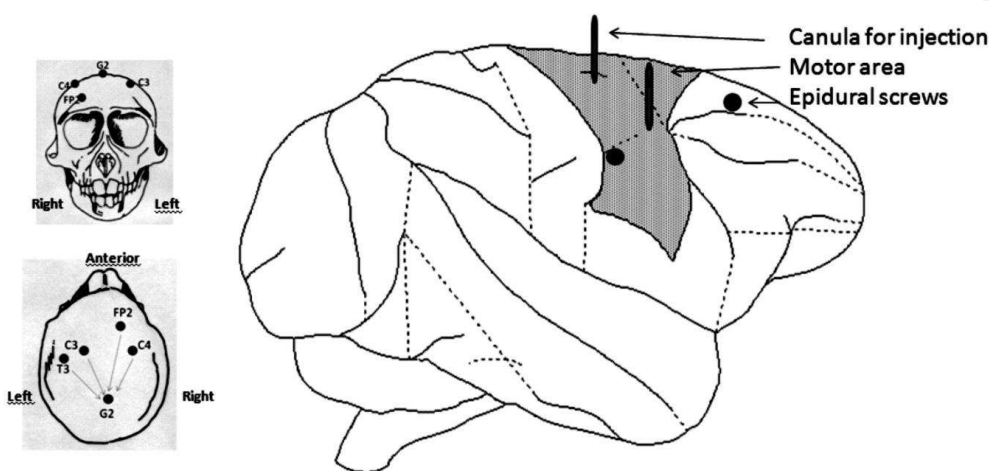


Figure 18 : Schematic Representation of location of electrodes for ECoG and canulae for injection
Four experiments in each monkey were completed for the characterization of model.

5.2.3 INDUCTION OF SEIZURE

Monkey was positioned on a primate chair (Crist Instruments, USA), with the head fixed to a head holder. This allowed free movements of limbs and permitted oral feeding of animals during the course of the experiments. Electroencephalogram (ECoG) was recorded for 10 minutes prior to seizure induction. Electromyogram (EMG) of the contralateral left forelimb and hindlimb was systematically monitored. PNC (PNC-G, Panpharma, Fougères, France) was diluted with sterile saline to achieve a strength of 500 IU/l. Using sterile technique, a total 2500 IU of PNC was injected at a rate of 1µl/min with Hamilton syringe and pump through the canula at a depth of 3+/-1 mm intracortically in the right motor cortex. After the end of injection of PNC, the injecting needle was kept in situ for 5 min before withdrawal. The dose rate and site of intracortical injection was not modified in the series of experiments in order to allow comparison. The injections were performed twice a week. A total of 11 purpose comparison. In a monkey, 3 additional experiments were performed to test resistance to antiepileptic drug (AED). In each experiment, seizures were recorded for an average of 5 hours continuously, paying attention to containment and comfort of animal in a restrained position.

5.2.4 VIDEO- ECoG- EMG RECORDINGS

Video- ECoG -EMG recording was performed using a commercial amplifier and software system synchronized with a video camera that can be used for standard clinical monitoring in human patients (System Plus, Micromed, Treviso Italy). ECoG and EMG signals were obtained with an analog acquisition band-pass filter between 0.05 Hz and 90 Hz and digitalized with a sampling rate of 250Hz. A 4 channel bipolar montage between ECoG electrodes was used for analyses. ECoG/ EMG synchronization with an analog video system permitted behavioral analysis of recorded seizures.

5.2.5 EFFECT OF DIAZEPAM

We studied the effect of Diazepam (Valium, Roche, Neuilly Sur Seine, France) on seizures in Monkey B. A dose of 0.5 mg/kg was injected intramuscularly one hour after the intracortical injection of PNC, after the first typical seizure manifested. A total of 3 experiments were completed. The results were compared with the 4 experiments in the same monkey when Diazepam was not administered.

5.2.6 STATISTICAL ANALYSIS

The seizures were analyzed for ictal onset, evolution patterns of ECoG abnormalities and temporal resolution of the events. Two examiners analyzed the data independently and post-hoc statistical analysis found no significant inter observer bias.

The variability in number of seizures, average duration of each seizure and total time spent during seizure in each hour were estimated for each monkey (intra subject) and between the two monkeys (intersubject). Statistical tests were performed using software GraphPad InStat3 (GraphPad Software Inc., California, USA). Intersubject variability in number of seizures, average duration of each seizure and total duration of seizure was assessed using a two tailed non parametric Wilcoxon–Mann–Whitney two-sample rank-sum test. The difference between datasets was quantified using the Hodges–Lehmann (HL) estimator. A nonparametric ANOVA was used for data obtained in each experiment (n=4) in each experimental animal (n=2). A difference was considered statistically significant for a p-value <0.05.

To study the effect of Diazepam, average duration of each seizure and total time spent in seizures in each hour was compared. Four control experiments and three experiments with intra muscular Diazepam were compared using a two tailed non parametric Wilcoxon–Mann–Whitney two-sample rank-sum test.

5.2.7 SPECTRAL ANALYSIS

Time-frequency analysis of 17 seizures recorded in Monkey B was performed. They were selected so that they contained no artifact throughout their duration, which was comprised between 23 s and 88 s (average duration: 48 s). ECoG signal was chosen as the monopolar derivation covering the primary motor cortex that received PNC-G (see figure 18). The amplitude (square-root of power) of oscillatory activity between 1 and 100 Hz was obtained using standard time-frequency analysis based on the Morlet wavelet transform (Le Van Quyen, 2001). The first and last spikes of each discharge were used to define its onset and

termination, respectively. Time window of analysis of each discharge was defined to contain at least ten seconds before seizure onset and after seizure termination. For each frequency, the amplitude was computed on 40 periods length sliding time-window, providing an effective frequency specific time resolution. Time-frequency sampling of the time frequency plane was 49 ms / 1Hz. Time-frequency data were normalized using the standard procedure: for each frequency, the mean of the baseline (periods of at least 10 seconds without interictal spikes chosen prior to each seizure) was subtracted to the data and then demeaned data were divided by the standard deviation of the baseline. Baseline was defined for every seizure as a period of at least 10 seconds without interictal spikes chosen just before seizure onset.

Finally, the typical time-frequency pattern of recorded seizure was defined as the median value over seizures of the normalized time-frequency charts computed as such. Before median averaging, time-frequency charts were resampled linearly on a time scale to normalize seizure duration to the observed average (48 s).

5.2.8 HISTOPATHOLOGY

Both animals were euthanized as per standard protocol after the end of experiments and brain histopathology was studied to document changes, if any, after repeated intracortical injections of penicillin.

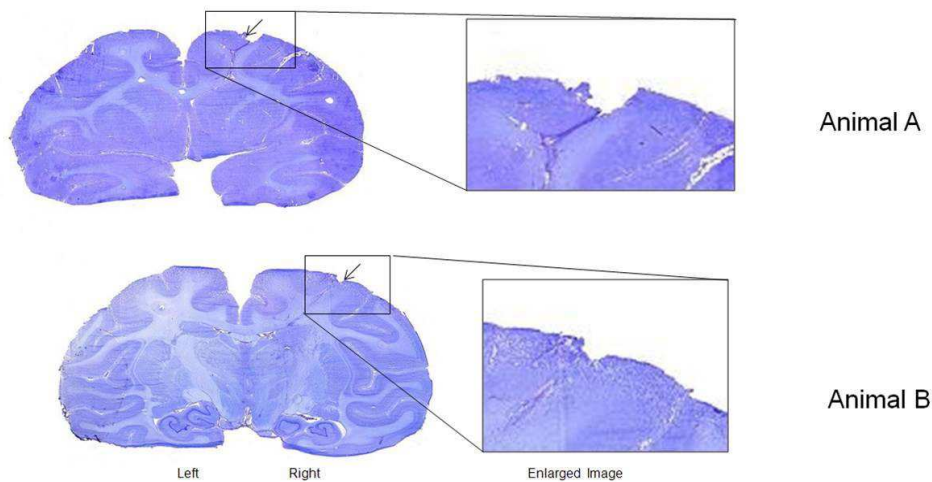


Figure 19 : Coronal sections of brains of monkey
Monkey A and monkey B, showing the site of intracortical injection of Penicillin marked by a black arrow. (Cresyl Violet Stain)

5.3 RESULTS

Clinical and electrical focal motor status was obtained after each single injection of PNC.

5.3.1 BEHAVIORAL AND ELECTROENCEPHALOGRAPHIC CHARACTERISTICS FOLLOWING A SINGLE INTRACORTICAL PENICILLIN INJECTION

We observed three distinct electrocorticographic patterns and matching behavioral presentations.

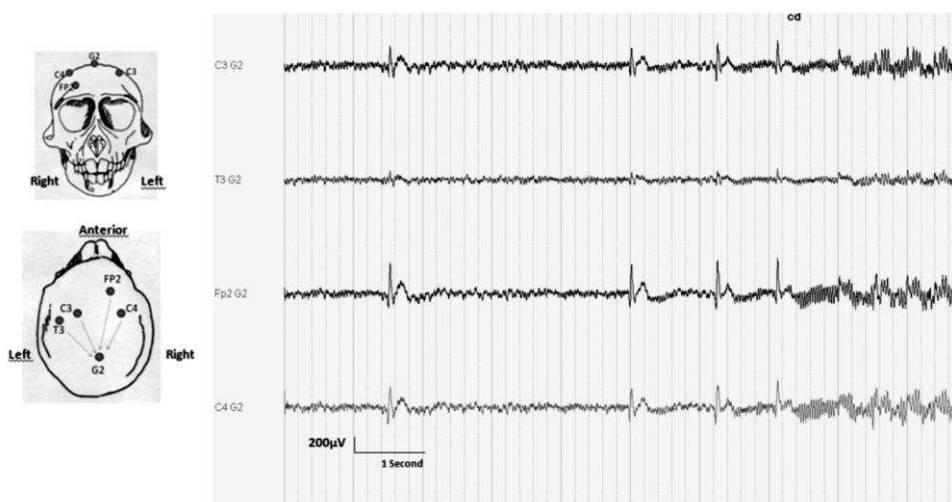


Figure 20 : Interictal spikes and beginning of a seizure

Pattern 1: Interictal spikes associated with contralateral myoclonic jerks

These interictal spikes involved single ECoG spiking with higher amplitude than baseline with brisk contraction of flexors of contralateral hind limb, sometimes associated with flexion of forelimb. The typical spike lasted 0.2 seconds, had an average amplitude in the range of 200 μ V to 400 μ V with a mean frequency of 0.3 Hz.

Pattern 2: Consisted of a train of interictal polyspikes with myoclonic contractions of contralateral hind limb occurring at an average of 3 to 6 in succession. Polyspikes lasted for less than 3 seconds, had average amplitude in the range of 200-400 μ V.

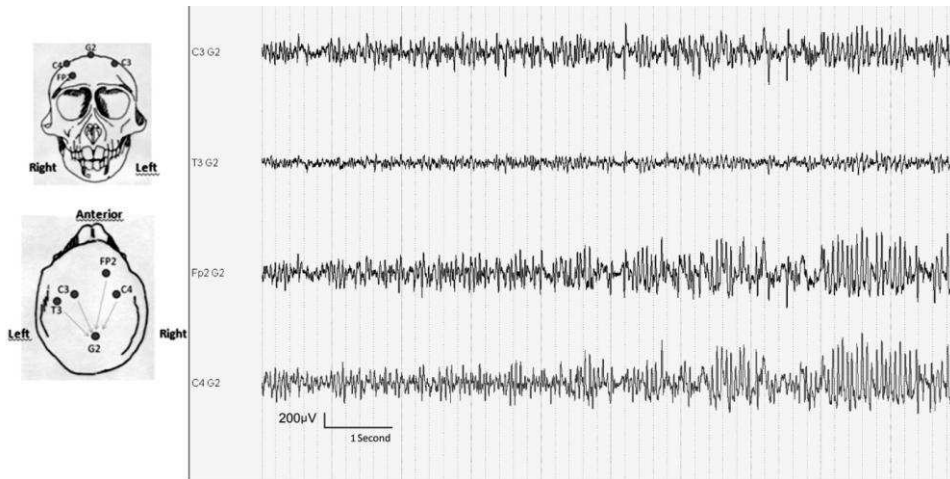


Figure 21 : Focal motor seizure

Pattern 3: Motor seizure (Figure 21)

This pattern followed pre ictal myoclonus that evolved into a sustained seizure lasting between 5 seconds and 120 seconds (mean 49+/-8 s.). The beginning of seizure was marked by ECoG spikes, similar to interictal ones, with amplitude in the range of in the range of 200 µV to 800 µV, at a frequency of 0.5 to 1 Hz and lasting less than 5 s. This was followed by ictal discharge on ECoG with a frequency in the range of 20 to 25 Hz. The amplitude increased to a range 1500 µV to 2500 µV (mean 1850+/-372.5 µV) during the seizure .The end of seizure (figure 22) was marked by abrupt return of ECoG to baseline.

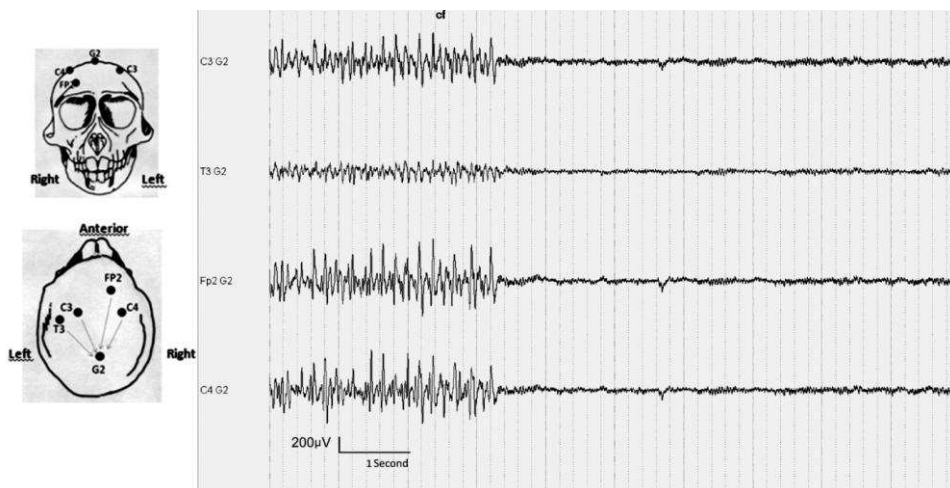


Figure 22 : The end of a seizure.

Marked by abrupt cessation of spiking. A period of about 3 to 5 seconds is noted after which the interictal spikes begin to appear again.

Time-frequency chart of the normalized amplitude of primary motor cortex activity during motor seizures (Figure 23) confirmed the primary role of beta oscillations (12-25 Hz) that started 3 s after seizure onset and remained steady until seizure termination. Seizure onset was characterized by a brief vertical column of activity between 1 and 70 Hz that corresponds to

first large spike. During the three seconds following the first spike, a fast drift of low-gamma activity, from 40 Hz to 25 Hz, could be observed. Low-gamma activity became broadly distributed in the second part of the seizure, and kept increasing until seizure termination, particularly between 25-40Hz.

This was accompanied by appearance of 4 Hz activity. These two features actually translate in the time frequency domain the bursty ECoG patterns (4 Hz beta-gamma bursts) that could be observed at the end of seizures.

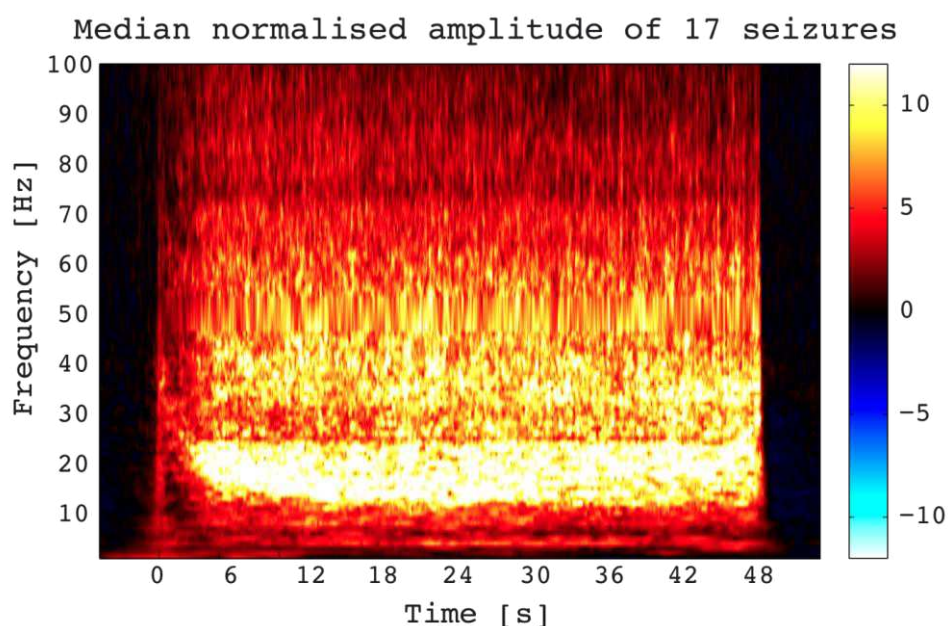


Figure 23: Time frequency analysis of Focal Motor Seizure

The clinical picture of a typical seizure demonstrated initial tonic contraction of contralateral hind limb often associated with involvement of contralateral fore limb. This was followed by clonic movements of contralateral limbs. It ended by abrupt cessation of motor activity with concurrent return to baseline of ECoG signal.

5.3.2 TEMPORAL EVOLUTION OF INTERICTAL SPIKES AND SEIZURES

In all experiments, a consistent succession of ECoG patterns in relation to seizure activity could be observed.

Occurrence of interictal spikes

Typically, interictal spikes were apparent within the 2 to 5 min following intracortical injection of penicillin. Interictal spikes and myoclonic jerks were most numerous during the first hour (figure 24) and were partially replaced by seizures afterwards. The number of interictal spikes gradually decreased in following hours, but they could still be clinically detected at the 8th hour post injection.

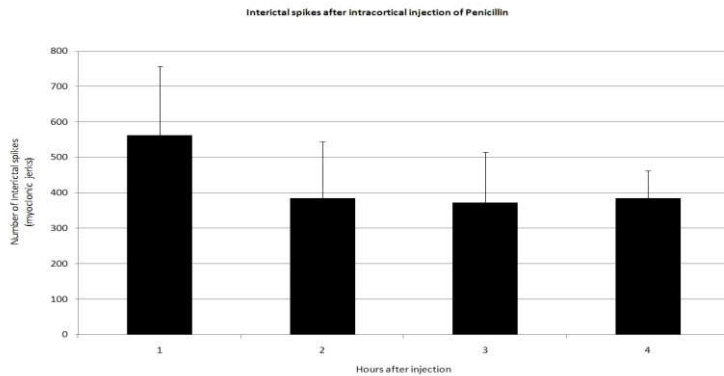


Figure 24 : Evolution of interictal spikes

Graph indicates average number of interictal spikes in one specimen during experiments. The number was maximum in the first hour after intra cortical injection of Penicillin. Thereafter it reached a plateau that lasted for several hours. X axis: Hours after intracortical injection.

Evolution of seizures

The first typical seizure appeared from 30 min to 54 min after the injection. The seizure duration and severity (in terms of involvement of muscle groups of the limbs in observed tonic clonic activity) increased gradually during subsequent hours, reaching a peak during the third hour before tapering off in the fifth hour of the post injection period. Even after removal of animal from the restrain chair, the behavioral seizures could be observed till seventh hour. In every experiment, no behavioral or ECOG abnormality could be detected the next day.

5.3.3 SEIZURE CHARACTERIZATION

Monkey A

The total time spent in seizures and average duration of seizure in each hour in four experiments is graphically described below (Figure 25).

The average number of seizures was 8.5 (± 4) in the first hour, and gradually increased in the second and third hour before decreasing to 10.5 (± 9.8) in the fourth hour. The average time spent in seizures was around 2020% of total duration for the first hour, around 30% in second and third hour and 40% of total duration in the fourth hour. The average duration of each seizure was 61.55 (± 38.84) in the first hour and was 73.07 s ($\pm 23.4s$) in last hour.

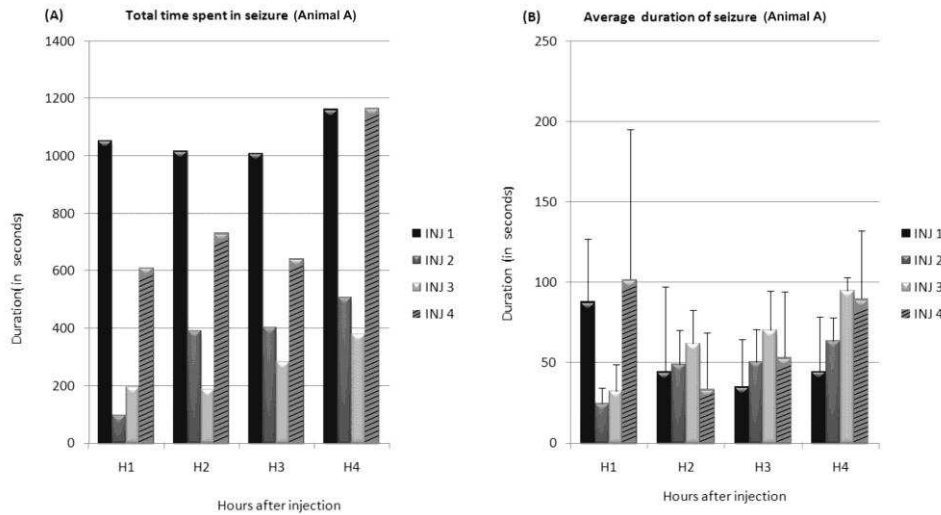


Figure 25 : Duration of motor seizure in monkey A

Part A of figure shows total time spent in seizures and part B shows average duration of seizure during each hour in each experiment (total 4)

X axis: Hours after intracortical injection

Y axis: Total time in spent in seizures in seconds

(Inj: injection of intracortical Penicillin)

Monkey B

The total time spent in seizures and average duration of seizure in each hour in four experiments is graphically described below (Figure 26)

The average number of seizures was 11 (+/-1.7) in first hour, increased in second and third hours before decreasing to 21.5(+/-8.6) in the 4th hour. The average time spent in seizures was around 15% of total duration for the first hour, around 28.30% and 29.70% in the second and third hour respectively and around 27% of total duration) in the fourth hour. The average duration of each seizure was 31.48 (+/-10.1) in the first hour and 48.35 s (+/-15) in the fourth hour.

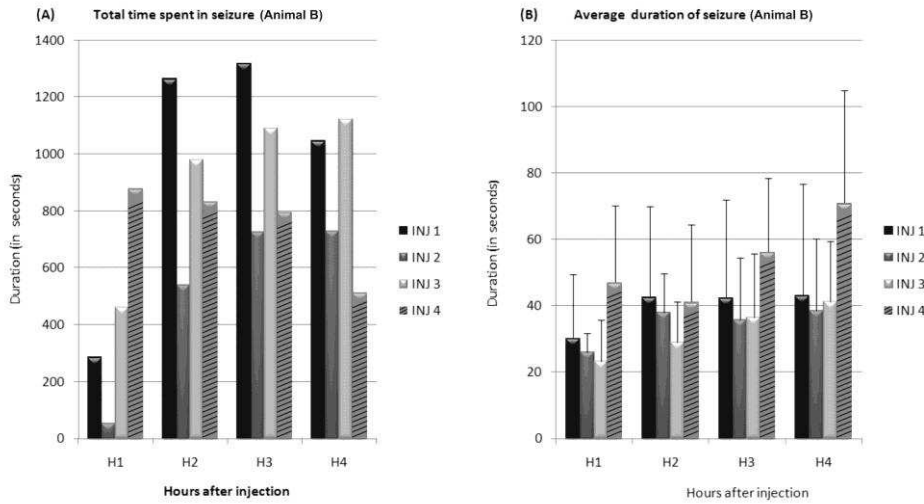


Figure 26 : Duration of motor seizure in monkey B

Part A of figure shows total time spent in seizures and part B shows average duration of seizure during each hour in each experiment (total 4)

X axis: Hours after intracortical injection

Y axis: Total time in spent in seizures in seconds

(Inj: injection of intracortical Penicillin)

5.3.4 INTERSUBJECT VARIABILITY

The pattern of seizure evolution was same in both specimens. The comparison between the two monkeys showed that average duration of seizures ($p \geq 0.05$) (figure 27a), number of seizures ($p \geq 0.05$) (figure 27b), and total time spent during seizure ($p \geq 0.05$) did not differ significantly.

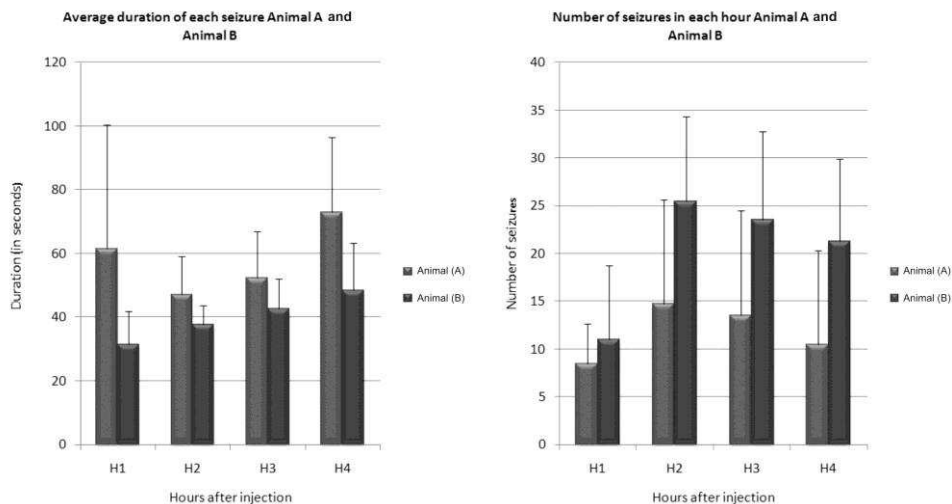


Figure 27: Intersubject variability between monkey A and B

Part A of figure shows comparison of average duration of seizure between two monkeys
 Part B of figure shows comparison of number of seizures between two monkeys
 X axis: Hours after intracortical injection
 Y axis: Total time in spent in seizures in seconds
 Monkey A (grey bars) Monkey B (black bars)

5.3.5 EFFECT OF DIAZEPAM ON SEIZURES

In Monkey B, compared to control experiments, administration of Diazepam decreased the total time spent in seizures (Figure 28A). However it remained steady (at around 200 seconds in each hour) throughout. The difference between average duration of seizure in each hour between control and experiments that included diazepam administration was not statistically significant ($p \geq 0.05$) (Figure 28B). The average number of seizures in each hour did decrease after administration of Diazepam.

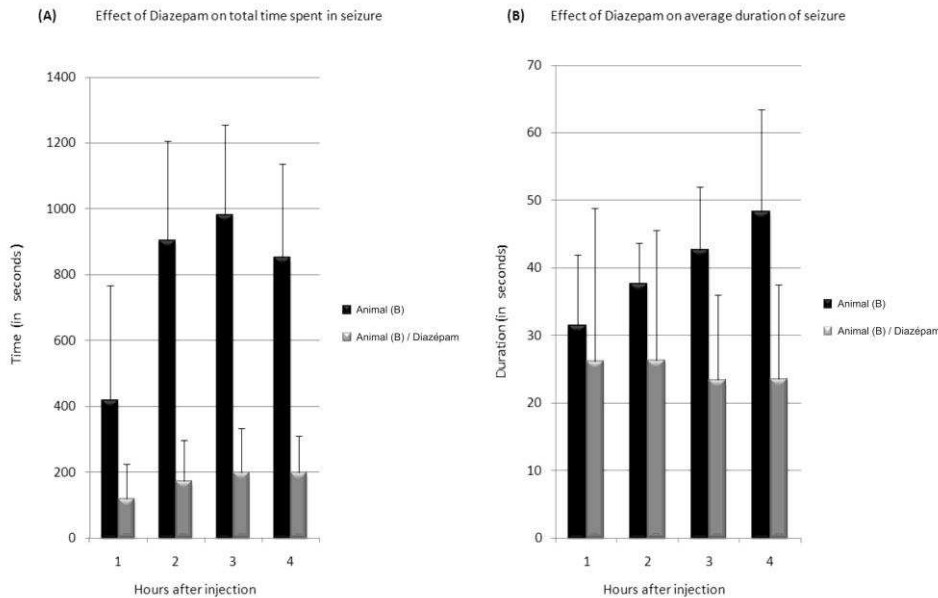


Figure 28: Effect of Diazepam on motor seizures

Part A of figure shows effect of Diazepam on total duration of Seizures
 Part B of figure shows effect of Diazepam on average duration of seizure in each hour
 X axis: Hours after intracortical injection
 Y axis: Total time spent in seizures in seconds
 Control experiments (Black bars) Diazepam (Grey bars)

The number of interictal spikes (myoclonic jerks) remained same even after the administration of Diazepam. The frequency of myoclonus remained in the range of 60 to 210 in each hour in three experiments (figure 29). It did not decrease significantly after administration of Diazepam.

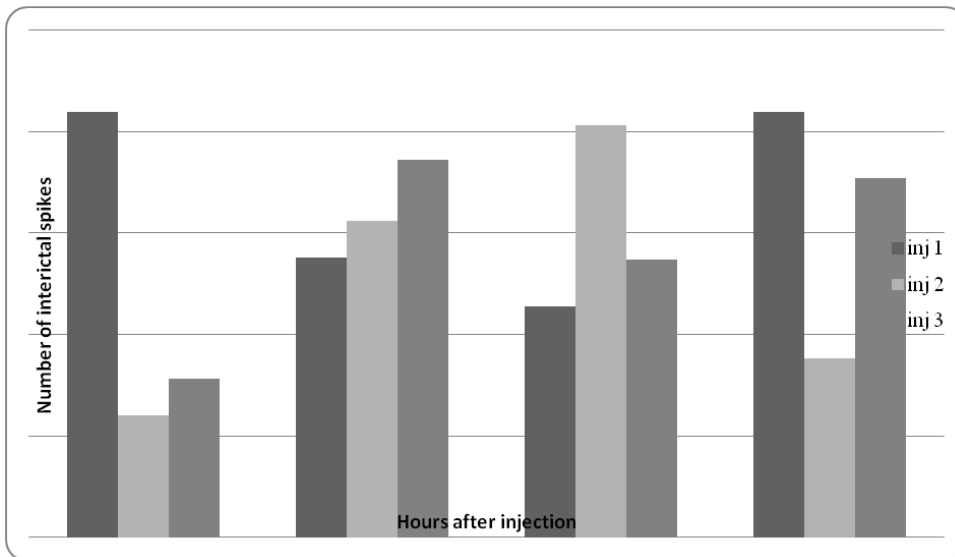


Figure 29 : Effect of Diazepam on interictal spikes

Number of interictal spikes recorded in each hour during three experiments when Diazepam was administered 1 hour after the intracortical injection of Penicillin

X axis: Hours after intracortical injection

Y axis: Number of interictal spikes

Inj: injection of Penicillin intracortically

5.4 DISCUSSION

In this study, we describe electrophysiological and clinical properties of a primate model of acute focal motor status epilepticus following intracortical injection of penicillin, which acts as a GABA blocker. The main results of our study are the following:

- 1) We could obtain on demand, a stable and reproducible motor status
- 2) The electro-clinical features of the seizures mimicked those seen in Kojelnikow syndrome
- 3) The seizures were resistant to benzodiazepine although their number was significantly decreased.
- 4) No major histopathological lesions were seen on brain specimen.

Models of focal neocortical epilepsy secondary to topically applied penicillin has previously been described in large animal models like cats (Yamamoto et al., 1995) rabbit (Pockberger et al., 1984), sheep (Opdam et al., 2002) and monkey (Kato et al., 1980), there is a paucity of studies aimed at characterizing and quantifying semi-acute focal motor status epilepticus in primates. The development of such a model in primate is important because seizure progression might differ from species to species (Gale, 2004). Critically, a primate model might be the most suited for preclinical testing of innovative therapies such as deep brain stimulation, local drug delivery, cooling of the epileptogenic zone or gene therapy, this was an important motivation in initiating this work.

5.4.1 CLINICAL SEMIOLOGY AND RESISTANCE TO AED

We found that focal intracortical injection of penicillin systematically led to a series of stereotypical and reproducible contralateral clinical signs that were strongly correlated with the ECoG spiking. These seizures closely mimicked those encountered in humans suffering from epilepsy partialis continua (EPC) and from Kojevnikov's syndrome.

Indeed, epilepsy partialis continua is described as a spontaneous regular or irregular clonic muscle twitching of cerebral cortical origin, confined to one part of the body and continuing for a period of hours, days, or even weeks²⁴. In most of the cases of EPC, the seizures are of focal cortical origin and motor activity remains localized. Motor activity (myoclonus) is often persistent, lasting for at least 60 minutes and sometimes extending for hours, days even weeks. Consciousness usually is preserved but postictal weakness is frequently evident (Bencaud, 1982). In Kojevnikov's syndrome, besides interictal spikes correlated with contralateral jerks, contralateral tonic seizures can occur. The clinical course seems to be not modified by use of anti epileptic drugs (Schomer, 1993). Failure of GABAergic inhibition and potentiation of excitatory (NMDA) synapses are considered as mechanisms for self-sustaining status epilepticus. This is also the reason for resistant to all AED (including benzodiazepine) except NMDA antagonists in such conditions (Mazarati and Wasterlain, 1997).

The intracortical injection of penicillin pointing to a cortical origin of seizures, strictly regional clinical manifestation in contralateral limbs, relatively stable number of myoclonic jerks observed in the inter ictal period, contralateral and regional tonic seizure, resistance to Diazepam are features of our model which closely resemble the description of epilepsy partialis continua and Kojevnikov's syndrome.

However, there is a need to test response to other classes of AED and document focal changes at the injection site by histopathology in order to characterize this model as a representative of human motor epilepsy. Our model has the distinct advantage of being in the non human primate thus incorporating anatomical pathways that may distinguish the primate (e.g. human) from rodent pathways and models. The semiology of the seizure bears strong resemblance to the human even if it does not replicate the pathology precisely nor the spontaneous aspects of human seizures. Furthermore, there is not underlying gross lesion (dysplasia, tumor, ischemic lesion) in the present model. However, our model is not a model of epilepsy syndrom but rather mimicks symptoms observed during motor seizures;

5.4.2 COMPARISON WITH OTHER MODELS

In a sheep model of focal epilepsy induced by intra cortical injection of PNC, Opdam and colleagues found that up to one third of the animals exhibited electroencephalographic seizures without any behavioral correlation.

This lack of motor response in association with the rhythmic ictal spiking may be due to methodological differences as Opdam et al injected the penicillin in the premotor cortex, in contrast to direct motor cortex injection in our protocol.

Penicillin injection models in newborn monkeys have been described in the past (Kato, 1980). However our model was characterized in adult monkeys and is suitable for pre clinical testing of therapies. Our model also differs from the more classical primate model of neocortical focal seizure obtained by intracortical application of alumina gel studied previously (Ribak, et

al., 2009). Indeed, in this model, the appearance of symptomatic epilepsy takes 4-8 weeks and behavioral characteristics are unpredictable with seizure frequency ranging from 1 per month to 10 per day (personal observation, unpublished data). Recently, focal seizures induced by electric cortical stimulation in primates have been studied (Spellman et al., 2009) to define optimal stimulation parameters for electroconvulsive therapy. Though the seizures induced were focal as recorded on EEG, it was not possible to observe clinical response in this model because anesthetics and muscle relaxants were used. Interestingly, our model of focal motor seizure in monkeys share electrical and clinical resemblances with those observed in rats (Chabardes, et al., 2008). This might suggest that the protocol used in the present study can be replicated in others species in rodents or big mammalian.

5.4.3 REPRODUCIBILITY

In our study, there was no secondary generalization of the seizures. The electrophysiological and behavioral abnormalities were usually absent after 24 hours after the injection. These are very attractive features of the model as they allow a rapid recovery of animal to a non epileptic state and improves safety in repeated experiments.

The various ECoG ictal patterns that were identified were reproducible even after several penicillin injections. The electrophysiological characteristics of this model are useful in evaluating treatment outcomes. Besides the usual duration and frequency of seizure, the number of interictal spikes and polyspikes are tangible abnormalities that can be assessed as parameters for testing effectiveness. This is possible because the inter ictal spikes are observed both as an electric and a clinical event in the form of contraction of contralateral limb.

The time frequency analysis representative of the 17 seizures indicated predominant beta rhythm activity throughout the course of a seizure. This beta rhythm, a marker of motor cortex activity, confirmed indirectly the site of intracortical injection of Penicillin.

5.4.4 CONCLUSION

The PC injection in motor cortex in primate leads to the induction of a reproducible acute focal motor status epilepticus. An animal model of epilepsy is considered suitable when it satisfies certain requisites. The model should be safe for the animal, simple to generate, easy to document and reproducible. Data obtained from ECoG recordings should be easy to use in automated analysis like automatic spike detection. Also for translational therapeutics of human diseases, the most important step is to validate novel therapies in closer species like primates. Our model described above satisfies these conditions.

5.5 GENERATION OF EPILEPSY BY TETANUS TOXIN IN PRIMATES: TECHNICAL NOTE

Between a good stable reproducible semi acute model of seizures by Penicillin injection at one end and a highly unpredictable chronic model of epilepsy induced by alumina application at the other end, a need was felt for characterizing an additional animal model of Epilepsy in primates, which could be chronic but stable and seizures generated in the model could be

predictable. As Epilepsy is an episodic disorder of cerebral dysfunction with multiple areas of brain developing abnormal oscillations and abnormal synchronization. A model generating epilepsy in chronic mode resembles better to actual pathology in Humans. With this aim we tried to establish a model of Tetanus toxin injection in primate motor cortex.

Tetanus Toxin as a pro-convulsant has been used for creating animal models of epilepsy for past several years. However most of these studies are related to non primate mammals. Below are few examples of different non primate models of epilepsy created using Tetanus Toxin Table:

Table 30 : Animals epilepsy induced with tetanus toxin

Study Author	Region of Brain	species	no	1 st Seizure onset	Last seizure
Carrea and Lanaria, 1962	Cerebral cortex	Dog	63	Two to seven days	2 months
Brooks and Asanuma, 1962	Motor cortex	Cat		Two to six hours	
Glaser and Yu, 1997	Dorsal hippocampus	Cat		Two hours	26 hours
Mellanby and George, 1977	Hippocampus	Rat		3 days	5 weeks
McGeer et al., 1980	Substantia nigra thalamus	Rat	>8	Immediately	five days (death)
McGeer 1980	Caudate	Rat	4	3 to 5 days	10 days
Louche et al., 1990	Motor cortex	Cat	5	2-18 days	Seizures persistent even after 38 days seizure types were focal motor seizures of variable complexity, focal motor seizures with secondary generalization, and epilepsia partialis continua
Barkmeier, Loeb, 2009	Somato sensory cortex	rat		Interictal spikes appeared between 4-2 days	In 6 weeks highly spiking animals developed generalized seizures

From the results of the studies above three conclusions emerged that:

- The model matches pathological dysfunction in brain in terms of chronicity.
- The seizures in rats and cats, dogs (see above) occur spontaneously over a time.
- Convenience of using single or few intracortical injections in an animal.

Action of Tetanus Toxin

1) Tetanus toxin acts as a protease, blocking the protein Synaptobrevin which plays an essential role in synaptic transmission. It has preference for inhibitory neurons. So the blockage of GABA release is more pronounced. After a single low dose, into the hippocampus or other cortical regions, it selectively blocks GABA release and associated IPSPs for a week or two.

2) After this period the inhibitory transmission recovers but this inhibition is much more weaker making the circuit more ‘epileptogenic’

Mossy fiber sprouting (axons of dentate granule cells) producing altered connectivity is well established in many chronic models of temporal lobe epilepsy and in human cases. The Tetanus Toxin model also shows mossy fiber sprouting (Mitchell et al., 1996).

Methods

1. One primate (macaque fascicularis) male, was used for this study three intracortical injections of tetanus toxin were made into motor cortex using the already implanted canula. Using Hamilton Syringe the Tetanus Toxin was injected intracortically at a rate of 1 microL/min. The needle tip was kept in situ and withdrawn after 5 min. Post injection, monkey was analysed for behavioural and electrophysiological seizures over several days.

2. Toxin Preparation Tetanus Toxin (Sigma Aldrich: 25micro G/r 250microL) diluted to produce 2nG/ microL.

Table 31 : Dose of tetanus toxin

Experiments	Dose of tetanus toxin	Time period between injections
1	5 microL (10nG)	0
2	5 microL (10nG)	8 weeks (between inj 1 and 2)
3	10 microL (20nG)	6 weeks (between inj 2 and 3)

Results

The animal tolerated the injection well and there were no side effects related to intracortical injection. The spikes and polyspikes and small seizures were observed. Three patterns could be noted: one with predominant spikes other with predominantly polyspikes and the third spikes followed by small duration clonic seizures noted in contralateral forelimb (figure 30, 31, 32 and 33).

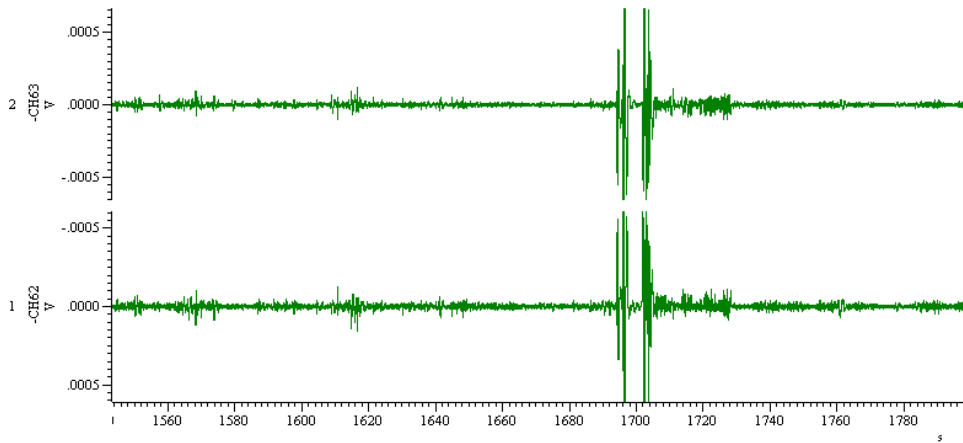


Figure 30 : Tetanus toxin model: Predominant Spikes
 Recorded in Spike 2® CED UK format using BIOMEA V2.3 ©CEA, LETI, France interface)

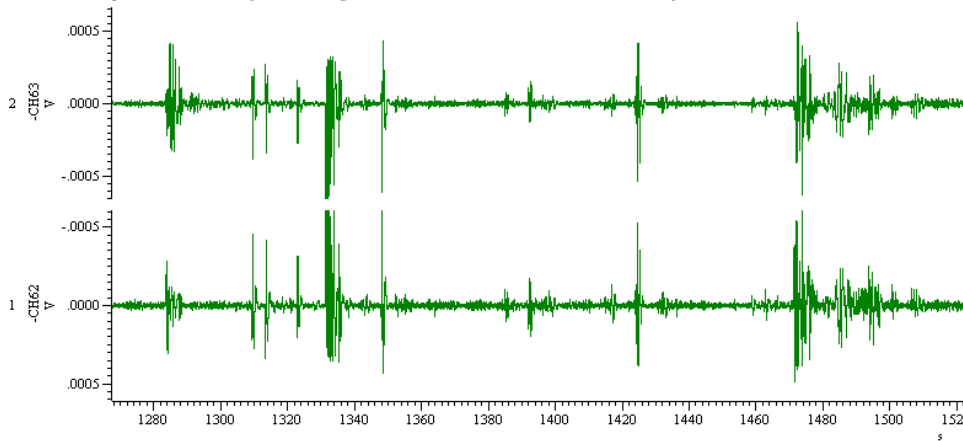


Figure 31 : Tetanus toxin model: Predominantly polyspikes.
 Recorded in Spike 2® CED UK format using BIOMEA V2.3 ©CEA, LETI, France interface)

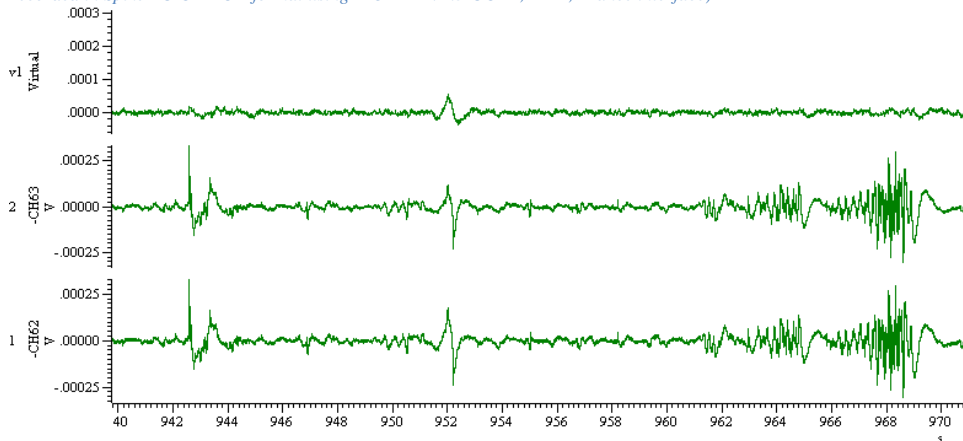


Figure 32 : Tetanus toxin model: Spikes followed by seizures.
 Recorded in Spike 2® CED UK format using BIOMEA V2.3 ©CEA, LETI, France interface)

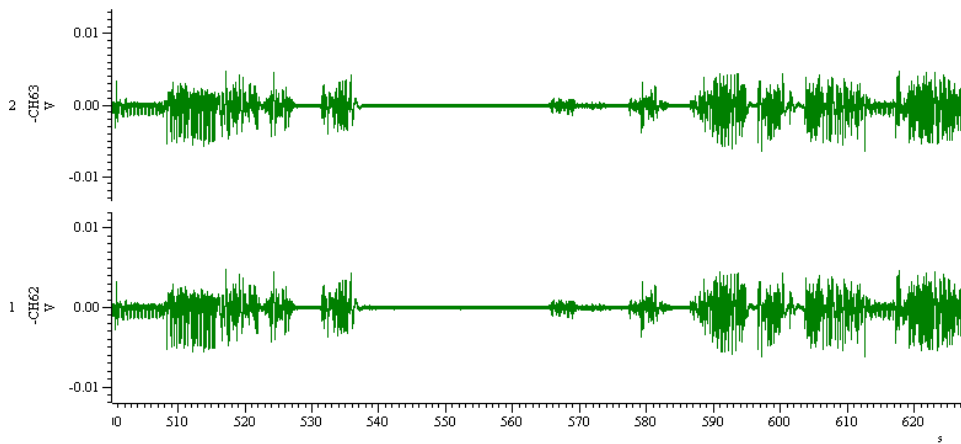


Figure 33 : Tetanus toxin model: A seizure.
Recorded in Spike 2® CED UK format using BIOMEA V2.3 @CEA, LETI, France interface)

Evolution of these electrographic abnormalities is summarised below:

Table 32 : Results of tetanos toxin experiments

Experiments	Spikes	Poly spikes	Seizures	Caesation of abnormality
1	3 rd post injection day	4 th post injection day	None	After 11 days
2	36 hours post injection	36 hours	None	Few spikes noted till two weeks
3	About 2 days	2 th day	Since the 2 nd day Few small duration clonic motor seizures	Seizures stopped after one day, ECOg abnormality remained even after 1 three weeks

Discussion

Though the three experiments demonstrated that intracortical injection of tetanus toxin in primate motor cortex is able to generate focal seizures, it might not be a suitable model to test effect of DBS. The evolution of seizures were unpredictable in terms of time it took for developing a seizure after the injection, the seizures were of small duration and stopped in one day after the third experiment. The dose increase carried out in the third experiment did produce EcoG abnormality that lasted more than three weeks. These shortcomings of model led to abandonment of further experiments till dose optimization and characterization of the model could be worked out and we decided to continue with the penicillin injection model.

CHAPTER VI

EXPERIMENTAL RESULTS

6.1 INTRODUCTION

Rationale for choosing STN and Putamen as targets

The extensive reviews of basal ganglia involvement in seizures (chapter 4) and evidence from animal studies as well as human case reports of DBS in epilepsy (chapter 3) indicate possibility of using STN and Putamen as targets. This decision was more justified by findings of dynamic changes in neural activity of these structures during focal motor seizures in primates. Few important findings from the work performed earlier by our group in Grenoble on the penicillin induced model of focal motor epilepsy in primates (Devergnas et al., 2012) are referred here.

Summary of previous work by Devergnas

Methods

In two monkeys, surgical access to basal ganglia structures was created by a trephine hole positioned appropriately. A recording chamber over this craniotomy, two cannuli positioned over motor cortex to facilitate injections of penicillin and five epidural screws for ECoG constituted assembly over the cranium. Micro electrode recordings performed in each basal ganglia structures during 65 seizures were used for analysis. Single unit activity and local field potentials were characterized.

Findings

Following figures summarizes the dynamic changes occurring in STN and Putamen during focal motor seizures from interictal state, to seizure onset, during the seizure and at the seizure offset.

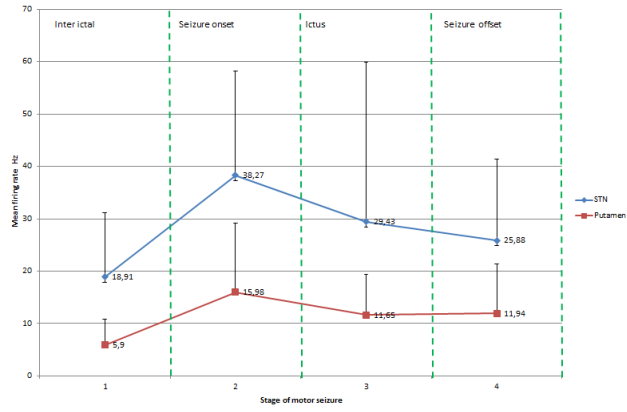


Figure 34 : Changes in mean firing rate during motor seizure

X axis: stage of seizure evolution

Y axis: mean firing rate (Hz).

(figure based on data by Devergnas, 2012)

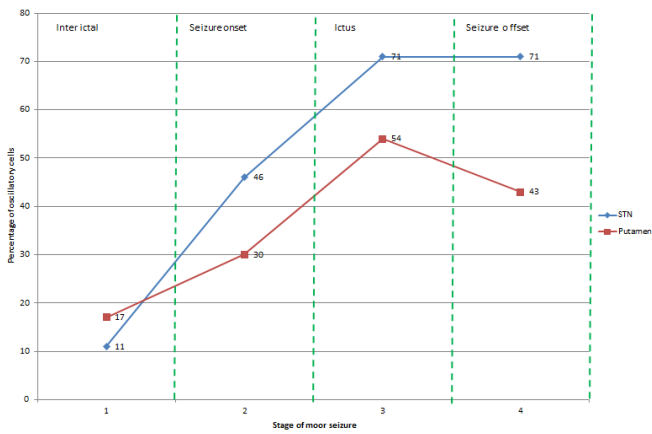


Figure 35 : Changes oscillatory pattern during motor seizure

X axis: stage of seizure evolution

Y axis: mean firing rate (Hz).

(figure based on data by Devergnas, 2012)

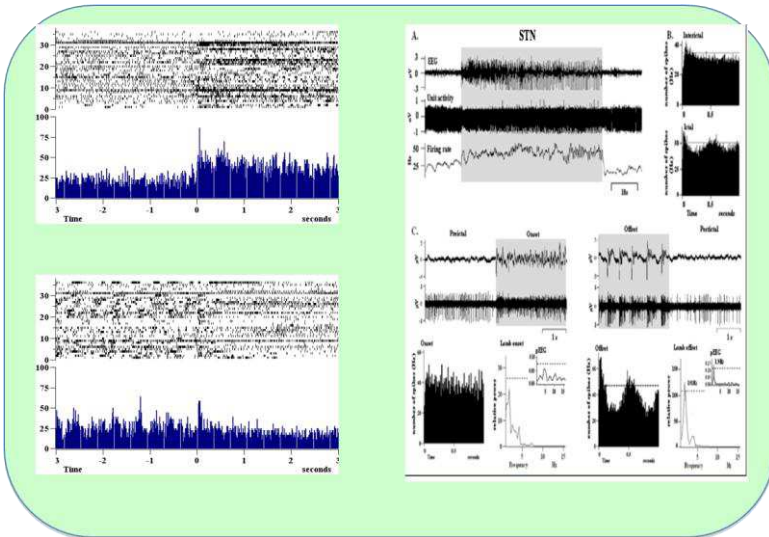


Figure 36 : Firing activity of one STN neuron.

Example of the typical evolution of spike firing activity of one STN neuron during interictal and ictal periods.

Example of complete seizure with EEG, unit activity and instantaneous frequency of the firing rate and autocorrelogram (Devergnas et al., 2012)

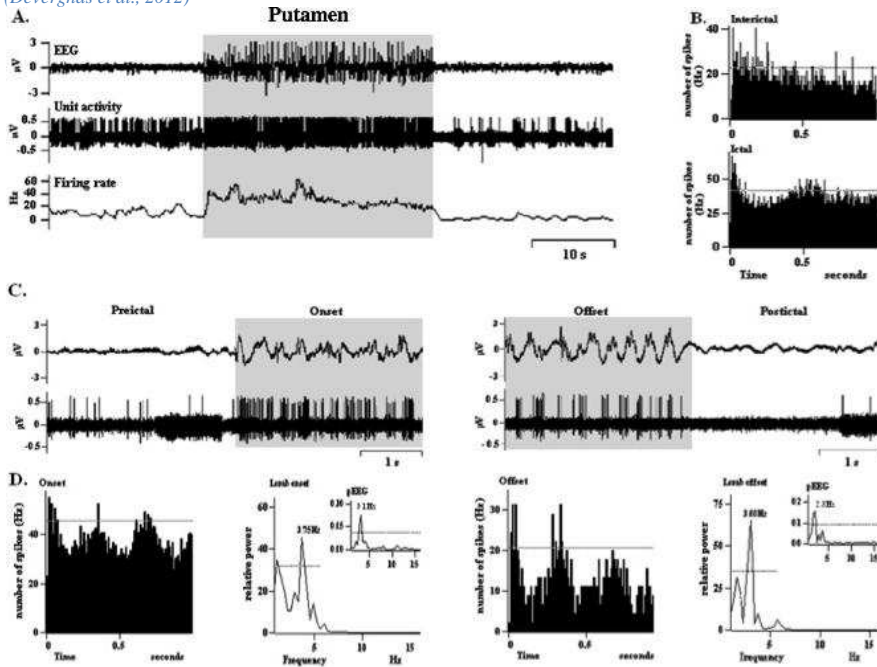


Figure 37: Firing activity of one Putamen neuron

Example of the typical evolution of spike firing activity of one Putamen neuron during interictal and ictal periods.

Example of complete seizure with EEG, unit activity and instantaneous frequency of the firing rate and autocorrelogram (Devergnas et al., 2012)

The findings of this investigation can be summarized as:

- STN (figure 35) and GPe (data not shown): The mean firing rate increased significantly at the seizure onset and decreased at the seizure offset as compared to inter ictal state. The percentage of oscillatory neurons increased from inter ictal state and remained high mainly in the seizure offset period.
- In Putamen the firing rate and percentage of oscillatory neurons increased during seizure. But the oscillator pattern was changing along the seizure and oscillatory frequency was twice high than cortical oscillation during seizure. This phase decoupling was more significant at the end of the seizure.
- There were no significant modification in firing rate of GPi and SNr neurons and oscillatory frequency was stable through the seizure.

Conclusion

From above findings it was concluded that the direct cortico- STN pathway is involved in motor seizure propagation and can be seen as a facilitating structure allowing the reoccurrence and spread of seizure. A reciprocating circuit between STN and GPe may participate in motor seizure. Putamen oscillatory bursts were almost twice as compared to cortical bursts. Thus for an excitatory cortical input received Putamen was transmitting twice the inhibitory signal downstream to basal ganglia output structures. Thus Putamen could be a physiological controller of the motor seizure propagation in this model.

There are many mechanisms postulated for explaining clinical effects of deep brain stimulation. But generally functional inhibition of structure being stimulated during high frequency stimulation and functional activation of structure during low frequency stimulation is more accepted views. Based on the dynamic changes of neuronal activity in STN and Putamen found during focal motor seizure reported above (Devergnas et al., 2012), we decided to test high frequency STN stimulation and low frequency putamen stimulation for control of seizures.

6.2 MATERIALS AND METHODS

Protocol was approved by a local Ethics Committee and experiments followed the European Communities Council Directives of November 24, 1986 (86/609/EEC) for care of laboratory animals.

6.2.1 ANIMALS

Study was performed on four *Macaca fascicularis* (CRP, Port Louis, Mauritius)

- Specimen 1 (male, 7 years old weighing 11.4 kg)
- Specimen 2 (female, 10years old weighing 5 kg)
- Specimen 3 (male 7.5 years old weighing 7.8 kg)
- Specimen 4 (male 9 years old weighing 5.8 kg)

6.2.2 SURGERY

The following text describes the implantation surgery for DBS of STN in details. The animals were kept fasting 10 hours before surgery.

The surgery was performed under general anesthesia with intra muscular injection of Ketamine (Imalgene, Merial laboratory, France) 0.4 mg at induction followed by 0.2 mg per hour/kg and Xylazine (Rompun 2%) 0.2 ml at induction followed by 0.1ml per hour. Additional local scalp anesthesia was provided with subcutaneous injection of Lidocaine with 1% Adrenalin. Prophylactic antibiotics, analgesics and anti-inflammatory therapy were given during perioperative period. Surgery was performed with a stereotactic frame (David Kopf Instruments, Tujunga California USA) under intraoperative radiographic control.

A midline scalp incision was made to expose skull, after obtaining hemostasis a craniotomy was performed prior to ventriculography.

Targeting the STN: The presumptive coordinates of the right Subthalamic nucleus were determined on pre operative MR images and refined by collating them with atlas of macaque fascicularis brain (Szabo Cowan, 1984) and actual orthogonal Xrays obtained during surgery. For these Xrays ventriculography was performed injecting 2ml water soluble iodine contrast medium (Iopamiron 200mg/ml Brac, Italy). Using outline of ventricles as landmark, anterior and posterior commissures and thalamic outlines were determined. The Guiot's method of determining the coordinates of STN based on outlines of ventricles in humans (Guiot et al 1976) was adapted to the primates and possible location of STN was determined. This targeting was refined according also to the position of the STN as seen in the pre op MRI.

After this the intraoperative mapping of STN in vertical plane was undertaken. A single sterile microelectrode (Tungsten microelectrode, impedance: 2 - 3 mega Ohm, FHC Inc, Bowdoin, USA) was used with specific software (lead point3, Medtronic USA) to map cortex, white matter, thalamus, subthalamic nucleus, substantia nigra in progressive descending plains in the vertical axis. The height, beginning and end of STN nucleus were determined. Considering anatomic information derived from atlas, pre-op MR and ventriculography and neurophysiological information obtained during microelectrode recordings together, the final implantation of STN was undertaken. On the atlas and AC- PC landmarks the coordinates of the STN were X (lateral): 5 mm, Y (anterio posterior): AC -6 mm, usually midpoint of AC- PC distance and Z (azimuth): 1/8 th of the hight of thalamus below the AC- PC plane.

Following figure explains the targeting STN based on atlas and AC- PC landmarks outlined on ventriculography.

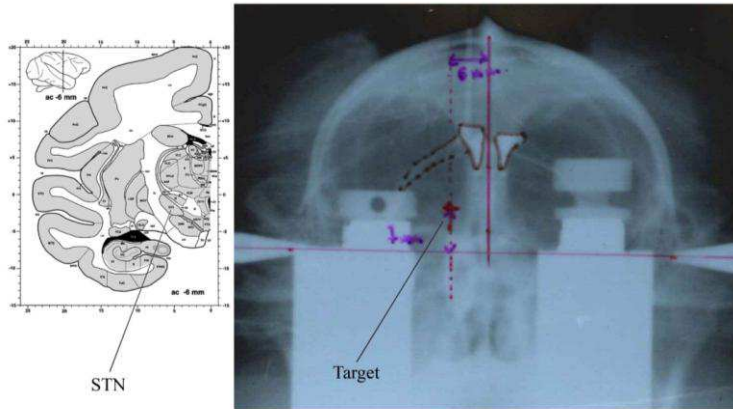


Figure 38 : Targeting STN

On right side shows atlas image of coronal section of Monkey brain at Ac -6mm showing the STN. Left side shows a AP projection Xray obtained by ventriculography during surgery outlining ventricles and target.

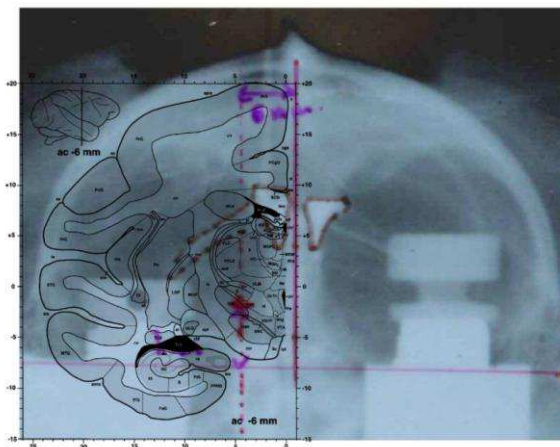


Figure 39 : Targeting STN.

Two images superimposed on each other.

Following figure displays the neuronal firing patterns recorded during intra operative electrophysiology.

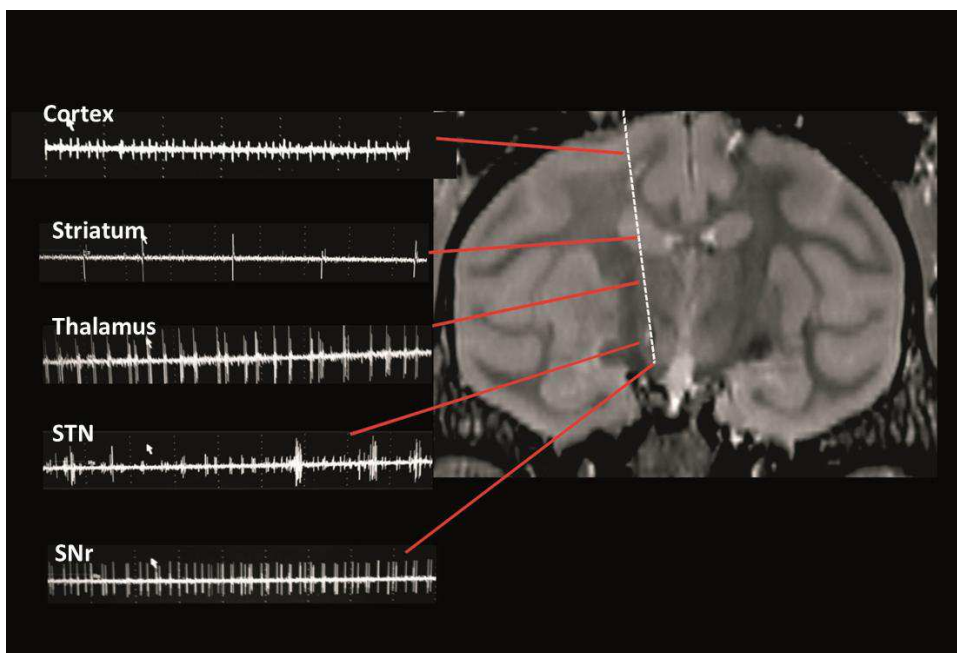


Figure 40 : Neuronal firing patterns during targeting STN
On right side shows the neuronal firing patterns as recorded during the intra op electrophysiology. On left side a T2W image in coronal section of monkey brain indicates the structures sampled. White interrupted line represents the tract of the recording electrode.

Implantation of the depth electrode: The electrode (quadripolar, lead length 20 cm, electrode length 0.5mm, outer diameter of electrode 0.029" spaced 0.5mm apart, Numed USA) was implanted so that all the four contact points were in the STN. It was anchored extra cranially to a screw and fixed with dental cement.

Two canulae were then screwed in the skull above the hand area of the right motor cortex to enable further injections of penicillin. Four stainless steel screws (radius of the head 2.25 mm length 20 mm, Safix France) were implanted after small craniotomies. The screws were secured taking care that the face of the screws was in contact with the dura. Finally a Head Holder (Crist Instrument Company, Hagerstown USA) was positioned, and secured with dental cement.

Then the back of animal was prepared. A skin incision was made to create a subcutaneous space which accommodated the neurostimulator (Solettra 7426, Medtronic, Minneapolis, USA). Lead extensions (lead extension 37086, length 40 cm, Medtronic, Minneapolis, USA) were tunneled through the subcutaneous space in the back and neck and connected with the implanted DBS electrode and the stimulator to complete the circuit. Skin incision was closed in two layers.

Animals were allowed to recover and monitored in the post operative period. Food and water was provided ad libitum. Experimental induction of seizures was performed after 10 days of recovery period.

The following images show the surgical steps:



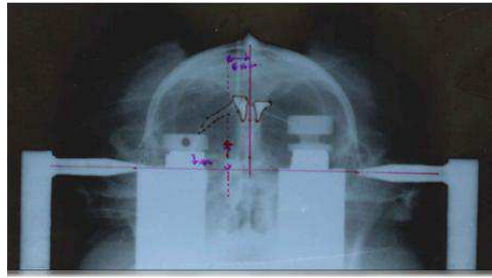
a) Positioning in the frame



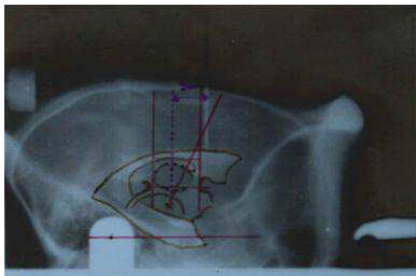
b) Midline incision



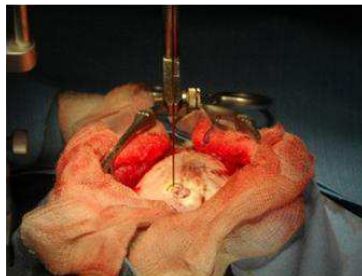
c) Ventriculography



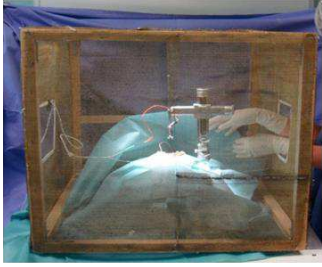
d) Anterio-posterior ventriculogram



e) Lateral ventriculogram



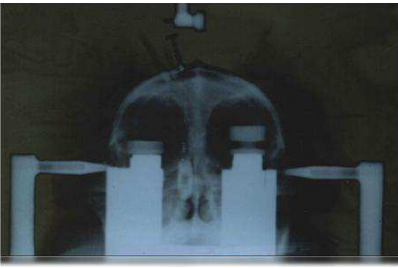
f) Intra- op single electrode recording



g) Faradic cage for neurophysiology



h) Screen shot of neuronal activity on Lead Point



i) A-P X ray with DBS electrode in situ (arrow)



j) Lateral X ray with DBS electrode in situ (arrow)



k) Neurostimulator in the back

Figure 41: Serial steps followed in implantation surgery

6.2.3 PUTAMINAL IMPLANTATION

The surgical implantation procedure (except the target location) was same as described for STN implantation. On the atlas and AC- PC landmarks the coordinates of the Putamen were X (lateral) 11- 12 mm, Y (anterio posterior) AC +1 mm, and Z (azimuth) 4 mm above the line drawn from outer canthus of orbit to tragus of the ear on X ray; so as to correspond to lateral and superior portion of the putamen mainly consisting of motor division (Nambu et al 2002).

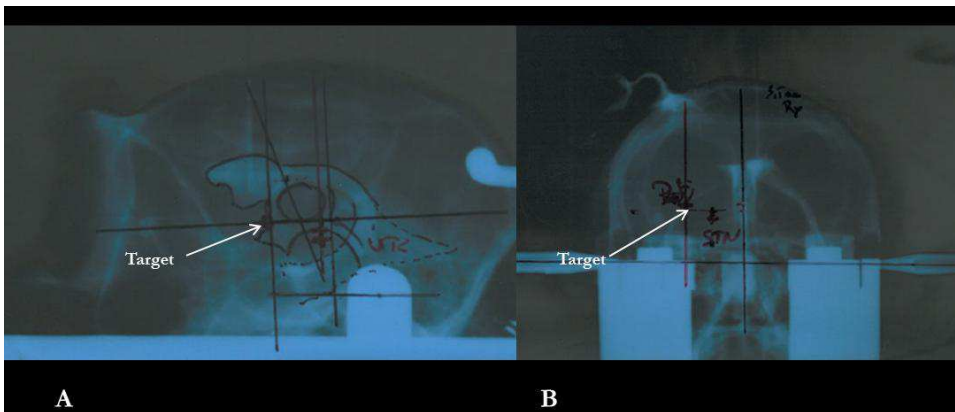


Figure 42: Targeting Putamen.

Part A shows a lateral Xray (ventriculogram) and putamen target.

Part B shows Anterio Posterior Xray (ventriculogram) and putamen target.

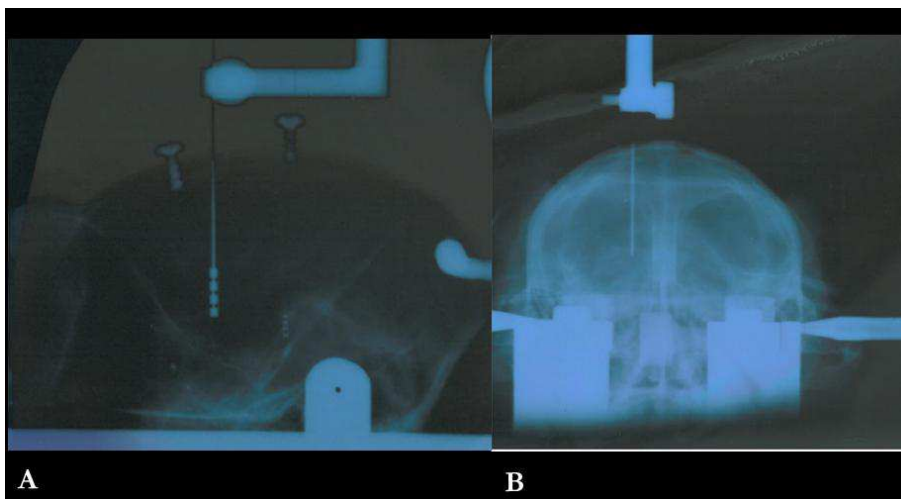


Figure 43: Targeting Putamen.

Part A shows a lateral Xray with depth electrode in the putamen target.

Part B shows Anterio Posterior Xray with depth electrode in the putamen target.

6.2.4 STN + PUTAMINAL IMPLANTATION

The surgical implantation procedure (except introduction of two electrodes one in STN and other in putamen), induction of seizures, recording and statistical analysis were same as described in details earlier.

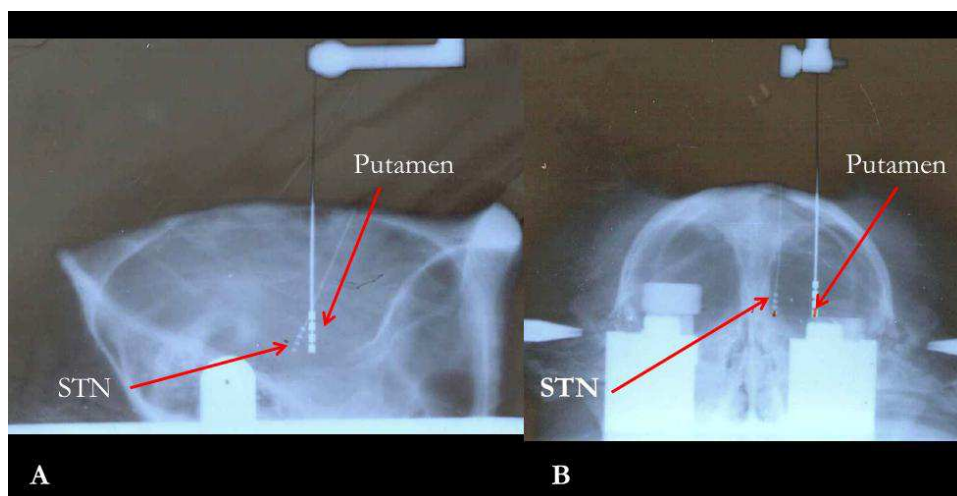


Figure 44 : Targeting STN and Putamen.

Part A shows a lateral Xray with depth electrodes in the STN and Putamen targets

Part B shows Anterio Posterior Xray with depth electrodes in the STN and Putamen targets

6.2.5 STIMULATION PROTOCOL

Continues unilateral STN HFS experiments were conducted in three monkeys with each monkey being its own control. The schedule of control and stimulation situation was in random order. The threshold of voltage at which motor side effects (dystonia on the contra lateral side of the stimulation) was determined for both primates. Then subthreshold high frequency Stimulation was delivered to STN by turning the stimulator 'on' as soon as the penicillin was introduced intracortically. It was turned off after 66 % of total time of recording in each session in specimen 1 and specimen 2 and 75 % of total time in Specimen 3. This allowed us to note if there was a 'rebound' phenomenon in seizure activity after the acute stimulation was turned off. Subthreshold for stimulation was 80 % below the strength when motor side effects apparent in each experiment seizures were recorded paying attention to containment and comfort of animal in a restrained position. For the Specimen 1 and 2 duration of each experiment was 6 hours for Specimen 3 this duration was 4 hours.

The best contact electrode contacts were determined in each monkey. This was determined by selecting different contact points and programming the neurostimulator accordingly. After switching on the stimulator, a step wise increase in the voltage was performed from the lowest setting till the appearance of side effects. This was noted for each contact point. The contact points which showed side effects at the minimal current strength, and where the appearance of

side effects was consistent after several trials were considered as best contact points. The voltage setting was then set at 80 % of the threshold value during stimulation.

Table 33 : Stimulation parameters

For STN HFS (pulse width 60 μ s, frequency 130 Hz)

	Best contact point	Threshold voltage
Specimen 1	Monopolar (case +); contact 2 -	2.4 V
	Bipolar contact 0+, contact 2 -	3 V
Specimen 2	Monopolar (case +)contact 3 -	2V
	Bipolar contact 2+, contact 3 -	2V
Specimen 3	Monopolar (case +) contact 3 -	2.8V
	Bipolar contact 0+ve, contactnt 3 -	3.3V

For Putamen LFS (pulse width 200 μ s, frequency 5 Hz, 20 Hz)

	Best contact point	Threshold voltage
Specimen 1	Monopolar (case +) contact 1 -	3 V
	Bipolar contact 0+, point 3 -	3.2 V
Specimen 4	Monopolar (case +) contact 3 -	3.4V
	Bipolar contact 2+, contact 3 -	3.8V

For STN HFS + Putamen LFS

	Best contact point	Threshold voltage
Specimen 2	STN Monopolar (case +) contact 3 -	2 V
	Putamen (case +), contact 2-ve, contact 3 -	3 V

Following figure illustrates the stimulation protocols

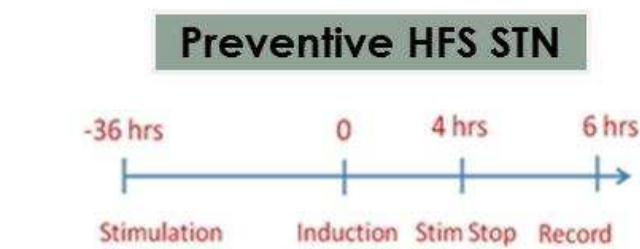
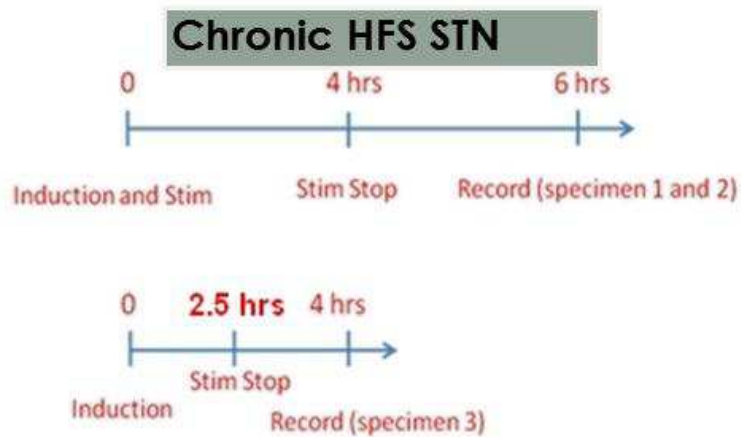


Figure 45 : Stimulation protocols

Preventive HFS STN stimulation

In one specimen we tested the effect of preventive STN Stimulation. The stimulator was turned on 36 hours before the induction of seizures by intra cortical injection of Penicilin. After the seizures were induced stimulation was continued for 4hours and then it was turned off. Recording was continued for 6 hours from the time of induction of seizures.

Continues LFS Putamen Stimulation

The stimulation protocol was same as described for continues HFS STN.

Combined HFS STN and LFS Putamen stimulation

The stimulation protocol was same as described for continues HFS STN.

6.2.6 ANALYSIS

Images below show an example of the actual tracings of ECoG recorded during the experiments.

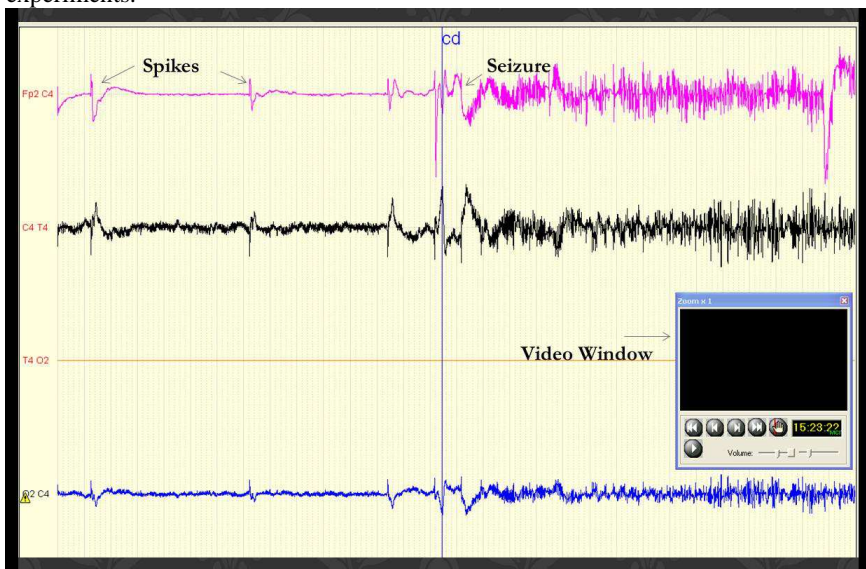


Figure 46 : ECoG records during STN stimulation (control experiment)
Tracings during control experiments when there was no stimulation.

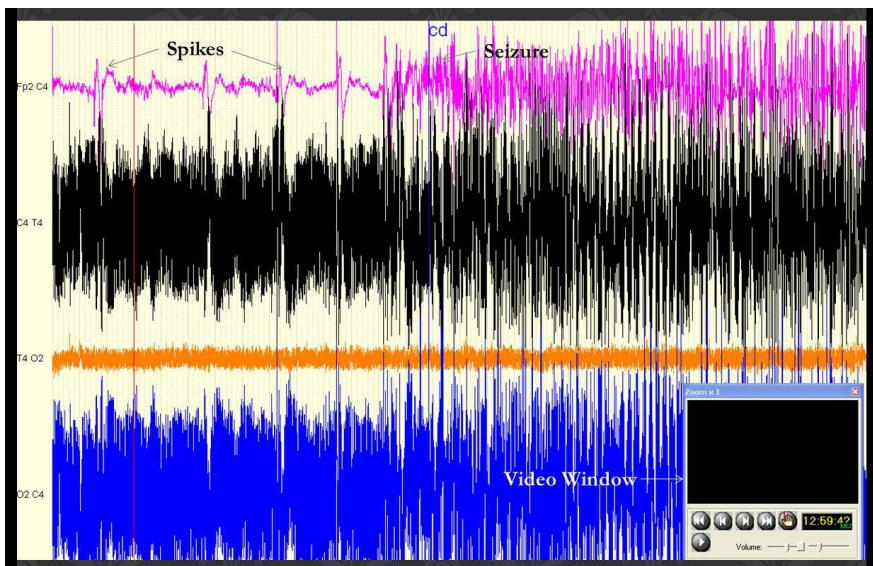


Figure 47 : records during STN stimulation (stimulation experiment)
Tracings contaminated by stimulation related electric artifacts.

In some experiments the stimulation related artifacts were severe and prevented easy counting of seizures.

We overcame this difficulty by marking the seizure onset and offset in real time, online during the conduct of experiment, observing the behavioral changes like contralateral motor activity evident in the real time video which was synchronized with the ECoG.

Further off-line analysis of the seizures was carried out for entire duration of the recording. At this time the video was replayed at reduced speed so as to precisely note the beginning and end of a seizure. Similarly the number of interictal spikes was also determined by observing and documenting myoclonic jerks that were time locked and matched with the ECoG spikes.

This off- line analysis was carried out by two persons independently, one of which was not involved in actual experiments. The data was compared between two observers. The difference between the values obtained (e.g. duration of seizures, number of interictal spikes) by two observers was not statistically significant. If on rare occasion the difference was found large then, the values were corrected by observing the seizure and video record again together.

Statistical tests were performed using software GraphPad InStat3 (GraphPad Software Inc., California, USA). "Mann Whitney test, two-tailed and nonparametric, to compare two groups of values, nonparametric ANOVA for each group of data. A difference was considered significant for a p-value < 0.05.

6.2.7 CONFIRMATION OF IMPLANTED ELECTRODES

The animals were sacrificed after completion of protocol. Post mortem MRI were obtained. These were compared with the final radiographs obtained during surgery which showed the intracerebral depth electrodes.

6.3 RESULTS

6.3.1 IMPLANTATION

The site of electrodes implanted was found to be correct that is in the STN in all specimens.

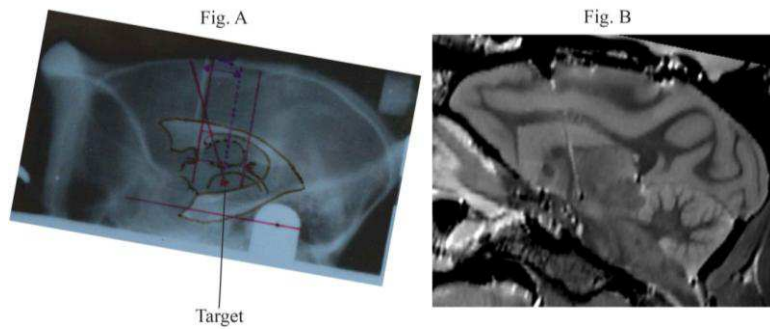


Figure 48 : Confirmation of implanted depth electrodes

Fig A: Lateral Xray projection shows the target (STN) based on the Anterior Commissure –posterior Commissure landmarks obtained by a ventriculography.

Fig B: Sagittal T2W post mortem MRI in same specimen showing the tract and placement of depth electrode.

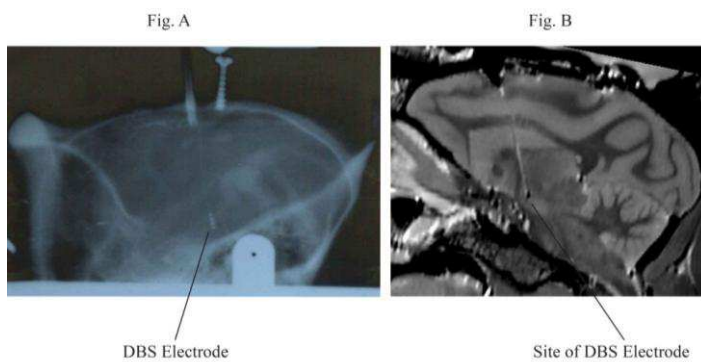


Figure 49 : Confirmation of implanted depth electrodes

Fig A: A lateral Xray projection obtained after completion of surgery shows the location of the depth electrode in STN.

Fig B: Sagittal T2W post mortem MRI in same specimen showing the tract and placement of depth electrode.

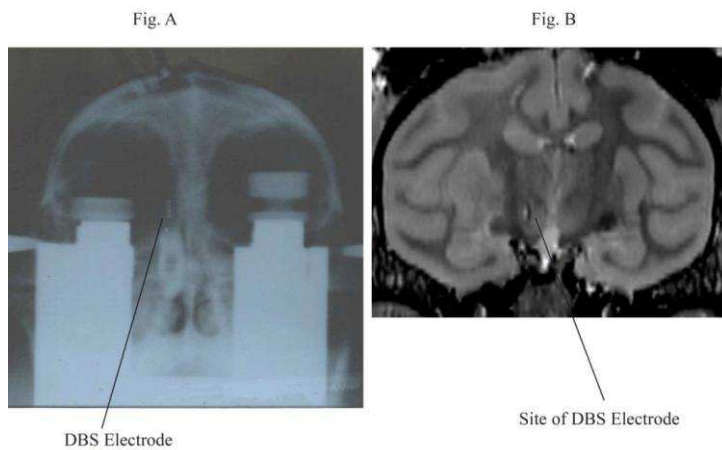


Figure 50 : Confirmation of implanted depth electrodes

Fig A: Anterio Posterior Xray obtained after completion of surgery shows the location of the depth electrode in STN.

Fig B: Coronal T2W post mortem MRI in same specimen showing the tract and placement of depth electrode.

6.3.2 EFFECT OF STN STIMULATION

In three monkeys a total of 1572 seizures were induced in 30 sessions.

Following table summarizes this.

Table 34 : Summary of seizures in STN experiments

Animal	Number of experiments	Number of Seizures
1	Control 6	473
	Stimulation 8	290
2	Control 5	280
	Stimulation 3	52
3	Control 4	328
	Stimulation 4	160
Total	30	1572

6.3.3 BEHAVIORAL EFFECT OF STN STIMULATION

The threshold for stimulation was determined by progressively increasing the current (voltage) and documenting the motor side effects. The frequent motor contractions and hypertonia in flexors in contralateral limbs indicated the threshold. All stimulation experiments were conducted with voltage set at 80 % below the threshold (see table above). Periodic assessment of threshold level was carried out in between experiments to check whether undesired effects like coagulation of the tissue or break in the integrity had occurred that would prevent effective current delivery to the target. During experiments a contralateral

motor seizure with tonic and clonic components was noted. The interictal period marked by brisk flexor contraction, representing interictal spike but no other motor abnormalities. The stimulation was well tolerated as no behavioral side effects like dyskinesia, agitation, restlessness or strange vocalization was noted during stimulation.

6.3.4 EFFECT OF HFS STN DBS ON NUMBER OF SEIZURES

Following table summarizes the effect of HFS STN on number of seizures. The data is presented separately as each monkey acted as it's own control, and the natural biological variability could possibly make the reponses different among the specimen. However the effect was consistent and similar in all specimens.

Table 35 : Reduction in number of seizures during STN stimulation
(the numbers represent percentage)

Hours →	1	2	3	4	5	6
Animal1	100%	93,18%	58,17%	33,26%	22,2%	36,98%
Animal 2	93,2%	69,70%	76,57%	43,49%	56,32%	14,62%
Animal 3	63,84%	49,34%	45,54%	54,45%		

Numbers represent percentage

The same results are graphically presented below:

Specimen 1

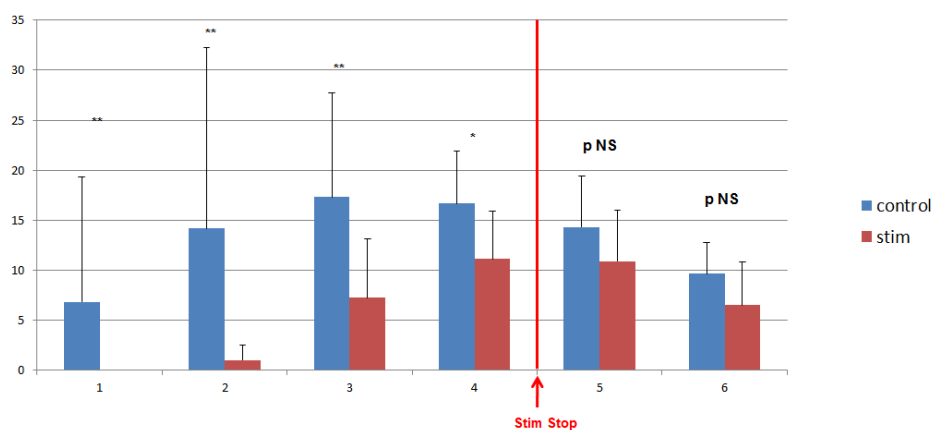


Figure 51 : Effect of DBS STN on number of seizures in specimen 1

X axis: hours after injection

Y axis: number of seizures

Specimen 2

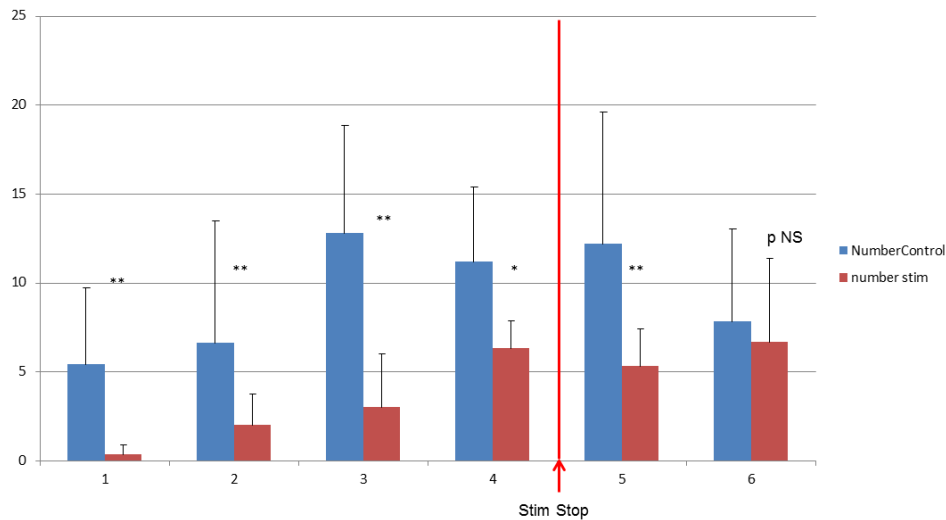


Figure 52 : Effect of DBS STN on number of seizures in specimen 2

X axis: hours after injection

Y axis: number of seizures

Specimen 3

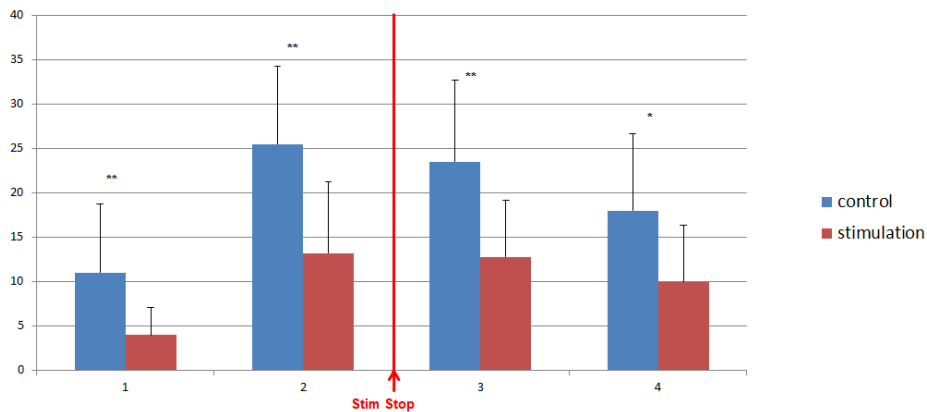


Figure 53 : Effect of DBS STN on number of seizures specimen 3

X axis: hours after injection

Y axis: number of seizures

6.3.5 EFFECT OF HFS STN DBS ON TOTAL DURATION OF SEIZURES

Following table summarizes the effect of HFS STN on total duration of seizures. The data is presented separately as each monkey acted as it's own control, and the natural biological variability could possibly make the responses different among the specimen. However the effect was consistent and similar in all specimens.

Table 36 : Reduction in total duration of seizures during STN stimulation
(the numbers represent percentage)

Hours →	1	2	3	4	5	6
Animal 1	100%	90,22%	69,16%	43,33%	46,69%	44,25%
Animal 2	97,54%	56,77%	70,84%	65,57%	81,82%	75,13%
Animal3	61,96%	79,66%	69,11%	59,66%		

Numbers represent percentage

The same results are graphically presented below

Specimen 1

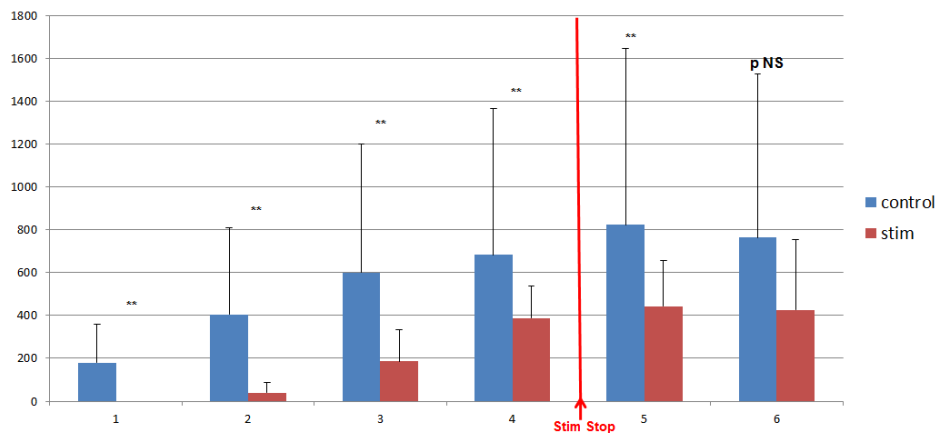


Figure 54 : Effect of DBS STN on total duration of seizures in specimen 1

X axis: hours after injection

Y axis: total duration in seconds

Specimen 2

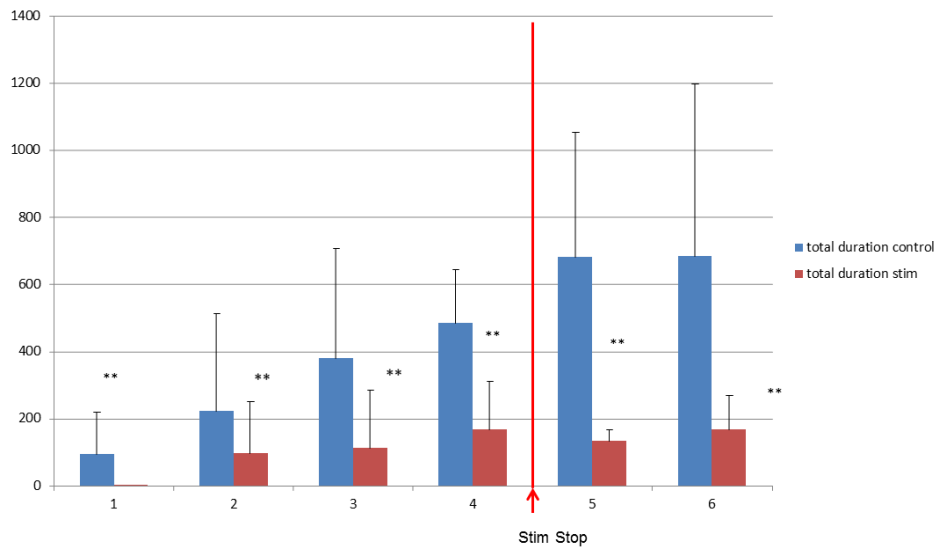


Figure 55: Effect of DBS STN on total duration of seizures in specimen 2.

X axis: hours after injection
Y axis: total duration in seconds

Specimen 3

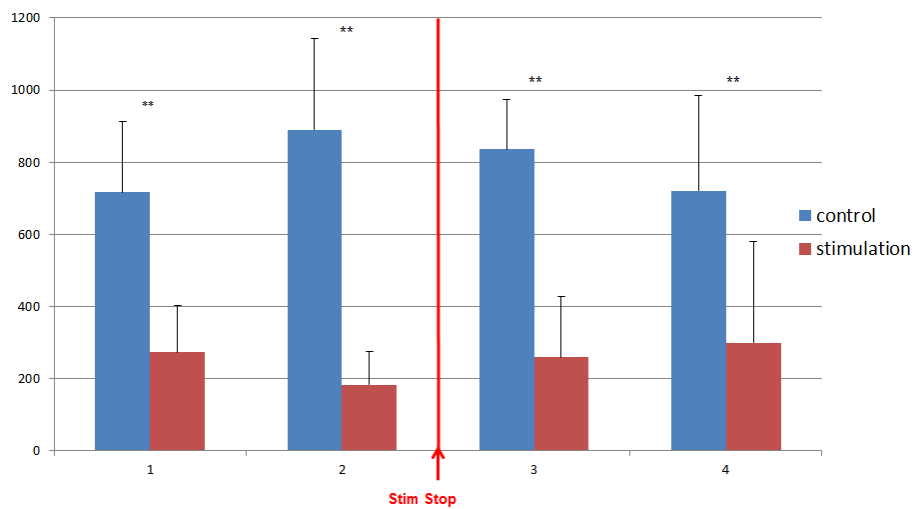


Figure 56: Effect of DBS STN on total duration of seizures in specimen 3.

X axis: hours after injection
Y axis: total duration in seconds

6.3.6 EFFECT OF HFS STN DBS ON AVERAGE DURATION OF SEIZURES

Following table summarizes the effect of HFS STN on average duration of seizures. The data is presented separately as each monkey acted as its own control, and the natural biological variability could possibly make the responses different among the specimen. The effect was similar in specimens 1 and 3. However there was an increase in the average duration during stimulation between second and fourth hour in specimen 2.

Table 37 : Reduction in average duration of seizures during STN stimulation
(the numbers represent percentage)

Hours →	1	2	3	4	5	6
Animal1	100%	48,15%	30,73%	7,04%	19,39%	24,37%
Animal2	80,52%	22,8%	11,66%	11,04%	31%	49,94%
Animal3	74,2%	67,57%	54,77%	59,45%		

Numbers represent percentage

The same results are graphically presented below:

Specimen1

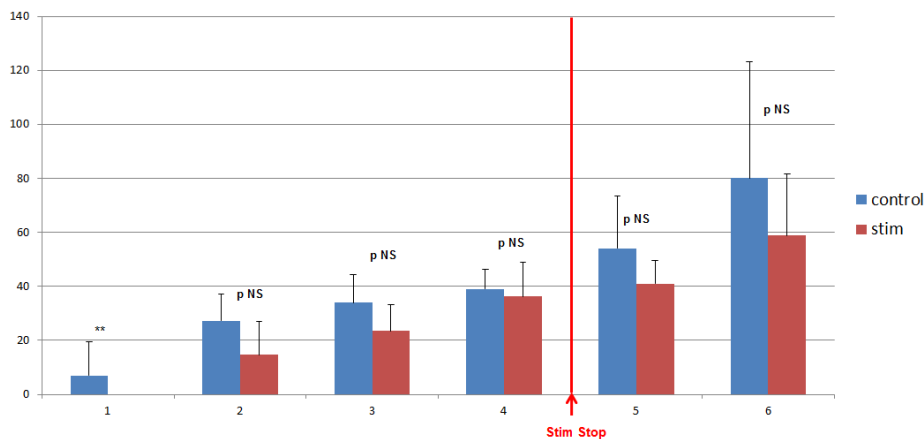


Figure 57 : Effect of DBS STN on average duration of seizures in specimen 1.
X axis: hours after injection
Y axis: total duration in seconds

Specimen2

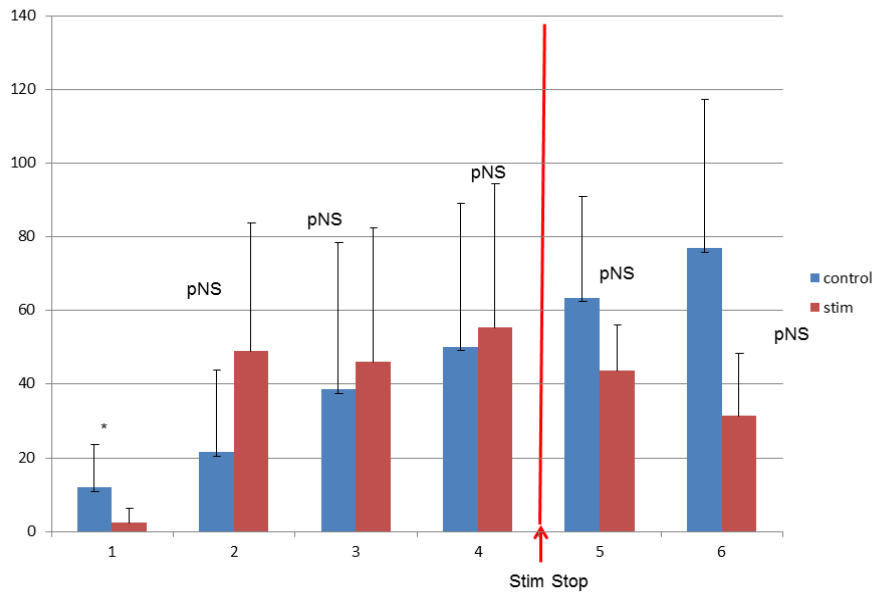


Figure 58 : Effect of DBS STN on average duration of seizures in specimen 2

X axis: hours after injection

Y axis: total duration in seconds

Specimen3

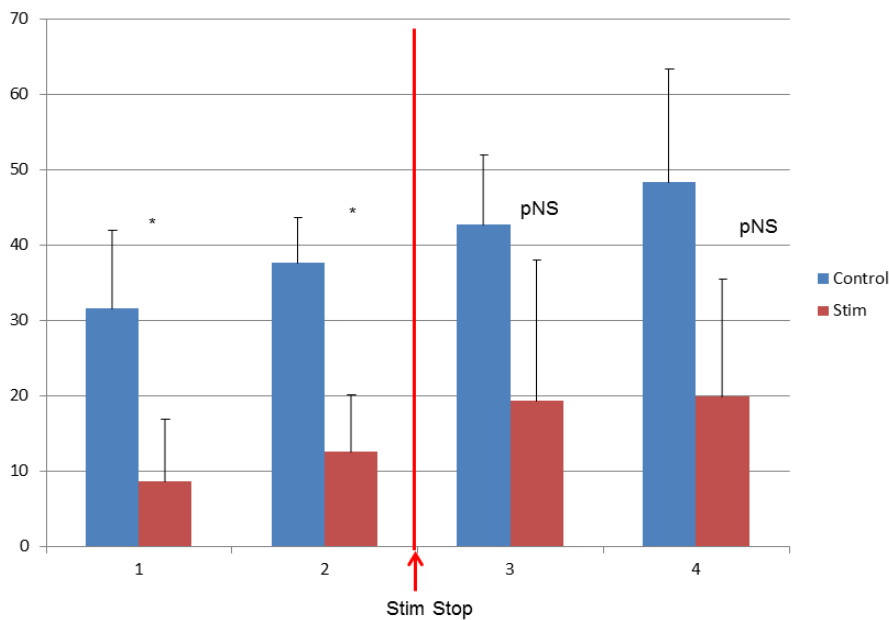


Figure 59 : Effect of DBS STN on average duration of seizures in specimen 3

X axis: hours after injection

Y axis: total duration in seconds

6.3.7 EFFECT OF HFS STN DBS ON NUMBER OF INTERICTAL SPIKES

In specimen 1 and 2 there was a trend of increasing in number of spikes during stimulation .In specimen 3 there was a decrease in number of spikes during stimulation but in all specimens the trend was not statistically significant.

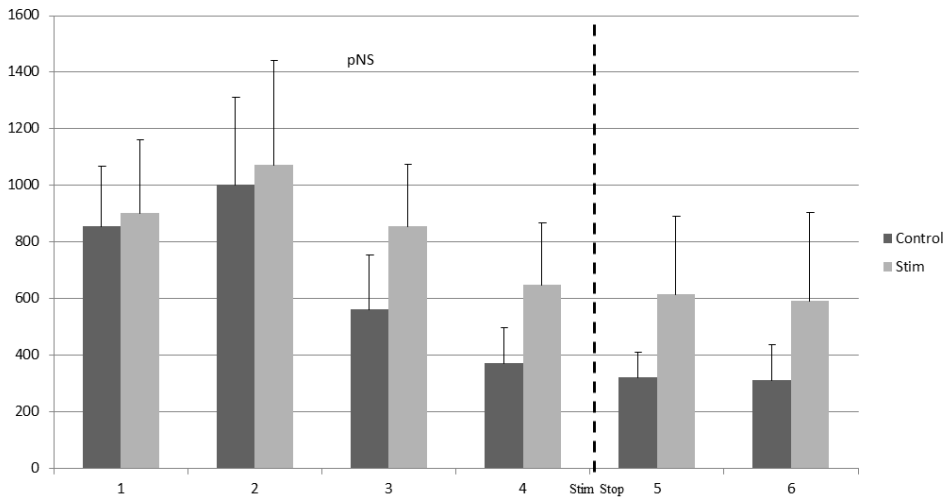


Figure 60 : Effect of DBS STN on number of interictal spikes in specimen 1

X axis: hours after injection

Y axis: number of spikes

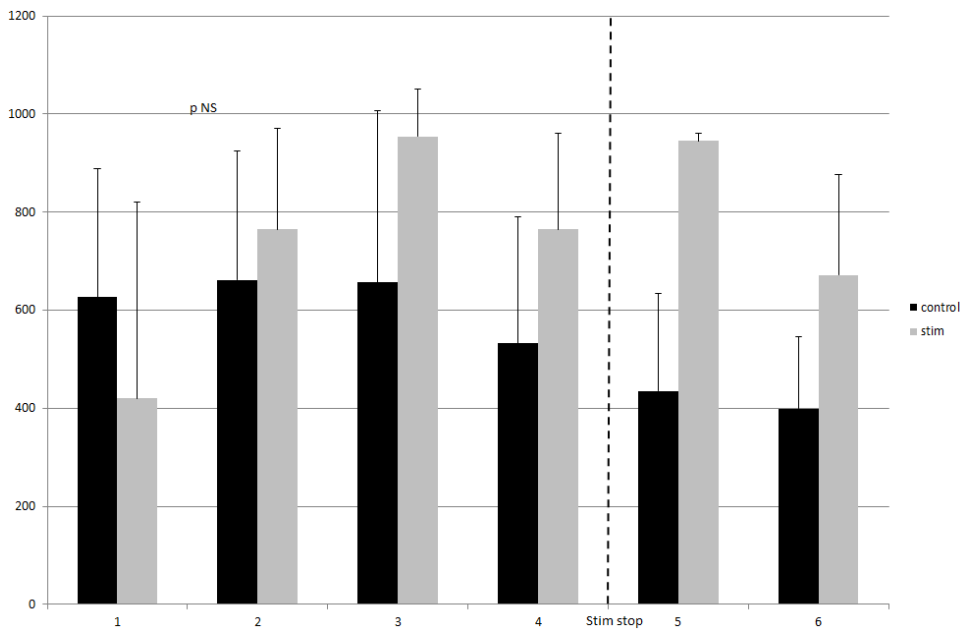


Figure 61 : Effect of DBS STN on number of interictal spikes in specimen 2

X axis: hours after injection

Y axis: number of spikes

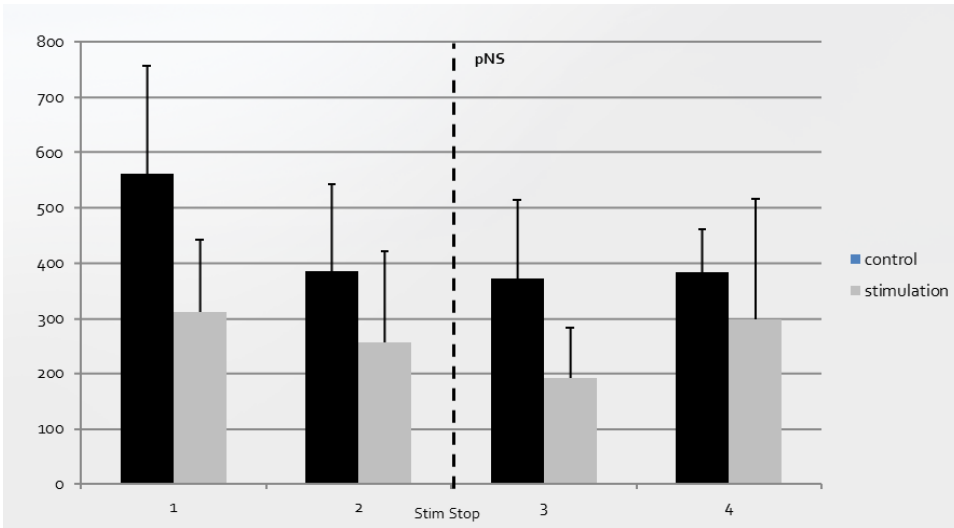


Figure 62 : Effect of DBS STN on number of interictal spikes in specimen 3
X axis: hours after injection
Y axis: number of spikes

6.3.8 Effect of preventive HFS STN

This effect was tested in one monkey during 10 experiments (5 control and 5 stimulation) in 454 seizures. Though there was an effect especially during the first hours during stimulation and last hours (5th and 6th hours) after stimulation on number and total time spent in seizures, it was not statistically significant.

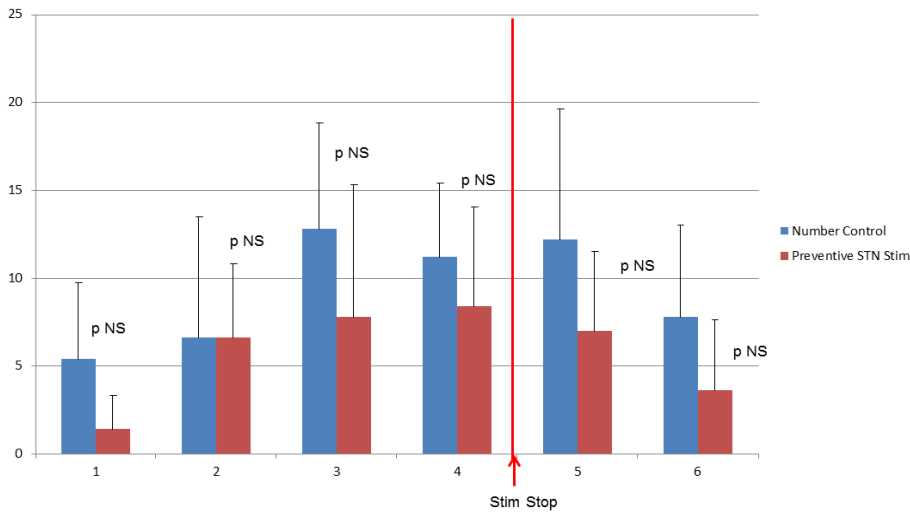


Figure 63 : Effect on number of seizures in preventive STN
Stimulation in one monkey (5 control experiments and 5 stimulation experiments).
X axis: hours after injection
Y axis: time in seconds

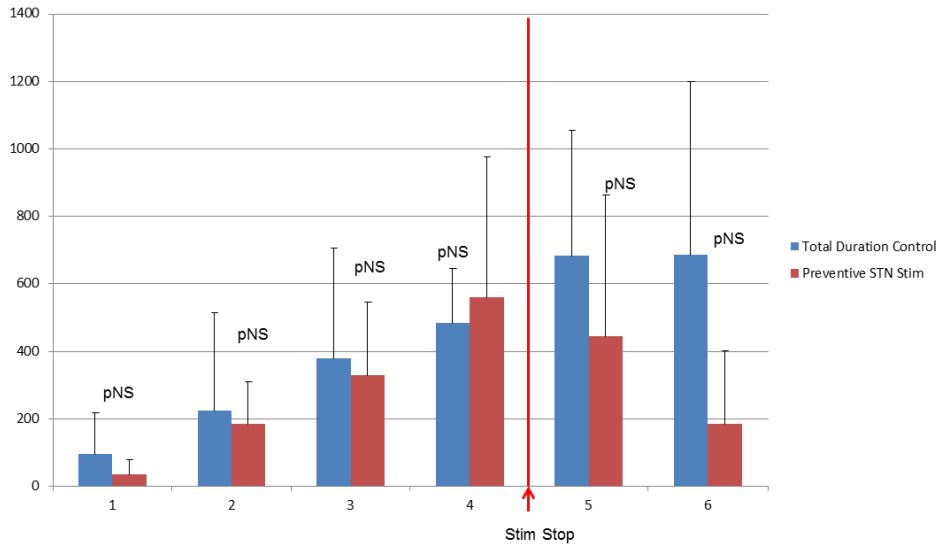


Figure 63 : Effect of preventive STN DBS on total duration of seizures
 Stimulation in one monkey (5 control experiments and 5 stimulation experiments).
 X axis: hours after injection
 Y axis: time in seconds

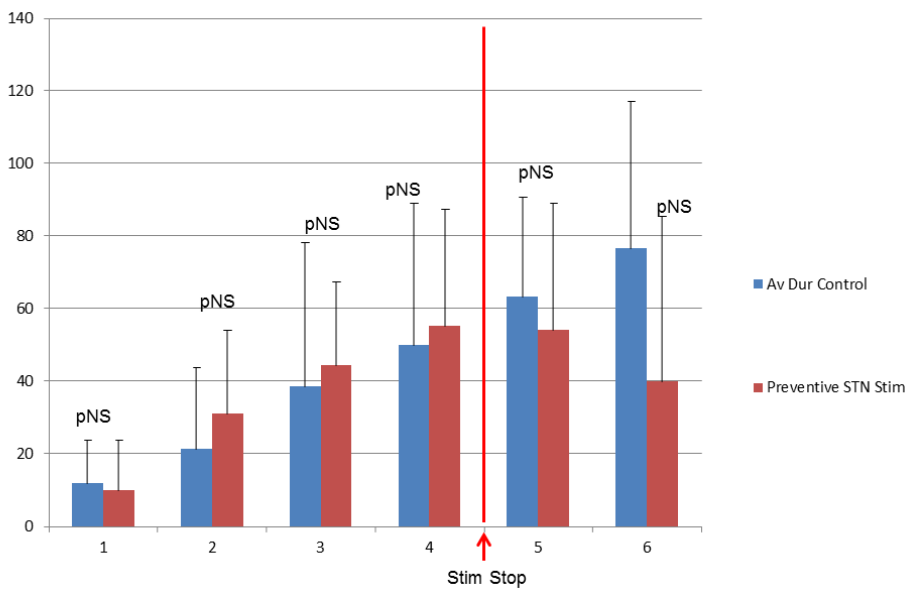


Figure 64: Effect of preventive STN DBS on average duration of seizures
 Stimulation in one monkey (5 control experiments and 5 stimulation experiments).
 X axis: hours after injection
 Y axis: time in seconds

6.4 RESULT OF PUTAMINAL STIMULATION

6.4.1 LOW FREQUENCY PUTAMEN STIMULATION

This effect was tested in two monkeys during 14 experiments (7 control and 7 stimulation) in 289 seizures. In specimen 4, the number of experiments were few (2 control, 2 stimulation) as the animal had to be sacrificed early due to its deteriorating health. Though there was an effect it was not statistically significant.

Table 38 : Summary of seizures in Putamen stimulation

ANIMAL	NUMBER OF EXPERIMENTS	NUMBER OF SEIZURES
1	Control 5	118
	Stimulation 5	109
4	Control 2	38
	Stimulation 2	24
Total	14	289

6.4.2 BEHAVIORAL EFFECT OF LFS PUTAMINAL STIMULATION

The threshold for stimulation was determined by progressively increasing the current (voltage) at two frequencies ie at 5Hz and 20 Hz and documenting the motor side effects. The frequent dystonia and facial muscle twitching indicated the threshold. All stimulation experiments were conducted with voltage set at 80 % below the threshold. Periodic assesment of threshold level was carried out in between experiments to check whether undesired effects like coagulation of the tissue or break in the integrity had occurred that would prevent effective current delivery to the target. During experiments a contralateral motor seizure with tonic and clonic components was noted. The interictal period was marked by brisk flexor contraction representing interictal spike but no other motor abnormalities. No other side effects like agitation, hyperactivity were noted indicating that the stimulation was well tolerated.

6.4.3 EFFECT OF LFS PUTAMEN DBS ON NUMBER OF SEIZURES

In the first specimen there was significant reduction in number of seizures during the first two hours of stimulation. Other specimen showed significant reduction only in second hour. Results are graphically represented below.

Specimen 1

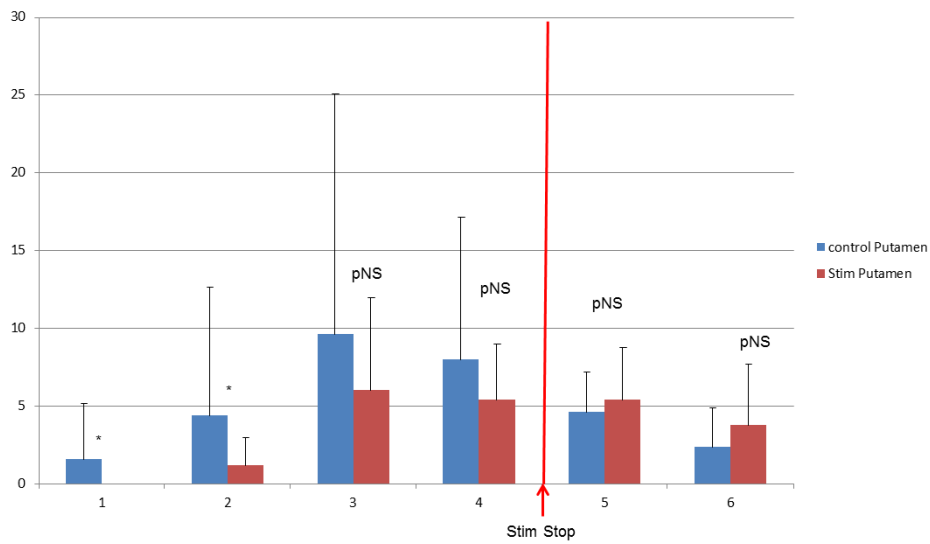


Figure 65: Effect on number of seizures LFS Putamen stimulation in specimen 1.
 (5 control experiments and 5 stimulation experiments).
 X axis: hours after injection
 Y axis: time in seconds

Specimen 4

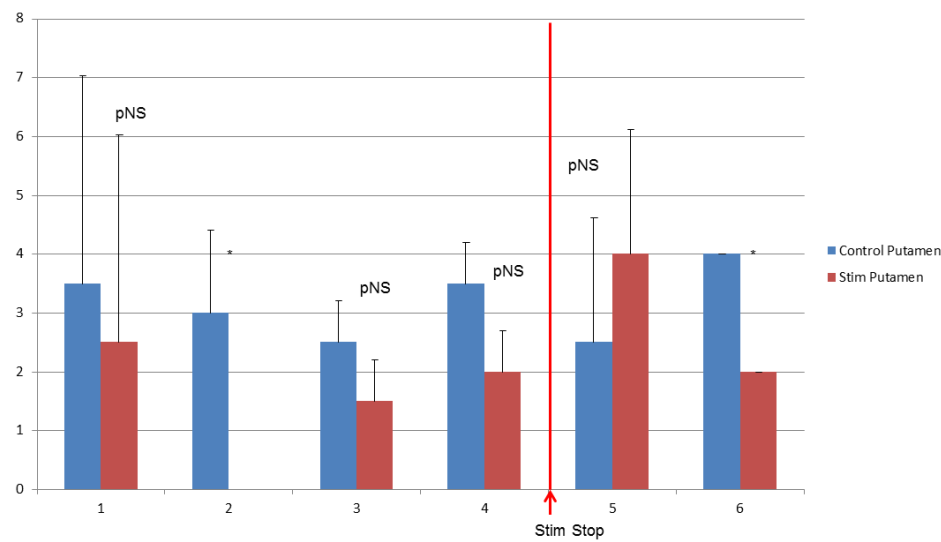


Figure 66: Effect on number of seizures LFS Putamen stimulation in specimen 4.
 (2 control experiments and 2 stimulation experiments).
 X axis: hours after injection
 Y axis: time in seconds

6.4.4 EFFECT OF LFS PUTAMEN DBS ON TOTAL DURATION OF SEIZURES

Following table summarizes the effect on total duration

Table 39: Reduction in total duration of seizures during Putamen stimulation.
(the number represents percentage)

Hours →	1	2	3	4	5	6
Specimen 1	100	88.94	53.37	12.53	11.40	▲ Almost 100% increase
Specimen 4	61.90	100	24.90	0	53.10	25

Specimen 1

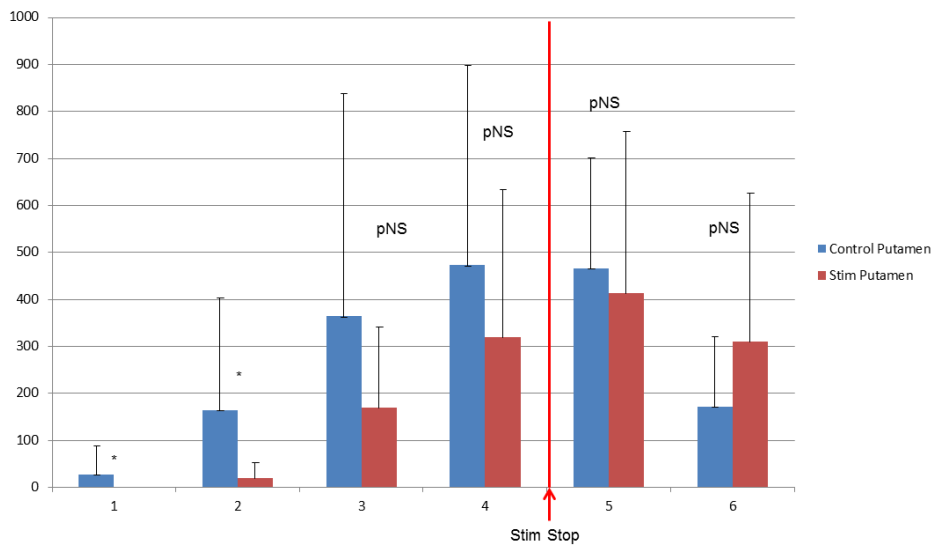


Figure 67: Effect on total duration of seizures LFS Putamen stimulation in specimen 1.
(5 control experiments and 5 stimulation experiments).
X axis: hours after injection
Y axis: time in seconds

Specimen 4

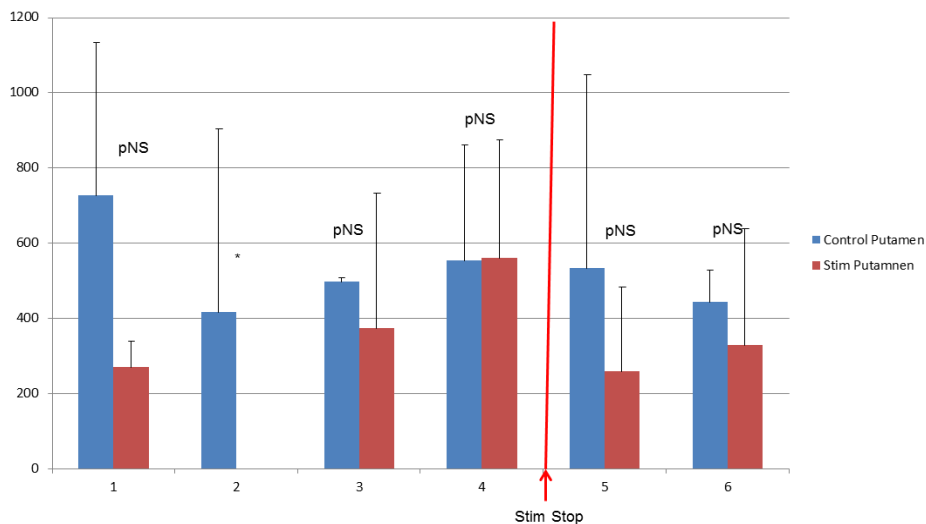


Figure 68: Effect on total duration of seizures LFS Putamen stimulation in specimen 4 (2 control experiments and 2 stimulation experiments).
X axis: hours after injection
Y axis: time in seconds

6.4.5 EFFECT OF LFS PUTAMEN DBS ON AVERAGE DURATION OF SEIZURES

The average duration was reduced in first two hours of stimulation in both specimens.

Specimen 1

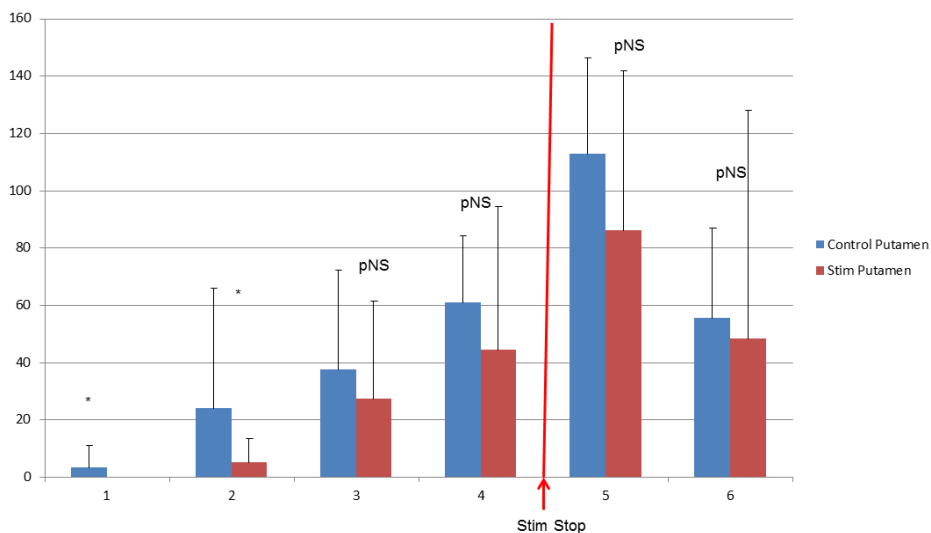


Figure 69: Effect on average duration of seizures LFS Putamen stimulation in specimen 1 (5 control experiments and 5 stimulation experiments).
X axis: hours after injection
Y axis: time in seconds

Specimen 4

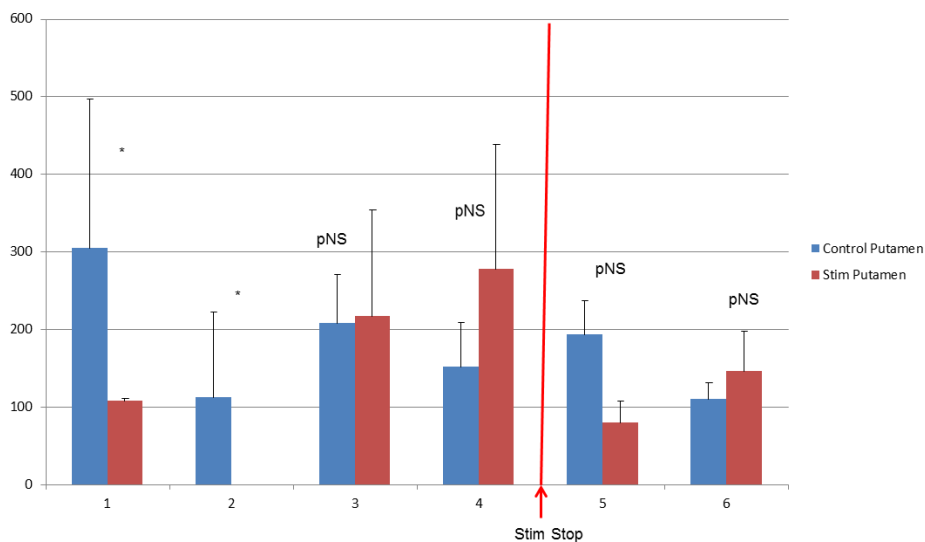


Figure 70: Effect on average duration of seizures LFS Putamen stimulation in specimen 4.
(2 control experiments and 2 stimulation experiments).
X axis: hours after injection
Y axis: time in seconds

6.5 RESULT OF HFS STN and LFS PUTAMEN STIMULATION

This effect was tested in one monkey during 10 experiments (5 controls and 5 stimulations) in 477 seizures analyzed. Results indicate that numbers of seizures seem to decrease significantly but the reduction in time spent in seizures seems to be more pronounced in the late hours of recording.

6.5.1 EFFECT OF STN AND PUTAMEN DBS ON NUMBER OF SEIZURES

A modest reduction of about 20 % was noted during first two hours of the stimulation. This effect was noted throughout the six hours of recording.

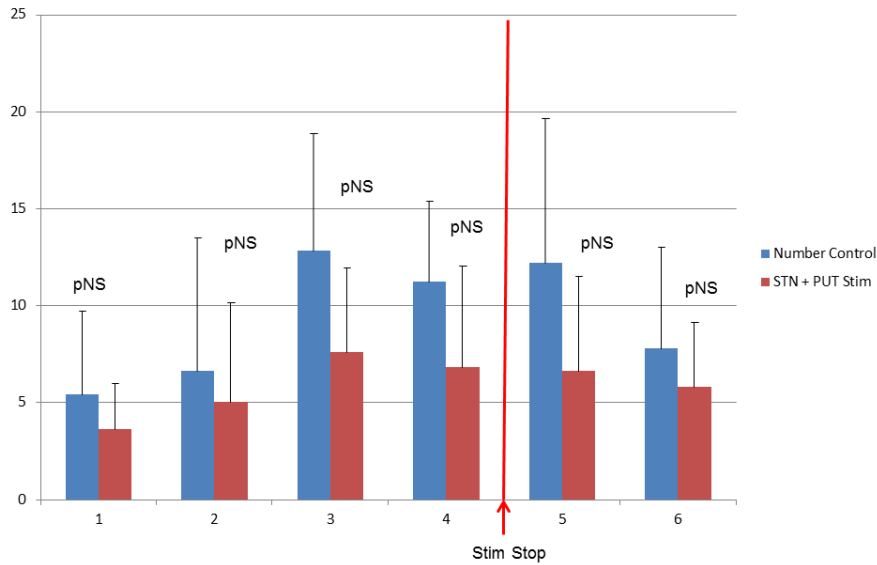


Figure 71 : Effect on number of seizures in simultaneous STN + Putamen stimulation

In one monkey (5 control experiments and 5 stimulation experiments)

X axis: hours after injection

Y axis: number of seizures

6.5.2 EFFECT OF STN AND PUTAMEN DBS ON TOTAL DURATION OF SEIZURES

A statistically insignificant reduction was noted throughout the six hours of recording. The effect was miniscule in second, third and fourth hour.

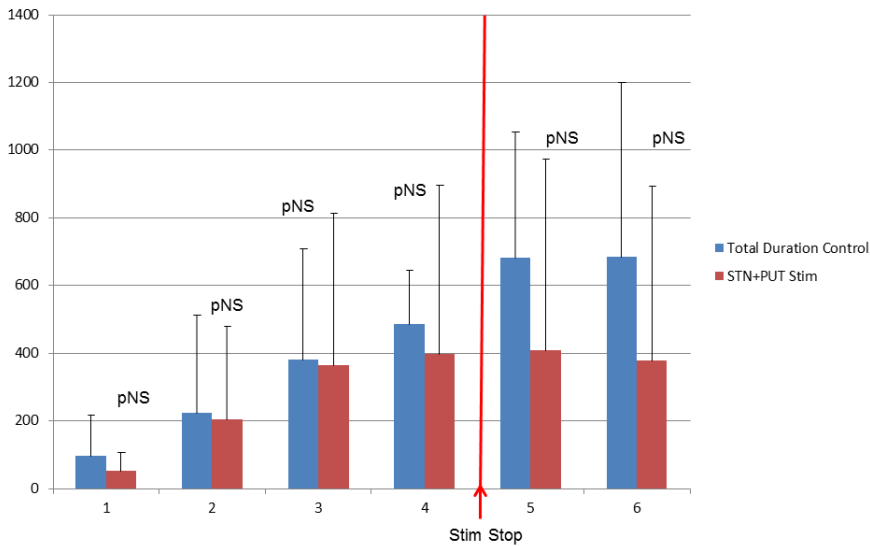


Figure 72 : Effect on total duration of seizures in simultaneous STN +Putamen stimulation

In one monkey (5 control experiments and 5 stimulation experiments)

X axis: hours after injection

Y axis: time in seconds

6.5.3 EFFECT OF STN AND PUTAMEN DBS ON AVERAGE DURATION OF SEIZURES

A statistically insignificant increase was noted during the 3 hours of stimulation. During the subsequent three hours there was a statistically insignificant reduction in the average duration of seizures.

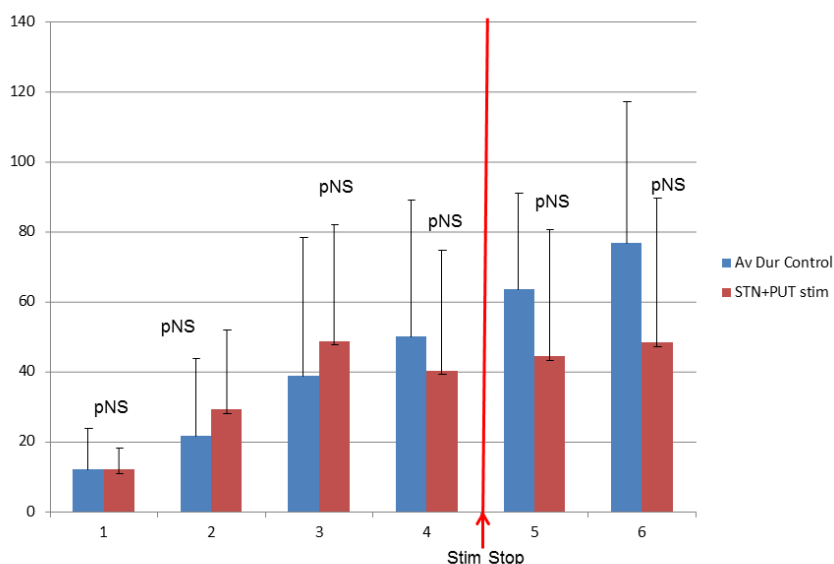


Figure 73 : Effect on average duration of seizures in simultaneous STN +Putamen stimulation
In one monkey (5 controls experiments and 5 stimulations experiments).
X axis: hours after injection
Y axis: time in seconds

6.6 Discussion

6.6.1 INTRODUCTION

Summary of results

We developed and characterized a stable reproducible model of focal motor seizures in primates and established its pharmac resistance. We then performed DBS in Subthalamic nucleus 3 specimens) Putamen (2 specimens) and combined HFS STN and LFS Putamen (1 specimen). The main findings were:

- Acute HFS STN was most effective in controlling number of seizures and the total time spent in seizures. Preventive HFS STN (in one specimen) was not found to be superior to acute stimulation.
- LFS Putamen alone was effective but mainly in first two hours of stimulation
- In a combined HFS STN and LFS Putamen stimulation tested in one monkey the effect of stimulation in terms of seizure control was modest and poor compared to HFS STN alone or LFS Putamen alone.

Thus we can conclude, within the constraints of the experiments conducted in our model that the best results in terms of seizure control were obtained by acute HFS STN DBS.

Though HFS DBS in STN is found effective for disorders like Parkinson's disease and is an already established clinical therapy for these movement disorders, the exact mechanism through which DBS produces results is open for debate. There are various explanations of the effect and DBS may act through one or several of the proposed mechanisms. We now explain our results in light of all these speculative mechanisms proposed for DBS. It is worth noting that the insight about these mechanisms was gained mainly from HFS DBS in animal experiments and Parkinson's patients. This is because HFS DBS in Parkinson's disease has a long history and newer indications for conditions like Epilepsy, OCD, depression are emerging just recently. Whether findings from Parkinson's disease could be extrapolated to epileptic disorders is a question. But we assume that though the clinical manifestations of the diseases are quite different, the HFS DBS of STN might operate through an identical way in both conditions. This assumption is strengthened by a study in which the results indicated that there is no statistically significant difference in the resting STN neuronal discharge rates or regularity in the discharge pattern between PD and epilepsy patients (Montgomery, 2008). In this study data was obtained from 9 PD patients with DBS electrodes implanted in STN and 4 patients of pharmaco-resistant epilepsy with implanted DBS electrodes in STN.

6.6.2 OUR RESULTS COMPARED TO PAST HUMAN CASE REPORTS

First we discuss our results in light of human case studies in the past About 20 patients have received HFS DBS of STN for intractable epilepsies so far (see chapter 3). This is a very small number to be used in comparison. Also the STN DBS surgery was undertaken in many cases after drug trials failed and patients were subjected to surgeries for control of epilepsy or had a VNS. For example, a report of 5 patients (Chabardes et al 2002) includes one patient with Rt premotor resection and one with VNS. Of 5 patients reported by Willi (Willi et al., 2011) one had received VNS. Both cases reported by Shon (Shon et al., 2005) had respective surgery and both cases reported by Capecchi (Capecchi, 2012) had anterior callosotomy. When the seizure control is considered the best responder (about 80% reduction in frequency) was noted in one case of cortical dysplasia in primary motor area reported by Benabid (Benabid et al., 2002). The best responders in Chabardes's series were patients who had epileptic abnormality originating in sensory motor area. The best responders in Willi's series of myoclonic patients (almost 100% benefit in myoclonic seizures) had an EEG with intermittent slow, spike and wave activity but no MRI abnormality. In Capecchi's report the patient who responded best (65% control over partial motor seizures and 100% control over generalized seizures) suffered from motor seizures. The patient who did not respond had absence seizures. In a case reported by Hammer (Hammer et al 2003) a bilateral STN stimulation in a refractory seizure patient did not produce satisfactory results. This patient had left fronto-central epilepsy due to cortical dysplasia in this region. He already had undergone multiple subpial resections of the face and motor area and focal cortical excision anterior to eloquent cortex. Also he had Vagus nerve stimulation. In contrast to this result a cortical dysplasia patient responded substantially (Benabid et al., 2002). This variation could be related to location of dysplasia and possible different networks involved in epilepsy. Other reported human case studies demonstrate good benefit in partial onset seizures (Handforth, 2006). Our results also match the results of STN HFS carried out in patients who already had undergone surgery for epilepsy or had Vagus nerve stimulation. Based on this data in limited

number of patients, HFS STN is found effective in patients with epileptic zone located in motor cortex or sensori motor cortex.

It seems that when comparing our results of the present study and those of the literature in humans, there a great convergence to think that seizures originating from the central region are the best candidates for STN-DBS. Of course, not all types of epilepsies were treated so far and we cannot come up with a final conclusion .But it is important to note that in a pilot study conducted at the University of Grenoble, patients treated by STN-DBS and who experienced atypical absences were not improved at all by STN-HFS (Chabardès et al., in preparation)

6.6.3 ACUTE STN STIMULATION

We now attempt to explain our results of HFS STN based on dynamic neuronal changes during motor seizure in the same model discussed in the introduction and the cortico - basal ganglia circuitry.

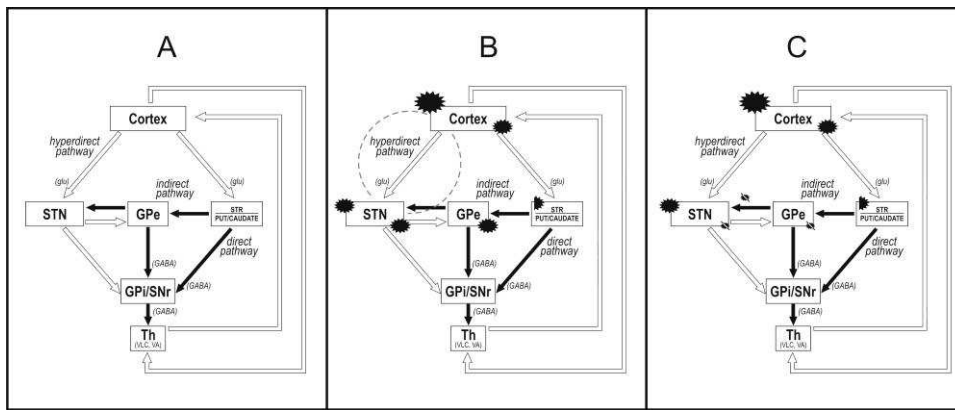


Figure 74 : The cortico basal ganglionic circuits implicated during focal motor seizures in primate (Modified from Nambu et al 2002)

The normal circuit. Filled black arrows show inhibitory pathway while hollow arrows indicate excitatory pathways.

Part B) Modification in focal motor seizures The STN and Gpi get display oscillatory synchrony with the Cortex during the seizure. The putamen comes into synchrony in the second half of a seizure.

Part C) Possible effect of HFS DBS of STN in controlling seizures. The reciprocating circuit between STN and Gpi might be influenced by the functional inhibition of STN during the HFS allowing a control over seizures.

STN subthalamic nucleus GPe Globus Pallidus externa GPi Globus Pallidus interna Th Thalamus STR Striatum PUT Putamen SNr Substantia Nigra glu Glutamate.

Oscillatory synchrony is indicated by



While disruption of this synchrony is indicated by



The STN occupies an important place in the basal Ganglia circuitry. From cortex it receives significant afferents. In turn it projects to both parts of the pallidum (GPe and GPi) Thus STN can be considered as a major input structure to basal ganglia along with Striatum. The cortico-STN-/pallidal pathway has been shown to exert powerful excitatory effects on the output nuclei of the basal ganglia, and is faster in signal conduction. Hence it is called hyperdirect pathway (Nambu et al., 2002). Striatum, the other input structure also is connected to output

of Basal ganglia through a 'direct' inhibitory connection to GPi and SNr and an indirect inhibitory path going through the GPe.

This is the normal stationary model of basal ganglia functioning. The STN is excitatory to GPe while GPe sends inhibitory connections to STN. This could be possible seizure sustaining pathway. Motor seizures induced by intracortical injection of Penicillin modify STN intrinsic properties due to powerful hyperdirect pathway. This in turn leads to changes in the STN - GPe reciprocal circuit.

In fact the MER studies performed on basal ganglia structures during focal motor seizures in primate earlier in the lab (Devergnas et al., 2012) indicate the presence of such mechanism. In this study it was found that 71% of STN neurons and 77% of GPe neurons show oscillatory synchrony with the cortical ictal spikes seen on EEG. This synchrony is evident from the beginning till the end of a focal motor seizure. Putamen shows a tendency to synchronize towards the second half of total duration of a seizure.

The local functional inhibition in the STN during HFS DBS might reduce the excitatory influence over GPe and disrupt the pathological oscillatory synchrony during the motor seizures in our model. Similarly the activation or inhibition of the downstream pathways may modulate influence of output structures over thalamic nuclei and restore disturbed thalamocortical network. The influence of HFS STN on cortical activity could be mediated by two pathways:

Orthodromic activation

It can be postulated that the reciprocal circuit between STN and GPe sustains seizures induced in the motor cortex. HFS DBS interferes with this circuit and controls the seizure.

The pallidothalamic pathway may influence intrinsic properties of thalamic nuclei during HFS STN stimulation. It is proposed that during low frequency stimulation of STN the ventral and intra laminar nuclei of the thalamus hyperpolarize producing rebound bursts in thalamo cortical relay (MacKinnon et al., 2005). This in turn activates the cortical neurons. HFS DBS of STN may act in opposite way and control the rebound bursts. This would result in net suppression of activity of cortical neurons.

It has been documented that the stimulation also activates axons in a radial fashion beyond the actual electrodes (Mcintyre, 2004). Zona Inserta (ZI) which is in close relation to STN might get stimulated during HFS STN. Zona Inserta is an important structure in the sensory motor integration with connectivity to frontal cortex, cingulate cortex, brain stem and thalamus. The GABAergic output from ZI to Ventral anterior nucleus of thalamus (Barth et al., 2002) might inhibit the thalamocortical neurons affecting the cortical activation.

The tracts in vicinity of STN are also likely to be activated during the stimulation. Medial fibers of the internal capsule, Forel field containing many fibers from brain stem to Striatum are two such systems likely to get modulated during the HFS DBS.

Antidromic conduction

In a recent study on MPTP primates (Devergnas and Wichmann, 2011) it was found that 10 Hz stimulation of STN produced short latency evoked potential in the motor cortex noted on EEG. This indicates an antidromic activation pathway that could be involved in the HFS DBS too.

Just as the presence of a monosynaptic pathway between cortex and STN is implicated in changes in neuronal activity of STN during focal motor seizures; a reverse pathway between STN and Cortex might be presumed to be involved in effects of HFS STN. However the presence of such a pathway has been demonstrated in rats (Degos et al., 2008) and not in primates.

Disruption of oscillatory synchrony and cortical excitability

As discussed earlier in our model an oscillatory synchrony was evident between cortex and STN during the focal motor seizures. We postulated that HFS DBS of STN may interrupt this synchrony and control seizures. Indirect evidence indicating this mechanism (though in Parkinson's patient) was found in a study by Whitmer (Whitmer et al., 2012). He found a spatially- specific suppression of beta synchrony in the motor cortex during STN HFS DBS supporting the hypothesis that DBS may treat Parkinsonism by reducing excessive synchrony in the functionally connected sensorimotor network.

A TMS study in Parkinson's patient with HFS DBS showed that cortical silent period increased during HFS DBS of STN. This indicated a possibility of modification of functions of cortical interneurons during STN stimulation and restoring of balance between excitability and inhibition (Fraix et al., 2008). Similar findings were also found by Dauper (Dauper et al., 2002).

Metabolic imaging and effect of HFS DBS of STN

The cortical excitability could be decreased by the HFS STN. PET, SPECT and fMRI are neuroimaging techniques that can indirectly inform about neuronal activity by recording alterations in associated factors such as blood flow, blood oxygenation and glucose consumption. However fMRI studies are rare in patients with implanted depth electrodes due to concern with the magnetic effect on electrodes, stimulator and potential tissue damage. We review here few PET studies in Parkinson's patients with HFS DBS of STN.

In a report involving 12 Parkinson's patients, a H₂O PET study showed that effective STN stimulation significantly deactivated sensorimotor and lateral premotor cortex ipsilateral to stimulation compared with ineffective STN stimulation (Limousin et al 1997). Another PET study in 12 patients found that STN stimulation reduced blood flow bilaterally in frontal, parietal, and temporal cortex (Hershey et al., 2003). Payoux et al found in a H₂O PET study that the main effect of high-frequency stimulation of left STN was to reduce regional cerebral blood flow in the left primary sensorimotor cortex and concluded that abnormal over activity of cortex is reduced during HFS DBS of STN in Parkinson's patient (Payoux et al., 2004).

Anasuma et al (Anasuma et al., 2006) studied PET in 9 patients of Parkinson's during HFS STN. A significant metabolic reduction in the putamen, globus pallidus, sensorimotor cortex and cerebellar vermis was found. In a study involving 48 PD patients bilateral STN DBS showed increased regional cerebral blood flow (rCBF) in the bilateral thalami, right midbrain, and decreased rCBF in the right premotor cortex, suggesting a network modulatory effect of STN stimulation (Karimi et al., 2008).

Other studies in recent years also have supported the findings above. In a study by Cilio et al (Cilio et al 2009) SPECT scan were obtained in 40 Parkinson's patients with STN DBS on and off and compared. These were also compared with 20 matched PD patients who had no DBS. rCBF decrements were found in motor cortical areas and prefrontal cortex bilaterally during stimulation. They concluded that effective STN DBS (one that produces clinical benefit) might be associated with stimulation-induced normalization of the abnormal over activity within the cortico-basal ganglia-thalamo-cortical motor loop in advanced PD.

A study by Geday et al indicated that HFS STN leads to subsequent deactivation of the thalamic anteroventral and ventrolateral nuclei and the supplementary motor area. (Geday et al 2009) supporting the hypothesis that STN stimulation would influence thalamo cortical system, a major component also implicated in seizure propagation.

Wang and his colleagues (Wang et al., 2010) studied FDG PET in 5 Parkinson's patients undergoing STN DBS in on and off condition. They found that HFS DBS decreased glucose metabolism in the right lentiform nucleus, cerebellum, the bilateral ventral thalamus and precuneus. The thalamic decreased metabolism might reflect a decreased thalamic activity, which ultimately influences the thalamo-cortical relay implicated in seizures. The spatial covariance pattern comparison between on and off stimulation condition led to a conclusion that there is likelihood of suppression of hyperactive motor circuitry following STN stimulation in these patients. The same mechanism might be operative in epileptic condition.

A combined SPECT + PET study in Parkinson's revealed significantly decreased glucose metabolism of the two superior frontal gyri without any attendant perfusion changes following STN DBS (Haegelen et al., 2010). Similarly another FDG PET study in 10 patients undergoing STN DBS in obsessive compulsive disorder found decreased metabolism in prefrontal cortex during stimulation (Le Jeune et al., 2010). These evidences of decreased cortical metabolism in HFS DBS of STN could be extrapolated to epilepsy and sustain our hypothesis that seizure control in our model during HFS STN could be due to decreased cortical metabolism and modulation of basal ganglionic- thalamo- cortical network.

Information processing in Computational models

The information processing models of various basal ganglia disorder indicate misinformation conduction (pathological oscillations) in the various parts of circuits as the basis of diseases. HFS is postulated to correct this situation. In a computational model of Gpi and thalamic activity during HFS DBS of Parkinson's monkeys it was shown that the thalamo cortical relay fidelity improves during STN stimulation restoring the 'normal' information process (Guo et al., 2008). The same mechanism could be hypothesized to work for epileptic hypersynchronization. In another computational model of M1 motor cortex excitability in normal and Parkinsonian monkeys the results suggested that therapeutic HFS DBS would restore the information processing capacity of the cortex by masking the misinformation coming from the BG-thalamic loop with more regular patterns (Santaniello et al., 2012).

Other animal models; the nigral control of epilepsy

The role of substantia nigra in control of seizures has been demonstrated earlier in rats. Gale and Iadorla in the 1980s showed that increase in GABA by inhibiting GABA transaminase in SNr augments anti convulsant effect (Iadorla and Gale, 1982)

Thus the nigral control of seizures was postulated (Depaulis, 1994). The SNr is involved in the control of seizures by its GABAergic output that inhibits the Dorsal Midbrain Anti Epileptic Zone (DMAZ). The DMAZ is formed by deep and intermediate layers of the superior colliculi, the intercollicular nucleus and the midbrain reticular formation. Blockage of GABA receptors in SNr disinhibits the DMAZ and consequently triggers a strong anticonvulsant effect in case of focal, tonic-clonic and absence seizure in rats (Redgrave, 1992). In GAERS, an animal model of absence epilepsy, (Deransart, 1996) beneficial effects of SN stimulation are also documented.

However in our focal motor seizure model induced by intracortical penicillin injection no modification of SNr neuronal activity during seizures was noted (Devergnas et al., 2012). Still it can be argued that output structures like SNr might be affected by HFS STN stimulation. Hence it can be conceptualized that HFS DBS of STN may influence the output structures and control focal motor seizures.

This is proposed based on secondary evidences of role of superior colliculus in movement disorders. Dystonic postures are often noted in temporal epilepsy and partial complex seizures. In fact dystonic events during temporal seizures can be considered as an expression of endogenous anti convulsant mechanism. In one such study occurrence of bilateral tonic or clonic behaviors and dystonia were negatively correlated (Cleto Dal-Cól et al., 2008).

In a primate model infusion of GABA agonist muscimol produced cervical dystonia. Infusion of muscimol in superior colliculus of these primates (the equivalent of DMAZ in rats) inhibited the structure and prevented cervical dystonia (Holmes et al., 2012). As an argument a disinhibition of superior colliculus would increase occurrence of dystonia during seizure, considered a marker of anticonvulsant action. This is similar to role of DMAZ proposed in rats. Thus proposed disinhibition of superior colliculus by SNr as a seizure controlling mechanism might be possible in primates too.

Mechanism of DBS and our model

Putative mechanisms of DBS are many. DBS is likely to either inhibit or stimulate activity in the target brain structure (Beurrier et al., 2001) The conventional view based on Parkinsonian models about HFS STN was that it acts like a functional lesion and inhibits the structure (Benabid et al., 2001). In Parkinson's patients, HFS DBS is found to inhibit local neuronal activity (Filali et al., 2004, Dostrovsky et al., 2000). But the different neural elements in the STN could be differentially activated. Somatic firing is known to get suppressed throughout the STN, whereas the myelinated axons of projection neurons will be activated. Animal studies inform us that mechanism of HFS DBS is not a simple effect. It may inhibit (Ma, 2007) or activate (Xu et al., 2008; Moran et al., 2012) the output structures of basal ganglia. The notion that during HFS STN output to the basal ganglia output nuclei may be increased is supported by different studies using microdialysis (Windels et al., 2005) imaging studies

like fMRI and PET, (Stefurak et al., 2003; Perlmutter et al., 2002; Hershey et al., 2003). If we assume that HFS DBS of STN activates Snr and GPi then increased inhibition of thalamus by Gabaergic output from GPi and SNr can be conceptualized to influence thalamus and thalamo cortical relay and influence seizures.

6.6.4 Preventive STN stimulation, chronic and responsive stimulation

In one monkey 174 seizures from 5 experiments of preventive stimulations were compared with 291 seizures obtained in 5 control experiments. Though the number of seizures and total duration of time spent in seizures was affected especially in the first hour and last hour of recording the difference was not statistically significant.

We tested the STN stimulation for control of focal motor seizures in a continuous, chronic mode. The other stimulation strategy currently attracting attention is acute responsive stimulation. Some consider responsive stimulation as a better for DBS in epilepsy. It appears as more physiological since epileptic seizures are episodic in nature, it also improves stimulator life. In our model there were characteristic changes in neuronal activity in STN during focal motor seizures (Devergnas et al 2012), so responsive stimulation by a specific electrode designed to sense these changes in STN and simultaneously deliver stimulation could be a possibility. However we choose the chronic mode considering that the long term neuromodulatory effects of chronic HFS STN stimulation, as noted in Parkinson's patients and neuropsychiatric patients could also contribute to seizure control. The observation that after withdrawing stimulation after 4 hours (specimen 1, 2) and after 2 hours (specimen 3) there was no increase either in the number of seizures or total duration of seizures in subsequent hours of recording and the beneficial effect of control over seizures persisted points out to possible superiority of chronic stimulation over responsive mode. It is also interesting to mention other study of cortical stimulation using the same primate model used here. In this study of focal motor seizures induced by Penicillin acute stimulation of the epileptic cortical focus failed to achieve control over seizures. A responsive stimulation of epileptic cortex, based on automatic seizure detection also failed in achieving seizure control (Blauwblomme et al 2011). Perhaps as mentioned above seizure generation in our model involves a powerful monosynaptic Cortico – STN pathway and seizure sustaining occurs through a STN GPe network. Both combined together might be too powerful mechanisms to be controlled by an acute responsive stimulation.

6.6.5 Putaminal Stimulation

As described at the beginning of the chapter in our model, the putamen showed phase decoupling with the cortex especially at the end of motor seizure. Hence the possible beneficial effect of Putaminal activation by low frequency stimulation was tested. During stimulation a trend towards decrease in number of seizures, and total duration of seizures was noted. The number of seizures seems to increase after the stimulation was stopped after fourth hour. The effect however seems statistically insignificant possibly due to large amount of variation (as reflected in standard deviation) in values of number of seizures and total duration of seizures during the control experiments (see Figure 66 to 71).

Commentaire [G2]:

The role of dopaminergic system in epilepsy has been previously postulated. The anticonvulsant action of dopamine was attributed to D2 receptor stimulation in the forebrain,

while D1 receptors were implicated in proconvulsant action as discovered by the proconvulsant properties of the selective D1 agonist drugs (Starr, 1996). Altered D2, D3 receptor binding in putamen of the patients of juvenile myoclonic epilepsy (Landvogt et al 2010) and patients of temporal lobe epilepsy (Werhahn et al., 2006) has been documented. Hence putaminal participation in modulating seizures especially motor seizures seems plausible. Despite the correct placement of stimulating electrodes in the motor part of the putamen, the results seem statistically disappointing. Putamen has different types of neurons (ref chapter 4) and it is possible that the effects depend upon the types of neurons being stimulated. In our model putamen came into synchrony with the cortex only in the second half of the total duration of motor seizures. Perhaps the effect might be weaker than the effect of STN HFS stimulation because of the powerful monosynaptic excitatory connection between cortex and STN that is implicated during the motor seizures in our model. Similarly the trend of rising number of seizures in the fifth hour and total duration of seizures in the sixth hour (after withdrawing stimulation in the fourth hour) of recording may be attributed to different properties ie D1 receptors with anticonvulsant action and D2 /D3 with pro convulsant action.

6.6.6 Combined stimulation

There was a trend of decrease in number and total duration of seizures during combined high frequency STN and low frequency Putamen stimulation however the difference is not statistically significant. One of the possible explanations is that the effect was studied in one monkey during few experiments (5 control and 5 stimulation experiments).

6.6.7 Effect on interictal spikes

There seems to be a contrasting trend when the number of interictal spikes is compared between control experiments and stimulation experiments. It seems that apparently the number of spikes increased (though not statistically significant) during STN stimulation in two monkeys and apparently decreased during stimulation in third monkey.

It was noted that in our model the number of interictal spikes are maximum during first hour and then though declined, remain steady for next few hours. The interictal spikes with a contralateral myoclonic jerk were still observed after the recordings ended at sixth hour.

The interictal spikes had a reciprocal relationship with the number and total duration of seizures. That is the number of interictal spikes was less when total duration of seizures in a particular time was prolonged and vice a versa. This could be the reason behind apparent increase in their number during stimulation experiments as the total duration of seizure got decreased in stimulation experiments. The interictal spikes represent the activity in the epileptic zone (the cortical area of penicillin injection in our model) and it seems logical that DBS in the basal ganglia modifies the 'expression' of the disease process (that is seizure duration,number of seizures etc...) and does not influence 'pathology' behind it .

6. 7 LIMITATIONS OF STUDY

6.7.1 IS REDUCING SEIZURE NUMBER ENOUGH?

Our results indicate that acute HFS STN controls seizures by reducing the numbers of seizures during stimulation .We know that controlling seizures is not controlling epilepsy. Still seizures are the obvious manifestations of epileptic process .Especially motor seizures can have potential of producing falls, accidents. In a clinical setting, frequent motor seizures also mean a restricted motor activity, loss of independence in some cases and need for supervision and monitoring by care takers for a patient .This may reflect negatively on quality of life (see chapter 1). So a good control, around 70% reported in our model is a promising option. There might be other long term cortical modulatory effects of chronic HFS DBS of STN which might become evident after months and years; that might improve seizure control. A study designed with these aims might be interesting.

6.7.2 UNILATERAL STIMULATION

Our model used a unilateral HFS STN to study seizure control .It seems rational because the epileptic zone was in unilateral primary motor cortex specific to location of canula for penicillin injection. We also noted strictly contralateral focal tonic clonic activity during seizures (see chapter 5). Bilateral implantation though possible is difficult in primates as it requires two large stimulators to be embedded in the back of the primate. All these considerations led to unilateral HFS DBS study in our model.

However in clinical settings when HFS DBS of STN is used generally bilateral stimulations are performed for its presumed overall larger modulatory effect over neuronal networks.Bilateral HFS STN is also found to be more effective than unilateral stimulation (Bastian et al., 2003, Ferrarin et al., 2007). We maintain that bilateral HFS STN is possible for motor epilepsy in human patients as bilateral implantations are standardized, routinely performed and have excellent safety profile .Curiously even unilateral stimulation is found to have bilateral effects. In a study of 37 Parkinson's patients with unilateral STN DBS, an improvement was found in the ipsilateral UPDRS subscores ($P < 0.001$, 54.6% at 1 year) too (Walker et al., 2009).

Commentaire [sC3]: You mean ipsilateral?

6.7.3 PRECISION OF IMPLANTATION

The exact location of the DBS electrodes within the STN after implantation would have provided a better clue to which region of STN was stimulated during the stimulation. However a post operative MRI was not possible due to presence of metallic screws on the scalp. But we believe that final placement of electrodes was indeed in the STN as indicated by composite study of pre op MRI, intra op ventriculography, final radiogram after completion of surgery showing the placement in AP and Lat direction and the post mortem MRI of head obtained after removal of the metal implants that showed the site of intracerebral electrodes.

In our study the preventive HFS STN stimulation was found to confer no additional benefit over acute continuous STN stimulation. However this study was conducted in one monkey and effect tested in few experiments as opposed to acute HFS STN which was studied in 3 experimental animals. A differently designed protocol of duration of preventive stimulation of STN might also be useful.

6.8 CONCLUSION AND GLOBAL PERSPECTIVES

Application to human disease condition

Summarizing the key findings in experiments, it can be stated that HFS STN is quite useful in controlling focal motor seizures in a primate model. The putaminal stimulation seems less effective, combined stimulation of STN and Putamen, and preventive STN stimulation might require more experiments and alternative stimulation protocol to arrive at a definitive conclusion.

The model used in this condition shares closely the clinical characteristics of Kojenikov's syndrome. Though it does not reproduce the pathophysiology of epilepsy implicated in human disease. As the seizures in this model reflect ictal semiology, the HFS DBS of STN might be useful in seizures arising due to cortical dysplasia, Rasmussen's encephalitis, and possibly those seen in refractory myoclonic epilepsy as well as seizures of frontal cortical origin. STN HFS DBS would be possibly beneficial when other surgical or stimulation strategies have failed. In conditions like Dravet's syndrome or autosomal dominant frontal lobe epilepsy the STN stimulation alone might not achieve optimum control over seizures (Chabardes et al., 2002) possibly due to the fact that, progressive nature of disorder and complex pathways of seizure progression might be present in these conditions.

STN is an important 'node' in many circuits. It has a motor component, as well as limbic and associative components. Information processing in basal ganglia is now considered not restricted to strictly segregated loops (see chapter 4). Thus we hypothesize that HFS DBS of STN with modification of target location in specific part of STN might be beneficial in seizures arising from other cortical areas besides motor cortex. It might have a potential in other epileptic disorders like limbic epilepsy. This of course is a hypothesis.

ANNEXES I

CLASSIFICATION OF SEIZURES AND EPILEPSIES

Introduction:

First systematic attempt to classify the seizures began in 1960 and the ILAE (International league against Epilepsy) published a comprehensive classification for seizures in 1981 and for epilepsies in 1989. Some attempts have been made to incorporate information gained from developments in modern neuroimaging, genomic technologies and concepts in molecular biology in classification. This might reflect more accurately the epilepsy type in its basic pathology as well as clinical aspects, but the official classification of the 1980s is still valid and no new system with universal consensus has been proposed yet.

The ILAE classification of seizures

The international League against Epilepsy has classified seizures in different categories:

I. Partial (focal, local) seizure

A) Simple partial seizure (consciousness not impaired)

1. With motor symptoms
2. With somatosensory or special sensory symptoms
3. With autonomic symptoms
4. With psychic symptoms

B) Complex partial seizure (with impairment of consciousness)

1. Beginning as simple partial sz & progressing to impairment of consciousness
 - a. With no other features
 - b. With features as in A 1-4
 - c. With automatisms
2. With impairment of consciousness at onset
 - a. With no other features
 - b. With features as in A 1-4
 - c. With automatisms

C) Partial seizure evolving to secondarily generalized

II. Generalized seizure

A) Absence seizures

1. Typical absence seizures
2. Atypical absence seizures

B) Myoclonic seizures

C) Clonic seizures

D) Tonic seizures

E) Tonic-clonic seizures

F) Atonic (astatic) seizures

III. Unclassified

A) Inadequate data

B) Neonatal seizure

Rhythmic eye movements
Chewing movements
Swimming movements

C) Special epileptic syndromes

Myoclonus and myoclonic seizure
Reflex epilepsy
Landau-Kleffner syndrome
Febrile seizures
Hysterical seizures

ILAE classification of epilepsy syndromes (Engel, 2006a)

1- Self-limited seizure types	<i>Generalized seizures</i>	Tonic-clonic seizures (includes variations beginning with a clonic or myoclonic phase) Clonic seizures Without tonic features With tonic features Typical absence seizures Atypical absence seizures Myoclonic absence seizures Tonic seizures Spasms Myoclonic seizures Eyelid myoclonia Without absences With absences Myoclonic atonic seizures Negative myoclonus Atonic seizures
	<i>Focal seizures</i>	Focal sensory seizures With elementary sensory symptoms (e.g., occipital and parietal lobe seizures) With experiential sensory symptoms (e.g., temporo parieto occipital junction seizures) Focal motor seizures With elementary clonic motor signs With asymmetrical tonic motor seizures (e.g., supplementary motor seizures)
	<i>Gelastic seizures Hemiclonic seizures Secondarily generalized seizures</i>	With typical (temporal lobe) automatisms (e.g., mesial temporal lobe seizures) With hyperkinetic automatisms With focal negative myoclonus With inhibitory motor seizures
2 Continuous seizure types	<i>Generalized status epilepticus</i>	Generalized tonic-clonic status epilepticus Clonic status epilepticus Absence status epilepticus Tonic status epilepticus Myoclonic status epilepticus
	<i>Focal status epilepticus</i>	Aura continua Limbic status epilepticus (psychomotor status) Hemiconvulsive status
3 Reflex seizures	<i>Precipitating stimuli for reflex seizures</i>	Visual stimuli Flickering light: color to be specified when possible Patterns Other visual stimuli Thinking Music Eating Praxis Somatosensory Proprioceptive Reading Hot water Startle

Modifications to this classification system have been suggested but no new system is proposed to replace the former widely accepted and widely used classification system (Engel, 2006b)

Multitier classification of epilepsy

There is a subtle difference between ‘epileptic seizures ‘and ‘Epileptic Syndrome ‘. The epileptic seizure is the paroxysmal ictal event with characteristic EEG changes .While the Epileptic syndrome includes specific signs and symptoms (various seizures) a certain pattern in age of onset, evolution and seizure frequency along with certain neurodeficits and prediction about prognosis.

In order to have a complete understanding of a patient clinical picture a rather extensive description of his epilepsy is necessary. Luders has proposed a five tier system of classification which cover both epilepsy and epileptic seizures (Luders, 2008).

Tier 1: Epilepsy

This tier describes the location of epileptogenic zone. This zone is defined by diagnostic tests like interictal and ictal EEG, and imaging like MRI PET SPECT, or more invasive EEG studies with subdural grids or depth electrodes etc...).

The following subdivisions can be defined:

1. Focal: epileptogenic zone
 - a- Frontal
 - b- Periorolandic
 - c- Temporal
 - i. Neocortical temporal
 - ii. Mesial temporal
 - d- Parietal
 - e- Occipital
 - f- Other
2. Multilobar:
 - a- Bilobar homotopic
 - b- Other
3. Generalized

Tier 2 : Semiological seizure classification

This tier explains the clinical overt expression of the epilepsy, usually in the form of a seizure or abrupt change in the physiology

1. Auras
 - a- Somatosensory auras
 - b- Visual auras

- c- Auditory auras
- d- Gustatory auras
- e- Olfactory auras
- f- Autonomic auras
- g- Abdominal auras
- h- Psychic aura

2. Autonomic seizures

These refer to objectively documented autonomic changes during seizures

3. Dialeptic seizures

Dialeptic seizures refer to change in the consciousness level during seizure

4. Motor seizures

- a- Simple Motor Seizures
 - i. Myoclonic Seizures
 - ii. Clonic Seizures
 - iii. Tonic Seizures
 - iv. Versive Seizures
 - v. Tonic-Clonic Seizures
 - vi. Epileptic Spasms
- b- Complex Motor Seizures
 - i. Automotor Seizures
 - ii. Hypermotor Seizures
 - iii. Gelastic Seizures

5. Special Seizures

- a- Atonic seizures
- b- Akinetic seizures
- c- Astatic seizures
- d- Negative myoclonic seizures
- e- Hypomotor seizures
- f- Aphasic seizures

Tier 3 : Etiology

Etiology can play a direct role in some epilepsy (for example epilepsy and a cerebral tumor)
Tier 3 provides etiological description platform.

1. Hippocampal sclerosis
2. Tumor
 - a- Glioma
 - b- Dysembrioplastic neuroepithelial tumor
 - c- Ganglioglioma
 - d- Other
3. Malformations of cortical development (MCD)
 - a- Focal MCD
 - b- Hemimegalencephaly
 - c- MCD with epidermal nevi
 - d- Heterotopic grey matter
 - e- Hypothalamic hamartoma
 - f- Hypomelanosis of Ito
 - g- Other
4. Malformations of vascular development
 - a- Cavernous angioma
 - b- Arteriovenous malformation
 - c- Sturge_Weber syndrome
 - d- Other
5. Central nervous system infections
 - a- Meningitis
 - b- Encephalitis
 - c- Abscess
 - d- Other
6. Central nervous system inflammation
 - a- Rasmussen encephalitis
 - b- Vasculitis
 - c- Other
7. Hypoxic ischemic brain injury
 - a- Focal ischemic infarction
 - b- Diffuse hypoxic-ischemic injury
 - c- Periventricular leukomalacia
 - d- Hemorrhagic infarction
 - e- Venous sinus thrombosis
 - f- Other

8. Head trauma
 - a- Head trauma with intracranial hemorrhage
 - b- Penetrating head injury
 - c- Closed head injury
 - d- Other

9. Inheritable conditions
 - a- Presumed genetic cause
 - b- Tuberous sclerosis
 - c- Progressive myoclonic epilepsy
 - d- Metabolic syndrome
 - e- Channelopathy
 - f- Mitochondrial disorder
 - g- Chromosomal aberration
 - h- Other

10. Structural, brain abnormality of unknown cause

11. Other

12. Unknown etiology

Tier 4 : Seizure frequency

The major goal of therapy for epilepsy is to reduce frequency and severity of seizure. Tier 4 classifies seizure based on frequency

1. Daily seizures
Seizure every day
2. Persistent seizures
At least one seizure per month
2. Rare or no seizures
Fewer than one seizure every six months
3. Undefined
Seizure frequency cannot be defined.

Tier 5 : Related medical condition

Additional information about existing medical condition is put in this tier.

ANNEXES II

PUBLICATIONS

List of Publication 2009-2012

Book Chapter:

Surgery for temporal lobe epilepsy: pros, cons and comparison between different procedures

Stephan Chabardès, Shivadatta Prabhu, Taner Tanriverdi in Mesial Temporal Lobe Epilepsies (Ed. Hans Luders, Rosenov) p 245-262, 2011 John Libby Eurotext

Papers:

The subcortical hidden side of focal motor seizures: evidence from micro-recordings and local field potentials

Annaelle Devergnas,1,2 Brigitte Piallat,1,3 Shivadatta Prabhu,1 Napoleon Torres,4 Alim Louis Benabid,1,4 Olivier David1 and Stephan Chabardès1,3,5
Published in 'Brain' Brain jJune2012: 135; 2263–2276 |

Posters:

1.Continuous high frequency Subthalamic nucleus DBS controls ongoing focal motor seizures in a primate model

S. Prabhu, B. Piallat, S.Michallat, O David and S. Chabardès
10 th Colloque, Société des Neurosciences Marseille ,24-27 May 2011(p 3.114)

2.Differential involvement of basal ganglia structures during motor seizures in a primate model

B. Piallat, A.Devergnas, S.Prabhu, S.Michallat, O.David and S.Chabardès
10th Colloque, Société des Neurosciences Marseille ,24-27 May 2011(p 3.110)

3.Could basal ganglia input structures control ongoing focal motor seizures? Results of Subthalamic nucleus DBS and further plan in a primate model

S. Prabhu, B. Piallat, S.Michallat, A.Sherdil, O David and S. Chabardès
8 th world congress of International Brain research Organization Florence, Italy July 14 18 2011 (p B 440)

4.The prefix 'Neuro' in terms like neuromarketing, neuroeconomics :Truly transdisciplinary approaches or just catchy hyped up syllables ?

S.Prabhu, H.Misra, B.Augier, A.Sherdil
8 th world congress of International Brain research Organization Florence, Italy July 14 -18, 2011(p T20)

5.Electric modulation of ongoing pharmacoresistent focal motor seizures by Subthalamic nucleus in a primate model

Prabhu S, Piallat B, Michallat S, David O, Chabardès S
29th International Epilepsy Congress of International league against Epilepsy Rome, Italy 28 August 1 st September2011 (p 867)

6.Treating Pharmacoresistant Focal Motor Seizures with HFS DBS of Subthalamic Nucleus: Rationale and Results in a Primate Model

S. Prabhu, B. Piallat, A. Devergnas, S.Michallat, O David and S. Chabardès
65th Annual Conference of American Epilepsy Society, Baltimore USA, December 2- 6, 2011(poster 3.070)

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