The study of neuronal noise correlations during cognitive flexibility and their phramacological regulation by Norepinephrine

Sameh Ben Hadj Hassen

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Sameh Ben Hadj Hassen

L'étude des corrélations du bruit pendant la flexibilité cognitive et de leur régulation pharmacologique par la norépinephrine

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The study of neuronal noise correlations during cognitive flexibility and their phramacological regulation by Norepinephrine

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Devant le jury composé de :

MACALUSO Emiliano	PU, UCBL, Lyon	Président
BOURET Sébastien	DR, CNRS, Paris	Rapporteur
KILAVIK Bjorg	CR, CNRS, Marseille	Rapporteure
CAPPE Céline	CR, CNRS, Toulouse	Examintarice
PROCYK Emmanuel	DR, CNRS, Lyon	Examinateur
BEN HAMED Suliann	DR, CNRS, Lyon	Directrice de thèse
WARDAK Claire	CR, INSERM, Tours	Invitée

Sameh Ben Hadj Hassen
Lyon, France, 2019
Personnel e-mail: belhadjhassen.sameh@gmail.com
The following thesis was carried out at:
L'institut des sciences cognitives - Marc Jeannerod
67 Boulevard Pinel
69657 Bron

Résumé

Le comportement normal d'un individu est le résultat de l'interaction entre les neurones, appelée la corrélation du bruit, qui se déroule entre et au sein des régions cérébrales bien identifiées. Cette corrélation joue un rôle important dans des fonctions cognitives majeures telles que l'attention, la mémoire, la perception et la prise de décision. Plusieurs études ont montré qu'il y a une diminution de la corrélation du bruit pendant les processus d'apprentissage et que son augmentation est corrélée avec les échecs comportementaux. De ce fait, comprendre comment cette corrélation est ajustée en fonction des changements du comportement est très important pour déterminer les processus neuronaux sous-jacents. En effet, ces processus neuronaux sont contrôlés par les neuromodulateurs. Plusieurs maladies neuropsychiatriques sont liées à une anomalie de régulation de ces neuromodulateurs. Par exemple, les personnes qui soufrent d'un trouble de déficit de l'attention avec hyperactivité (TDAH) ont un déficit attentionnel très handicapant de la vie quotidienne. Ce déficit attentionnel est atténué par une augmentation sélective de la neuromodulation noradrégergique. Cependant les mécanismes d'action des molécules utilisées, telles que la Ritaline, un agoniste noradrénergique, sont inconnus.

L'objectif de ma thèse est d'étudier et de comprendre les processus neuronaux liés aux mécanismes d'action des agonistes noradrénergiques. Plus précisément, j'ai étudié comment les corrélations du bruit sont ajustées en fonction des changements de l'engagement attentionnel chez des sujets sains et des sujets ayant reçu une manipulation pharmacologique de leur neuromodulation noradrénergique. Afin de réaliser mes travaux de recherche j'ai utilisé la technique d'enregistrement élecrtophysiologique chez le primate non-humain combiné avec des injections pharmacologiques. Mes travaux de recherche ont montrés que cette corrélation du bruit diminue quand l'engagement attentionnel augmente. De plus, cette corrélation du bruit change d'une manière rythmique dans le temps afin de s'adapter aux changements comportementaux. Enfin, mes travaux montrent que la modulation noradrénergique diminue ces corrélations du bruit au sein des réseaux neuronaux mimant une mise en œuvre des processus attentionnels.

Abstract

Optimal behavior is the result of interactions between neurons, called noise correlation, both within and across brain areas. Noise correlations play an important role in attention, memory, perception and decision-making. Many studies have shown that noise correlations decrease in the process of learning and to correlate with overt behavioral performance, higher noise correlations predicting behavioral failures. Identifying how these neuronal interactions adjust to the ongoing behavioral demand is key to understand the neuronal processes and computations underlying optimal behavior. Optimizing these neuronal processes depends on tightly controlled activity in brainstem neurons that release neuromodulators at their target sites. Understanding the link between neuromodulation and the variation in noise correlation within distance brain regions would help to describe the mechanisms by which neuromodulators exerts their functional effects.

My thesis aims to investigate how noise correlations are adjusted to cognitive and task engagement both in healthy brain state and after the targeting of the attentional function by systemic noradrenergic modulation. To do so, I combined pharmacology, behavioral and electrophysiology in non-human primate. Overall, we show that within the prefrontal node of the attentional parieto-frontal network, noise correlations decrease across tasks as cognitive engagement and task demands increase and that noradrenergic modulation further decreases noise correlations mimicking attentional orientation effects.

Mots Clés

Attention

Atomoxétine

Corréation du bruit

LFP

Noradrénaline

Spikes

Trouble de deficit de l’attention avec ou sans hyperactivité(TDAH)

Abbreviations

ATX	Atomexitine
ADHD	Attention Deficit Hyperactivity Disorder
FEF	Frontal Eye Fields
fMRI	Functional Magnetic Resonance Imaging
LIP	Lateral IntraParietal area
LFP	Local field potential
MUA	MultiUnit Activity
NE	Norepinephrine
SUA	SingleUnit Activity
SFC	spike field coherence

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II. **Determinants and function of shared neuronal noise variability**. *Ben Hadj Hassen S., Ben Hamed S. Review (in preparation).*

III. **Neurophysiology of Noradrenaline**. *Ben Hadj Hassen S., Ben Hamed S. Review (in preparation)*

IV. **Norepinephrine improves attentional orienting in a predictive context**. *J. Reynaud A., Froesel M., Guedj C., Ben Hadj Hassen S., Clery J., Meunier M., Ben Hamed S., Hadj-Bouziane F. (Neuropharmacology, 2019)*

V. **Neuronal correlates of noradrenergic modulation of attention within the frontal eye field**. *Ben Hadj Hassen S., Ben Hamed S (in preparation)*

Other relevant work by the author that is not included as a part of this doctoral thesis (in preparation):

Attention flexibly selects visual information during goal-directed behaviors

Di Bello F., Ben Hadj Hassen S., Ben Hamed S.

Abstract: Immersed in a permanent flow of stimulations, the avoiding of distracting information is critical to accomplishing daily tasks. In order to guide the selection of relevant visual information and the exclusion of irrelevant and distracting stimuli, attention implements two mechanisms. Individuals can proactively prioritize some aspect of relevant stimuli, such that the processing of attended objects result enhanced at the expense of distracting information. However, more often it happens that salient but irrelevant stimuli succeeded in capturing attention, and the subsequent visual processing has to be reactively suppressed. Spatial attention has been often described as a spotlight that includes a focal point in which visual processing results maximized. Despite the great amount of investigations, we still have very vague indication regarding the functionality of the attentional spotlight in stimuli selection. Although the exact mechanisms of distractor rejection are still to be discovered, researchers agree that prefrontal cortex is responsible for filtering task-irrelevant information and controlling distractor suppression. In this work, we provided to two monkeys a 100% validity cued detection task in which one of two distractor typologies could be presented on half of trials, while decoding spatial attention exploiting intracranial recording in left and right FEFs. After reproducing the detection benefit induced by attentional orienting, we provided neural evidences that proactive and reactive distractor rejection mechanisms can be both implemented throughout detection tasks, depending on situational factors like distractor location and orienting of attention. In the present study, we validate the decoding procedure as a reliable tool to accede to the actual attentional spotlight by showing that selectivity is implemented flexibly according to internal and external contingencies.

Specific network states underlying correct detection in Prefrontal cortex

Di Bello F., Ben Hadj Hassen S., Amengual J., Ben Hamed S.

Abstract: Visual attention improves perception for attended locations. Neurons in prefrontal cortex show both attention-related enhancements in firing rates to visual targets, and strong activity associated with perceived stimuli. Given the complex tuning that characterized cells of this brain area, coherent and testable neural mechanisms can be fully disclosed only at the level of the population. Dimensionality reduction methods produce low-dimensional representations of high-dimensional data, that has been proved to produce

representations able to highlight features of interest in the data. To characterize attentional fluctuations and determine how these are associated with stimuli detection, we explored the low-dimensional trajectories generated by the neural population recorded in the left and right FEFs of awake monkeys trained to detect stimulus presence. Although the neural network reproduces the decoded attentional orienting irrespectively from trial categories, we found that correct detections present specific characteristics. For instance, the pre-target period result more stable and characterized by a distinct state, linearly separable to detection failures. Overall, our results indicate that correct detections are characterized by a specific configuration of the network in prefrontal cortex.

The prefrontal attentional spotlight continuously explores space at an Alpha rhythm

Prefrontal attentional saccades explore space at an alpha rhythm

Reconciling the attentional spotlight and attentional rhythmic sampling of space

Gaillard C., Ben Hadj Hassen S., Di Bello F., Bihan-Poudec Y., VanRullen R., Ben Hamed S

Abstract: Recent behavioral studies suggest that attention samples space rhythmically (Landau and Fries, 2012, Kastner et al., 2013; VanRullen et al., 2013, Dugué et al., 2016). Oscillations in brain activity have been described as a possible mechanism supporting attentional processes. However, the precise mechanism through which this rhythmic exploration of space is subserved remains unknown. In a previous study (Astrand et al., 2016), we applied machine learning methods to ongoing monkey prefrontal multi-unit population activity, to decode, in real-time, the (x,y) location of the attentional spotlight. Here, we further demonstrate that the overall decoded spatial attention information that can be extracted from population multi-unit activity oscillates at a 7-12Hz rates. These oscillations in attentional information account for stimulus encoding. On trials in which the target is correctly detected, how much information about the target is available in the neuronal population oscillates at the same frequency as attentional information. The same is true for the encoding of the distractor on false alarm trials, in which the distractor is mistaken for a target. Oscillations in the decoded attentional spotlight also account for variations in overt behavior, whether hit rates in response to a target or false alarm rates in response to a distractor. Importantly, these oscillations characterize displacements of the decoded attentional spotlight. While these oscillations are task-independent, we demonstrate that how space is explored by the decoded attentional spotlight is task specific. In other words, while 7-12Hz oscillations mediate attentional displacement, top-down control flexibly adjusts these displacements to the ongoing behavioral demands.

Decoding multiplexed attention, temporal expectation and response preparation information from the prefrontal cortex

Gaillard C., Ben Hadj Hassen S., Di Bello F., Astrand E., Ben Hamed S

Abstract: The frontal eye fields (FEF) plays a key role in top-down attentional control (Ibos, et al. 2013). In a recent study, we estimate in real-time the (x,y) position of covert spatial attention, i.e. the position of the attentional spotlight, using classification methods applied to the ongoing monkey FEF multi-unit activity (Astrand et al., 2016). However, like in other prefrontal cortical areas, information in the FEF is highly multiplexed both at the single cell level and at the population level. As a result, identifying the information that is multiplexed with spatial attention information, thus explaining part of the unaccounted for neuronal response variability, is expected to notably improve our estimation of attentional locus position. In the present study, we consider three multiplexed variables that are expected to contribute to FEF activity: 1) temporal expectation, 2) response preparation and 3) intra-trial attention attentional oscillations. These variables are modeled and implemented in our attention decoding algorithm. Confirming our working hypothesis, we show that taking into account these variables notably improves our access to the attentional informational content of neuronal activity in this prefrontal region.

Real-time decoding of covert attentional spotlight from monkey prefrontal local field potentials

De Sousa Ferreira C., Gaillard C., Loriette C., Ben Hadj Hassen S., Di Bello F., Ben Hamed S.

Abstract: The ability to access brain information in real-time is important both for a better understanding of cognitive functions and for the development of therapeutic applications based on brain-machine interfaces. Great success has been achieved in the field of neural prosthesis. Progress is still needed in decoding higher-order cognitive processes such as covert attention. Recently, we showed that we can access the position of the covert attentional spotlight in real-time using classification methods on frontal eye fields multi-unit activity (MUA) in the non-human primate (Astrand et al., 2016). Importantly, we demonstrated that the (x,y) decoded covert attentional spotlight parametrically correlates with the behavioural perceptual responses of the monkeys thus validating our decoding of covert attention. To extend our findings and get closer to non-invasive techniques, we here replicate our previous work using local field potentials (LFP) signals collected during a cued spatial target detection task. Specifically, we evaluate the performance of major machine learning methods at extracting the covert attentional spotlight both from the overall LFP frequency content, and from specific functional frequency bands. We further quantify how much this extracted information (whether a discrete attentional locus or a continuous (x,y) attentional locus) correlates with overt behaviour. These results are compared to our previous MUA decoding results. Overall, this study confirms that the covert attention spotlight can be accessed from LFP frequency content, in real-time, and can be used to drive high-information content cognitive brain machine interfaces for the development of new therapeutic strategies.

Project summary

Attention is the process that enables us to select the most relevant information that is captured by our senses for further processing, while setting aside the remaining information. It is a complex, multi-faceted function. However, in certain pathological conditions, dysfunctions of attentional processes lead to dramatic impairments. For example, children, adolescents, and adults suffering from ADHD (attention deficit hyperactivity disorder, a developmental syndrome), have great difficulty in maintaining their concentration on a task long enough to perform it properly. Their deficit is thus most marked in the time domain of attention. This attention deficit can potentially be alleviated by selectively increasing noradrenergic neuromodulation. However, to date, the specific neuronal mechanisms of action by which noradrenergic agonists exert their therapeutical effects remain unknown, and the neural bases of their behavioral effects still need to be described. How does norepinephrine boost up attention? Does it always work? My thesis project will explore the behavioral determinants and neural bases of the attention boosting effects of enhanced noradrenergic neurodomulation. The frontal eye field FEF is a cortical area which has been shown to be at the source of spatial attention top-down control (Buschman et Miller 2007; Wardak et al. 2006; Ibos et al., 2013; Ekstrom et al. 2009). On the other hand several studies have demonstrated that functional neuronal correlations between pairs of neurons, otherwise known as noise correlations, play an important role in perception and decision-making (Ts'o, Gilbert, et Wiesel 1986; Engel et al. 1991; Ahissar et al. 1992; Zohary, Shadlen, et Newsome 1994; Vaadia et al. 1995; Narayanan et Laubach 2006; Cohen et al. 2010; Poulet et Petersen 2008; Stark et al. 2008).

In the first part of my project I will review the current understanding of the role and contribution of these neuronal noise correlations to neuronal and cognitive processes **(Chapter I)**. I will then investigate, in non-human primates, the contribution of noradrenergic modulation to local, short-range and long-range neural processes underlying normal attention and by studying the link between interneuronal noise correlation in FEF and attentional processes (**Chapter II**). The second part of my project, I will review the physiological and behavioral data describing the LC-NE system as a major source of NE then I described the implication of NE in attention and the models proposed for LC-NE activity and **(Chapter III)**. I will then present a behavioral study investigating the effect of systemic injection of

atomexetine (ATX), a neroepinephrine (NE) reuptake inhibitor, on attentional processes **(ChapterIV)**, on which I have collaborated. The third part of my project is an investigation of ATX effects on prefrontal neuronal processes during active behavioral tasks, by recording the neuronal activity from the FEF areas after systemic injection of ATX **(ChapterV)**.

Chapter I

Determinants and function of shared neuronal noise variability

In our daily life, our brain is confronted to many stimuli at the same time. A major endeavor of modern neurosciences is to understand how the brain encodes this information and then decodes it and reads it out in order to guide behavior optimally. However, the response of a given neuron to the exact same stimulus varies from one presentation to the next. In other words, the spiking rate of the neurons is not deterministic. This also applies to the baseline response of the neurons which fluctuates in time and across trials. In this context, understanding how neurons communicate between each other turns out to be crucial. Indeed, baseline response fluctuations as well as response neuronal variability are thought to be shared among neurons and are often referred to as noise correlations. ***These noise correlations express the amount of co-variability, in the trial-to-trial fluctuations of responses pairs of neurons, to repeated presentations of identical stimuli, or under identical behavioral conditions.***

Noise correlation have received a lot of attention and have been measured in a variety of brains areas, and under a variety of behavioral and stimulus conditions. They appear to have a profound impact on cortical signal processing as well as onto behavioral performance (Abbott and Dayan, 1999; Averbeck et al., 2006; Kanitscheider et al., 2015, 2015; Moreno-Bote et al., 2014; Sompolinsky et al., 2001). Recent populational approaches show that while several repetitions of the same stimulus elicit different responses, an accurate representation of the stimulus is obtained by considering the shared response between all neurons (Averbeck et al., 2006; Shadlen and Newsome, 1998; Tolhurst et al., 1983). Relevant to the present review, the accuracy of such population codes strongly depends on neuronal correlations, sometimes deteriorating populational information (Abbott and Dayan, 1999; Averbeck et al., 2006; Sompolinsky et al., 2001; Zohary et al., 1994) and other times improving it (Froudarakis et al., 2014). It has also been proposed that noise correlations provide important information about how the brain adjusts, how it codes and decode sensory stimuli, as a function of the behavioral context or the stimulus being processed (Ahissar et al., 1992; Cohen and Newsome, 2008a; Gutnisky and Dragoi, 2008; Kohn and Smith, 2005; Poulet and Petersen, 2008; Vaadia et al., 1995). As a result, several groups have been interested in characterizing the possible sources of noise correlations, ranging from the internal dynamics of cortical systems (Ben-Yishai et al., 1995, p.; Ly et al., 2012), the global fluctuations in the excitability

of cortical circuits (Arieli et al., 1996; Schölvinck et al., 2015) or the shared functional connectivity across cortical regions (Shadlen and Newsome, 1998). The prevailing hypothesis is that noise correlations result from random shared fluctuations in the pre-synaptic activity of cortical neurons (Bair et al., 2001; Bryant et al., 1973; Shadlen and Newsome, 1998; Zohary et al., 1994). It is however important to note that these different hypotheses on the functional origins of noise correlations are non-exclusive and possibly reflect the different facets of a same functional mechanism. Importantly, all of these hypotheses imply a functional and behavioral role of noise correlations as well as a dependence of noise correlations onto global physiological states.

In this chapter, we will first provide an operational definition of noise correlations, and we will review the extent to which noise correlations vary as a function of such parameters as neuronal distance, cortical layer, neuronal selectivity and cortical area. We will then discuss the dependence of noise correlation, on cognitive processes within global and local network.

I. Low level structural and functional determinants of shared neuronal variability

1. Good practice when computing noise correlation statistics

How noise correlations are measured vary from one study to the other. Cohen and Kohn, (2011) have offered guidelines for interpreting noise correlation and the best way to evaluate the effects of noise correlations onto cortical processing. Most studies compute noise correlation on the evoked response to a sensory stimulus over multiple presentations (Aertsen et al., 1989; Ahissar et al., 1992; Bair et al., 2001; Constantinidis and Goldman-Rakic, 2002a; Espinosa and Gerstein, 1988; Kohn and Smith, 2005). However, some studies have computed noise correlations during attention processes, ranging from spatial attention (Astrand et al., 2016; Cohen and Maunsell, 2009a), spatial memory (Meyers et al., 2012) or cognitive engagement (***Section II of present Chapter I).***

Noise correlations represent shared neuronal variability. This variability can be computed across single well identified neurons (**SUA**, Bair et al., 2001; Bedenbaugh and Gerstein, 1997; Constantinidis and Goldman-Rakic, 2002; Kohn and Smith, 2005; Rosenbaum et al., 2010). In this context, spike sorting conventions could affect noise correlation values and systematically bias their estimates. Alternatively, this variability can be computed across multi-unit activity (**MUA**) at distinct recording sites (Cohen and Maunsell,

2009a; Schölvinck et al., 2015; Stark et al., 2008; Womelsdorf et al., 2007). This affects both the amplitude of reported noise correlations as well as their range of fluctuations, these being expectedly higher when computed on MUA rather than on SUA. However, this does not affect the qualitative observations relative to noise correlations (Cohen and Kohn, 2011).

Noise correlations can be calculated on different time intervals. Most studies use time intervals ranging between 200ms and 3000ms. Short time intervals will be corrupted by the spiking variability of individual signals. Longer time intervals will blur dynamic changes in noise correlations **(*Section III of present Chapter I*).**

From a statistical point of view, several methods can be used to assess these correlations (e.g. Pearson, Spearman). The most ubiquitous method is the Pearson correlation coefficient of spike counts between pair of neurons to repeated presentations of identical stimulus or behavioral conditions. Because this measure can be affected by overall neuronal response strength (Astrand et al., 2016; Cohen and Maunsell, 2009a), it is of good practice, when comparing noise correlations between two different conditions, to compute these noise correlations on z-scored neuronal responses (Cohen and Kohn, 2011).

Reported ranges of noise correlations vary from one study to the other, but correlations are typically small and positive. As discussed above, these values depend on the considered time interval, on whether they are computed onto MUA or SUA, on whether they are during at sensory or during cognitive processing, as well as on overall response amplitude. Reported noise correlations varies between 0.01 (Averbeck et al., 2006; Averbeck and Lee, 2003; Cohen and Maunsell, 2009a; Ecker et al., 2010a; Herrero et al., 2013; Mitchell et al., 2009; Nevet et al., 2007; Smith and Sommer, 2013) up to 0.4 (Astrand et al., 2016; Bair et al., 2001; Cohen and Newsome, 2008a; Gawne et al., 1996; Gawne and Richmond, 1993; Gutnisky and Dragoi, 2008; Hansen et al., 2012; Herrero et al., 2013; Kohn and Smith, 2005; Smith and Kohn, 2008; Zohary et al., 1994)

Last, noise correlations also depend on structural and functional aspects of cortical organization. This touches onto the functional role of noise correlations and will be discussed below.

2. *Noise correlations and population information*

When a given stimulus is encoded in large populations of neurons, the problem of the trial to trial response variability can easily be resolved by averaging. However, the efficiency of averaging depends on the pattern of noise correlation across neurons (Moreno-Bote et al., 2014). In this context theoretical studies have shown that the information capacity of a population code depends on the correlated noise among neurons (Abbott and Dayan, 1999; Averbeck et al., 2006; Sompolinsky et al., 2001; Tremblay et al., 2015). Noise correlations can either increase or decrease the encoded information as compared to an uncorrelated population, depending on the relationship between noise correlations and signal correlations (Snippe and Koenderink, 1992) as well as the cortical distance between the neurons (Froudarakis et al., 2014). Theoretical work suggests that, depending on the structure of the correlations in the neural population, information can either saturate as the number of neurons increases (Sompolinsky et al., 2001; Zohary et al., 1994) or information can grow together with the number of neurons in a population increases (Abbott and Dayan, 1999; Shamir and Sompolinsky, 2004; Wilke and Eurich, 2001). This is still a matter of discussion and recent studies suggest that the variables that mediate the impact of noise correlation on coding are complex (Ecker et al., 2011a; Kanitscheider et al., 2015; Moreno-Bote et al., 2014).

3. *Structural determinants of shared neuronal variability*

a. ***Cortical distance effects.*** Noise correlations reflect co-fluctuations within neuronal networks. As it's calculated between pairs of neurons, and as inter-neuronal distance is a key determinant of the strength of coupling between neurons (Dombeck et al., 2009; Kerr et al., 2007), it's important to investigate how distance between neurons affects noise correlation. Whatever the type of electrodes used during recordings, distance between two neurons is relative to the distance between the contacts on which neurons pairs are recorded. Recorded pairs could be located in the same hemisphere (intra-hemispheric noise correlation) or in opposite hemispheres (inter-hemispheric noise correlation). Most studies have investigated intra-hemispheric noise correlations because pairs recorded from opposite hemispheres have very low correlation (Cohen and Maunsell, 2009a). Several studies have demonstrated that, for non-human primates, distance between pairs of neurons affect noise correlation value. They tend to be highest for pairs of neurons that are closest to each other (Constantinidis and Goldman-Rakic, 2002a; Lee et al., 1998a; Smith and Sommer, 2013). This generalizes in other species including mice (Komiyama et al., 2010). Importantly, noise correlations are not limited to local populations but persist even between neurons separated

as much as 10 mm in cortex (Nauhaus et al., 2009; Smith and Kohn, 2008). Variations in noise correlations as a function of distance in the prefrontal cortex is further explored in ***Chapter II*** of the present document. Overall, inter-neuronal distance is thus a key structural determinant of the strength of coupling between neurons.

b. ***Cortical layer.*** The spiking activity of neurons is determined by the inputs (excitatory or inhibitory) they receive from other neurons in their local network. As a result, one would expect that differences in the source and strength of inputs to neurons in different cortical layers would impact the degree of correlation in noise. Usually, multilaminar electrode is used to record neurons across cortical depth (Figure1.A) (Hansen et al., 2012). Briefly, cortical layers can be subdivided as follows; granular layer, where neurons receive geniculate input, and in which the spatial spread of connections is small (Adesnik and Scanziani, 2010; Briggs and Callaway, 2005); supragranular layer, where neurons receive recurrent input from large cortical distances (up to several mm) via long-range horizontal circuitry (Bosking et al., 1997; Gilbert and Wiesel, 1983; Karube and Kisvárday, 2011; Ts'o et al., 1986); and infragranular layer, where neurons receive short-range recurrent input the other cortical areas and project onto other cortical regions through feedback connections (Bosking et al., 1997; Gilbert and Wiesel, 1983; Karube and Kisvárday, 2011; Ts'o et al., 1986). Due to these structural differences, the strength of noise correlations between pairs of cells are expected to vary in a laminar depend manner. Part of this effect is expected to be accounted for by sheer inter-neuronal distance effects. However, one also expects an additional source of inter-layer difference in noise correlations to arise from the functional nature of the long-range and short-range inputs. As a result, one expects an important difference in layer effects onto noise correlations between cortical regions (e.g. primary sensory cortices vs. associative cortices).

Very few studies have actually investigated the effect of neuron layer localization onto noise correlations. Buffalo et al. (2011) compared noise correlations between pairs of neurons localized in either V1 deep or superficial layers, and didn't find any significant difference in noise correlations across layers. In contrast, Hansen et al. (2012, figure 1.B) show that neuronal noise correlations in the granular layer of V1 are an order of magnitude weaker than neuronal noise correlations in the supragranular layers. In V4, attention decrease variability in superficial layers while it decreases it in the input layer (Nandy et al., 2017). Variations in

noise correlations as a function of cortical layer in the prefrontal cortex is further explored in ***Chapter II*** of the present document.

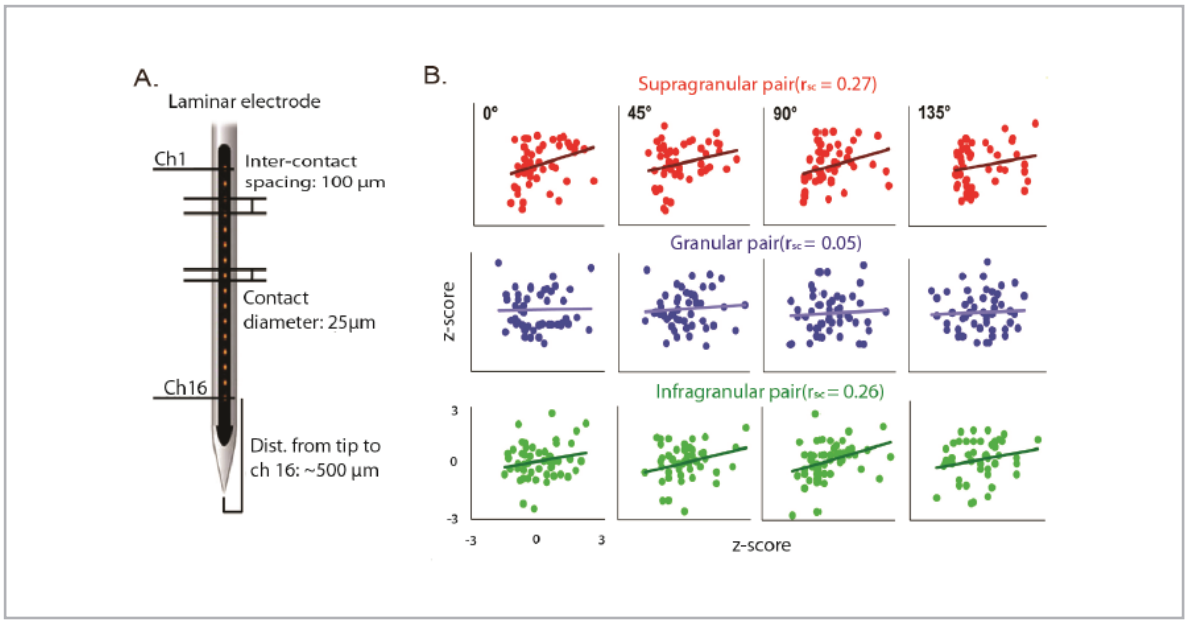

Figure1. (A) *Multicontact laminar electrodes used to record neuronal activity across cortical depth.* ***(B)*** *Each scatter plot represents the Z score–transformed responses for three example pairs of cells recorded simultaneously in supragranular , granular, or infragranular layers during the presentation of a particular stimulus orientation (columns: 0°, 45°, 90°, and 135°). The trend line represents the linear regression fit for each pair of cells;* r_{SC} *for each layer represents the Pearson correlation coefficient extracted from all eight stimulus orientations. Adapted from (Hansen et al., 2012)*

c. ***Functional selectivity.*** Neurons sharing functional selectivity (e.g. coding the same sensory modality, coding the same spatial location, coding the same motor output or function etc.), have a stronger coupling than neurons with distinct functional selectivities (Kohn and Smith, 2005; Shadlen and Newsome, 1998; Zohary et al., 1994). Functional selectivity is thus expected to affect noise correlation levels. It has been shown that while correlated variability strongly influences population coding, whether noise correlations are detrimental or beneficial depend on the functional selectivity of the neuronal pairs (Figure 2.A), Kanitscheider et al., 2015). This includes the orientation tuning similarity of the neuronal pair (Averbeck and Lee, 2006; Shadlen and Newsome, 1998; Zohary et al., 1994) as well as their spatial selectivity (Figure2.B) (Cohen and Maunsell, 2009a; Constantinidis et al., 2001; Constantinidis and Goldman-Rakic, 2002a; Ferster and Miller, 2000; Huang and

Lisberger, 2009; Seriès et al., 2004). For example, noise correlations in V1 are higher amongst neurons with similar spatial tuning (Constantinidis et al., 2001; (Constantinidis and Goldman-Rakic, 2002a)**;** Smith et Kohn 2008a). Likewise, noise correlations in the parietal cortex are shown to be strongest for similarly spatially tuned neurons and weakest between cells with opposite preferences (Smith et Kohn 2008; Cohen et Maunsell 2009a). Thanks to attention, the important stimulus is selected to prioritize the processing of relevant over irrelevant information.

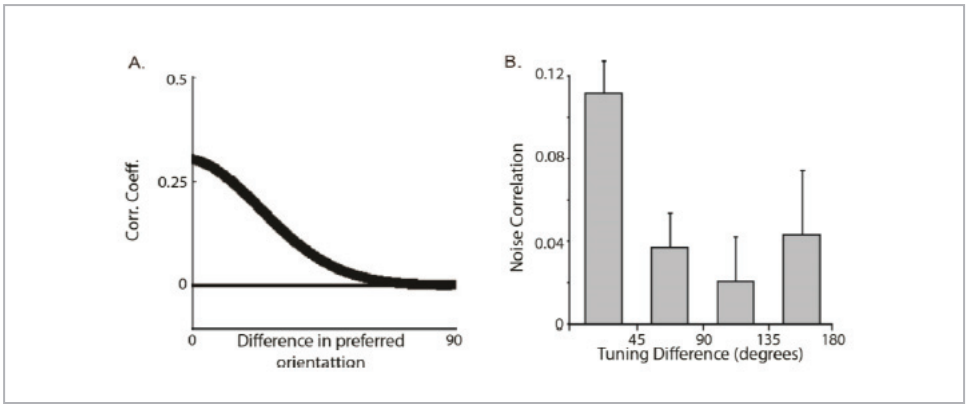

Figure2. Noise correlations as a function of spatial selectivity. (A) *Average pairwise noise correlations in the network (V1) are positive and decay with the difference in preferred orientation. Adapted from (Kanitscheider et al., 2015).* ***(B)*** *Noise correlation is plotted as a function of tuning difference in* ***prefrontal cortex****. Adapted from (Constantinidis and Goldman-Rakic, 2002a).*

II. Functional changes in noise correlations

1. ***Sleep and wake states.*** The brain's internal dynamics and responsiveness to external stimuli vary widely across different behavioral contexts. Internal brain state can fluctuate even in the absence of overt behavioral changes. The most notable transitions are the well-characterized sleep/wake transition and the transitions within the different stages of sleep (Alexander S. Ecker et al., 2014; Greenberg et al., 2008). Noise correlations are generally lower during desynchronized states of wakefulness than during synchronized states of sleep (Alexander S. Ecker et al., 2014; Ecker et al., 2010a; Renart et al., 2010).

2. ***Wake states.*** Further, changes in arousal and neuronal excitability modulate the level of correlated variability in sensory cortex (Alexander S. Ecker et al., 2014; Ecker et al., 2010a; Goris et al., 2014) . Recent work in the mouse suggests that the overall level of noise correlations varies across different wakeful brain states (Gentet et al., 2010; Poulet and Petersen, 2008; Reimer et al., 2014; Vinck et al., 2015). Last, in monkeys, higher noise correlations are shown to correlate with more behavioral errors, possibly suggesting

fluctuations in on-task behavioral states (Astrand et al., 2016). These effects are much stronger than the classical attention effects described below. This is further discussed in Chapter 3 of the present document.

3. ***Anesthesia.*** Many commonly used anesthetics, such as isoflurane, urethane, and ketamine, substantially alter neural activity by suppressing sensory responses and increasing response latencies (Drummond, 2000; Kohn et al., 2009) as well as inducing so-called up and down states (Harris and Thiele, 2011; Renart et al., 2010). Opioids, such as fentanyl or sufentanil (Kohn and Smith, 2005; Reich, 2001; Smith and Kohn, 2008) have less dramatic effects onto neural activity (Constantinople and Bruno, 2011; Drummond, 2000), though they still do affect neural response properties (Schwender et al., 1993) and induce low-frequency oscillations (Bowdle and Ward, 1989). Ecker et al. (2014) show that spontaneous transitions in network state under anesthesia induce noise correlation between neurons. These transitions are absent in awake, fixating monkeys. This indicates a clear qualitative difference between the awake and the anesthetized states, this despite similar firing rates. The precise neuronal mechanisms through which anesthesia affect neuronal shared variability is still unknown.

4. ***Perceptual learning.*** It has been shown previously that learning induces changes in the response magnitude and selectivity of individual neurons (Dragoi et al., 2002; Muller, 1999; Sharpee et al., 2006). It's also usually assumed that both learning processes and faster adaptation processes are mediated by lasting changes in synaptic efficacies, a phenomenon known as synaptic plasticity. Understanding how learning influences population coding requires understanding how correlation between neurons is affected by this phenomenon. Many studies have been interested in studying the variation of noise correlations during learning (Cohen and Maunsell, 2009a; Gu et al., 2011; Mitchell et al., 2009; Ni et al., 2018). Theoretical studies suggest that learning or adaptation should reduce neuronal correlations and hence increase available neuronal population information (Reich, 2001; Schneidman et al., 2003). In an early experimental study, Ahissar et al. (1992) have studied how noise correlations are affected by synaptic plasticity. They found that changes in noise correlations between neurons are often necessary, but not sufficient, for cortical plasticity to take place. Interestingly, Gutnisky et Dragoi (2008) have found that brief adaptation to a stimulus of fixed structure reorganizes the distribution of neuronal correlations across the entire network in V1 by selectively reducing their mean and variability. This contrasts with the finding that, in mice motor cortex, there is an increase of temporal

correlation with learning, specifically among neuron pairs of the same response type (Komiyama et al., 2010).

From a more general behavioral perspective, Gu et al. (2011) show (Figure3) that correlated neuronal noise is significantly higher in untrained animals versus trained animals. More recently, Ni et al. (2018) describe that unlike in V1, there is a robust relationship between correlated variability and perceptual performance in V4. They suggest that learning-related changes in average noise correlations are linked to performance and to optimal readout of visual information by the neuronal population (Ni et al., 2018). These two studies thus bridge the gap between the above described neuronal mechanisms and overt behavior.

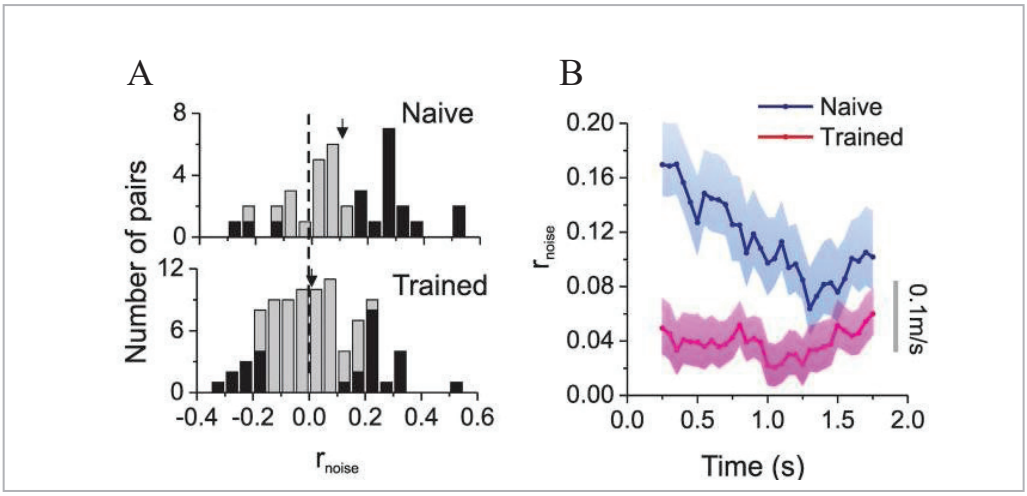

Figure3. Training effects on behavior and interneuronal correlations. ***(A)*** *Distributions of noise correlations for 'naïve' (top, n=38) and 'trained' (bottom, n=89) animals. Black bars indicate* r_{noise} *values that are significantly different from zero. Arrows: population means.* ***(B)*** *Average (± sem) time course of noise correlations in 'trained' (red, n=89) and 'naïve' animals (blue, n=38). Adapted from (Gu et al., 2011).*

5. ***Attention.*** Attention is a functional process that enables subjects to select relevant information for the ongoing behavior and improve her/his ability to detect and discriminate the features of incoming sensory stimuli. This sensory improvement is accompanied by an increase in the mean firing rates of neurons driven by the attended stimulus as well as with a decrease in the mean firing rate of neurons driven by irrelevant stimuli (for review, see (Reynolds and Chelazzi, 2004). Most studies have investigated how attention affect noise correlations when attention is spatially focused in the responses fields of the neurons. Globally, attention decreases noise correlations (Cohen and Maunsell, 2011, 2009b; Herrero et al., 2013; Mitchell et al., 2009; Nandy et al., 2017). Attention reduction in noise correlations in V4 is proposed to account for benefit decision making in other parts of the brain and at the behavioral level (Cohen and Maunsell, 2009b; Mitchell et al., 2009). If

this is the case, on would expect this reduction to be localized to the output layer of V4. However, a recent study reports that attention significantly reduces noise correlations in the V4 input layers. The authors propose that this superficial deccorrelation in V4 neurons is an active mechanism that serves to remove correlations from the inputs received from the earlier visual cortices (Nandy et al., 2017).

Neuronal decorrelation by attention may not be systematic but dependent onto stimulus input. Indeed, Poort and Roelfsema (2009) report, in V1, no effect of attention on noise correlations specifically when noise correlations are shown to have no effect on the sensitivity of the population of V1, in other words, when population information is maximal. In the same lines, Ni et al. (2018) show a robust relationship between noise correlations and the subjects' performance on an attentional task. Specifically, their attention-related changes in average noise correlations closely linked to overt behavioral performance. Importantly, this correlation between noise correlation changes and overt performance was weaker if the monkeys read out visual information optimally. This suggests a coupling between sensory processing and subsequent noise correlations changes for optimal cognitive processing.

The studies mentioned above, have only dealt with the spatial orientation of attention for the detection of one sensory stimulus. An important question is how noise correlations are affected by attention during the dynamic change of sensory stimuli. Downer et al. (2017) demonstrate that, in primary auditory cortex A1, attention effects on noise correlations do not depend only on population tuning to the relevant stimulus but also onto the tuning to the distractor feature, indicating that noise correlations reflect global sensory input processing rather than segregated input processing.

The function of attention networks depends onto controlled activity of neurons that release neuromodulators at their target sites. Herrero et al. (2008) report that attention-induced firing rate modulations of V1 neurons depend on cholinergic mechanisms. However, more specifically to noise correlations, they highlight a role of NMDA receptors in V1 noise correlation regulation (Herrero et al. 2013). Unfortunately, a comprehensive role of neuromodulation in changes in neuronal response variance and noise correlations under spatial attention processes is still missing. This will be further discussed in chapter 4 of the present document.

6. ***Task effects.*** In awake animal spontaneous cortical activity switches between discrete synchronized and desynchronized states (Engel et al., 2016). During the synchronized states neuronal pairwise correlations are positive and the population rate has a large variance, which is indicative of coordinated global fluctuations. In the desynchronized

states, the variance of neuronal population responses is small and the spontaneous fluctuations are weaker (Bair et al., 2001; Kohn and Smith, 2005; Smith and Kohn, 2008; Thiele and Hoffmann, 2008; Zohary et al., 1994). The variations in fluctuation strength partially correlates with ongoing behavior, such as whisking and locomotion (Crochet and Petersen, 2006; Ferezou et al., 2007). In words, the de-synchronization is limited to neuronal population that represents the ongoing relevant functions (e.g. attended stimulus) while neurons that are not engaged in the ongoing computations (e.g. non-attended information) are in a more synchronized state. As a result, one would expect a continuous adjustment in noise fluctuations as a function of the ongoing behavior.

Generally speaking, producing optimal behaviors in regard to external and internal demands, requires an adaptive cognitive control system for selecting relevant information, and for organizing and optimizing processing pathways. Given the above described relationship between shared interneuronal variability and noise correlations and optimal behavior, one expects important changes in noise correlations during adaptive cognitive control and this at multiple time-scales. This will be addressed in chapter 3 of the present document.

III. Bridging the gap between local and global desynchronization processes

During decorrelated cortical states (low noise correlations), the number of neurons necessary to achieve highly accurate network performance is thought to be reduced (Abbott and Dayan, 1999; Ecker et al., 2010a; Shadlen and Newsome, 1998). An important question is to identify the global network measure that coincides with the changes in shared neuronal variability. A possible correlate of these changes in interneuronal shared variability is global cortical network changes in functional connectivity.

Resting-state global functional co-activation patterns. In the absence of any task and any stimulation, brain activity can be characterized by a specific pattern of cortical co-activation pattern, known as a resting-state functional signature. Spontaneous brain activity during this rest state is highly structured into characteristic spatiotemporal patterns (resting-state networks or RSNs, (Fox et al., 2007, 2006; Greicius et al., 2003; Vincent et al., 2007). Analyzing the patterns of co-activation of these spontaneous brain activities reveal a set of

organized cortical network, whose activity are ongoing during rest and suspended during the performance of externally cued tasks. This supports the idea of a default mode of brain functions (Raichle, 2015). Specifically, the resting state networks that are not associated with sensory or motor regions have been thought of as a default-mode network, including medial prefrontal, parietal, posterior and anterior cingulate cortices (Greicius et al., 2003). Similar networks are identified in humans and monkeys during deep anesthesia, suggesting that this resting-state default-mode network organization is not only specific to human cortical functions but also transcends levels of consciousness (Vincent et al., 2007). More recently, resting state dynamics has been shown to be non-stationary (Allen et al., 2014), the set of functional correlations between brain areas, the so-called functional connectivity (FC), changing on a time scale of tens of seconds to minutes, the baseline being probably defined by rest with eyes closed (Raichle *et al.,* 2015).

Regardless of the technique used, the analysis of these spontaneous fluctuations usually involves the identification of correlations between remote brain areas, commonly referred to as functional connectivity. Biswal et al., were the first who demonstrated that there is a resting state correlation between the activity in the primary motor cortex (M1) and other brain regions (Biswal et al., 1995). Consequently, several studies have been interested to identify and characterize these networks (Greicius et al., 2003). In human, these spontaneous fluctuations were found to be temporally coherent within the neuro-anatomical system that recapitulates the functional architecture of responses evoked by experimentally tasks (Biswal et al., 1995; Damoiseaux et al., 2006; Fox et al., 2006; Greicius et al., 2003; Vincent et al., 2007). Similar results were found in non-human primate (Vincent et al., 2007). These results have been confirmed and extended to several other systems, including auditory, visual, dorsal and ventral attention systems and language processing networks (Biswal et al., 1995; Fox et al., 2006; Greicius et al., 2003; Hampson et al., 2002; Van de Ville et al., 2010). Correlated fluctuations have been demonstrated between frontal and parietal areas often observed to increase activity during task performance (Laufs et al., 2003) and within the network of regions commonly exhibiting activity decreases during task performance (Greicius et al., 2003; Greicius and Menon, 2004; Laufs et al., 2003). The collective result of the above studies is that regions similarly modulated by tasks or stimuli tend to exhibit correlated spontaneous fluctuations even in the absence of tasks or stimuli. This result holds true even at different spatial and temporal scales, for example, in orientation columns in the visual cortex (Kenet et al., 2003).

1. ***Functional resting-state networks.***

In this context, an important question is to understand the relationship between regions with dissimilar task related functional responses. To answer this question Fox et al. (2005), specifically checked if the task-related dichotomy between regions routinely exhibiting task-positive responses and those routinely exhibiting task-negative responses were intrinsically represented in the resting brain. They have shown that in resting state widely distributed neuro-anatomical networks are organized through both correlated spontaneous fluctuations within a network and anticorrelations between networks (Fox et al., 2005, Figure6). Within these resting state cortical networks, a specific pattern of deactivation is described. This pattern is often accompanied by increased cognitive demands. This pattern of deactivation is observed within a specific set of cortical regions known as the Default Mode Network, in an anti-correlated manner with most of other resting-state cortical networks (Greicius et al., 2003; Raichle et al., 2001). It is proposed that these patterns of activation and deactivation represented a shift in the balance from a focus on the subject's internal state to the external environment (Shulman et al., 1997).

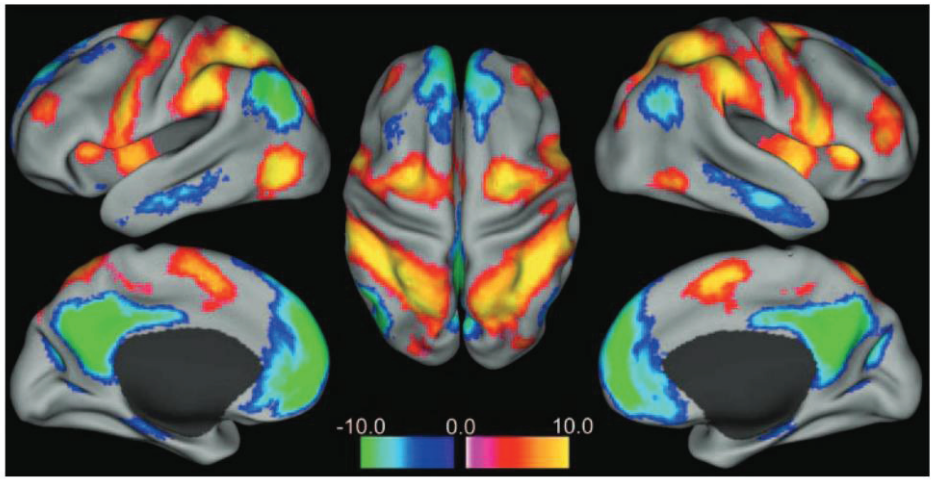

Figure4. Intrinsically defined anticorrelated processing networks in the brain. *Positive nodes are significantly correlated with seed regions involved in focused attention and working memory (task-positive seeds) and significantly anticorrelated with seed regions routinely deactivated during attention demanding cognitive tasks (task-negative seeds). Negative nodes are significantly correlated with task-negative seed regions and significantly anticorrelated with task-positive seed regions. (*Left*) Lateral and medial views of left hemisphere. (*Center*) Dorsal view. (*Right*) Lateral and medial views of right hemisphere. From (Fox et al., 2005).*

2. ***Missing link between global co-activation patterns and local noise correlations?***

This missing link is yet unclear. Recent studies in the non-human primate show that resting state fMRI fluctuations are controlled by arousal both as demonstrated through behavioral modulations (Chang et al., 2016) or direct modulation of deep sub-cortical structures such as the basal forebrain (Turchi et al., 2018) or the thalamus (Liu et al., 2018). Importantly, these global fluctuations correlate with specific spectral shifts in local field potentials (LFPs) toward low frequencies (Chang et al., 2016; Liu et al., 2018), thus identifying the electrophysiological correlated of resting-state network fluctuations. A parsimonious hypothesis would be that these resting-state network fluctuations would also coincide with local changes in noise correlations, thus bridging the gap between microscopic (noise correlations), mesoscopic (LFPs) and macroscopic (fMRI functional connectivity) functional fluctuations.

IV. References

Abbott, L.F., Dayan, P., 1999. The Effect of Correlated Variability on the Accuracy of a Population Code.

Adesnik, H., Scanziani, M., 2010. Lateral competition for cortical space by layer-specific horizontal circuits. Nature 464, 1155–1160.

Aertsen, A.M.H.J., Gerstein, G.L., Habib, M.K., Palm, G., 1989. Dynamics of Neuronal Firing Correlation: Modulation of "effective connectivity."

Ahissar, E., Vaadia, E., Ahissar, M., Bergman, H., Arieli, A., Abeles, M., 1992. Dependence of Cortical Plasticity on Correlated Activity of Single Neurons and on Behavioral Context. Science 257, 1412–1415.

Allen, E.A., Damaraju, E., Plis, S.M., Erhardt, E.B., Eichele, T., Calhoun, V.D., 2014. Tracking Whole-Brain Connectivity Dynamics in the Resting State. Cereb. Cortex N. Y. NY 24, 663–676.

Arieli, A., Sterkin, A., Grinvald, A., Aertsen, A., 1996. Dynamics of ongoing activity: explanation of the large variability in evoked cortical responses. Science 273, 1868–1871.

Astrand, E., Wardak, C., Baraduc, P., Ben Hamed, S., 2016. Direct Two-Dimensional Access to the Spatial Location of Covert Attention in Macaque Prefrontal Cortex. Curr. Biol. CB 26, 1699–1704.

Averbeck, B.B., Latham, P.E., Pouget, A., 2006. Neural correlations, population coding and computation. Nat. Rev. Neurosci. 7, 358–366.

Averbeck, B.B., Lee, D., 2006. Effects of noise correlations on information encoding and decoding. J. Neurophysiol. 95, 3633–3644.

Averbeck, B.B., Lee, D., 2003. Neural Noise and Movement-Related Codes in the Macaque Supplementary Motor Area. J. Neurosci. 23, 7630–7641.

Bair, W., Zohary, E., Newsome, W.T., 2001. Correlated firing in macaque visual area MT: time scales and relationship to behavior. J. Neurosci. Off. J. Soc. Neurosci. 21, 1676–1697.

Bedenbaugh, P., Gerstein, G.L., 1997. Multiunit normalized cross correlation differs from the average single-unit normalized correlation. Neural Comput. 9, 1265–1275.

Ben-Yishai, R., Bar-Or, R.L., Sompolinsky, H., 1995. Theory of orientation tuning in visual cortex. Proc. Natl. Acad. Sci. U. S. A. 92, 3844–3848.

Biswal, B., Yetkin, F.Z., Haughton, V.M., Hyde, J.S., 1995. Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. Magn. Reson. Med. 34, 537–541.

Bosking, W.H., Zhang, Y., Schofield, B., Fitzpatrick, D., 1997. Orientation Selectivity and the Arrangement of Horizontal Connections in Tree Shrew Striate Cortex. J. Neurosci. 17, 2112–2127.

Bowdle, T.A., Ward, R.J., 1989. Induction of anesthesia with small doses of sufentanil or fentanyl: dose versus EEG response, speed of onset, and thiopental requirement. Anesthesiology 70, 26–30.

Briggs, F., Callaway, E.M., 2005. Laminar Patterns of Local Excitatory Input to Layer 5 Neurons in Macaque Primary Visual Cortex. Cereb. Cortex N. Y. N 1991 15, 479–488.

Bryant, H.L., Marcos, A.R., Segundo, J.P., 1973. Correlations of neuronal spike discharges produced by monosynaptic connections and by common inputs. J. Neurophysiol. 36, 205–225.

Chang, C., Leopold, D.A., Schölvinck, M.L., Mandelkow, H., Picchioni, D., Liu, X., Ye, F.Q., Turchi, J.N., Duyn, J.H., 2016. Tracking brain arousal fluctuations with fMRI. Proc. Natl. Acad. Sci. U. S. A. 113, 4518–4523.

Cohen, M.R., Kohn, A., 2011. Measuring and interpreting neuronal correlations. Nat. Neurosci. 14, 811–819.

Cohen, M.R., Maunsell, J.H.R., 2011. When attention wanders: how uncontrolled fluctuations in attention affect performance. J. Neurosci. Off. J. Soc. Neurosci. 31, 15802–15806.

Cohen, M.R., Maunsell, J.H.R., 2009a. Attention improves performance primarily by reducing interneuronal correlations. Nat. Neurosci. 12, 1594–1600.

Cohen, M.R., Maunsell, J.H.R., 2009b. Attention improves performance primarily by reducing interneuronal correlations. Nat. Neurosci. 12, 1594–1600.

Cohen, M.R., Newsome, W.T., 2008. Context-dependent changes in functional circuitry in visual area MT. Neuron 60, 162–173.

Constantinidis, C., Franowicz, M.N., Goldman-Rakic, P.S., 2001. Coding Specificity in Cortical Microcircuits: A Multiple-Electrode Analysis of Primate Prefrontal Cortex. J. Neurosci. 21, 3646–3655.

Constantinidis, C., Goldman-Rakic, P.S., 2002. Correlated discharges among putative pyramidal neurons and interneurons in the primate prefrontal cortex. J. Neurophysiol. 88, 3487–3497.

Constantinople, C.M., Bruno, R.M., 2011. Effects and Mechanisms of Wakefulness on Local Cortical Networks. Neuron 69, 1061–1068.

Crochet, S., Petersen, C.C.H., 2006. Correlating whisker behavior with membrane potential in barrel cortex of awake mice. Nat. Neurosci. 9, 608–610.

Damoiseaux, J.S., Rombouts, S.A.R.B., Barkhof, F., Scheltens, P., Stam, C.J., Smith, S.M., Beckmann, C.F., 2006. Consistent resting-state networks across healthy subjects. Proc. Natl. Acad. Sci. U. S. A. 103, 13848–13853.

Dombeck, D.A., Graziano, M.S., Tank, D.W., 2009. Functional Clustering of Neurons in Motor Cortex Determined by Cellular Resolution Imaging in Awake Behaving Mice. J. Neurosci. 29, 13751–13760.

Downer, J.D., Rapone, B., Verhein, J., O'Connor, K.N., Sutter, M.L., 2017. Feature-Selective Attention Adaptively Shifts Noise Correlations in Primary Auditory Cortex. J. Neurosci. 37, 5378–5392.

Dragoi, V., Sharma, J., Miller, E.K., Sur, M., 2002. Dynamics of neuronal sensitivity in visual cortex and local feature discrimination. Nat. Neurosci. 5, 883–891.

Drummond, J.C., 2000. Monitoring depth of anesthesia: with emphasis on the application of the bispectral index and the middle latency auditory evoked response to the prevention of recall. Anesthesiology 93, 876–882.

Ecker, A.S., Berens, P., Cotton, R.J., Subramaniyan, M., Denfield, G.H., Cadwell, C.R., Smirnakis, S.M., Bethge, M., Tolias, A.S., 2014. State dependence of noise correlations in macaque primary visual cortex. Neuron 82, 235–248.

Ecker, A.S., Berens, P., Keliris, G.A., Bethge, M., Logothetis, N.K., Tolias, A.S., 2010. Decorrelated Neuronal Firing in Cortical Microcircuits. Science 327, 584–587.

Ecker, A.S., Berens, P., Tolias, A.S., Bethge, M., 2011. The effect of noise correlations in populations of diversely tuned neurons. J. Neurosci. Off. J. Soc. Neurosci. 31, 14272–14283.

Engel, T.A., Steinmetz, N.A., Gieselmann, M.A., Thiele, A., Moore, T., Boahen, K., 2016. Selective modulation of cortical state during spatial attention. Science 354, 1140–1144.

Espinosa, I.E., Gerstein, G.L., 1988. Cortical auditory neuron interactions during presentation of 3-tone sequences: effective connectivity. Brain Res. 450, 39–50.

Ferezou, I., Haiss, F., Gentet, L.J., Aronoff, R., Weber, B., Petersen, C.C.H., 2007. Spatiotemporal dynamics of cortical sensorimotor integration in behaving mice. Neuron 56, 907–923.

Ferster, D., Miller, K.D., 2000. Neural mechanisms of orientation selectivity in the visual cortex. Annu. Rev. Neurosci. 23, 441–471.

Fox, M.D., Corbetta, M., Snyder, A.Z., Vincent, J.L., Raichle, M.E., 2006. Spontaneous neuronal activity distinguishes human dorsal and ventral attention systems. Proc. Natl. Acad. Sci. U. S. A. 103, 10046–10051.

Fox, M.D., Snyder, A.Z., Vincent, J.L., Corbetta, M., Van Essen, D.C., Raichle, M.E., 2005. The human brain is intrinsically organized into dynamic, anticorrelated functional networks. Proc. Natl. Acad. Sci. U. S. A. 102, 9673–9678.

Fox, M.D., Snyder, A.Z., Vincent, J.L., Raichle, M.E., 2007. Intrinsic fluctuations within cortical systems account for intertrial variability in human behavior. Neuron 56, 171–184.

Froudarakis, E., Berens, P., Ecker, A.S., Cotton, R.J., Sinz, F.H., Yatsenko, D., Saggau, P., Bethge, M., Tolias, A.S., 2014. Population code in mouse V1 facilitates read-out of natural scenes through increased sparseness. Nat. Neurosci. 17, 851–857.

Gawne, T.J., Kjaer, T.W., Hertz, J.A., Richmond, B.J., 1996. Adjacent visual cortical complex cells share about 20% of their stimulus-related information. Cereb. Cortex N. Y. N 1991 6, 482–489.

Gawne, T.J., Richmond, B.J., 1993. How independent are the messages carried by adjacent inferior temporal cortical neurons? J. Neurosci. Off. J. Soc. Neurosci. 13, 2758–2771.

Gentet, L.J., Avermann, M., Matyas, F., Staiger, J.F., Petersen, C.C.H. (Eds.), 2010. Membrane potential dynamics of GABAergic neurons in the barrel cortex of behaving mice. Neuron.

Gilbert, C., Wiesel, T., 1983. Clustered intrinsic connections in cat visual cortex. J. Neurosci. 3, 1116–1133.

Goris, R.L.T., Movshon, J.A., Simoncelli, E.P., 2014. Partitioning neuronal variability. Nat. Neurosci. 17, 858–865.

Greenberg, D.S., Houweling, A.R., Kerr, J.N.D., 2008. Population imaging of ongoing neuronal activity in the visual cortex of awake rats. Nat. Neurosci. 11, 749–751.

Greicius, M.D., Krasnow, B., Reiss, A.L., Menon, V., 2003. Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. Proc. Natl. Acad. Sci. U. S. A. 100, 253–258.

Greicius, M.D., Menon, V., 2004. Default-Mode Activity during a Passive Sensory Task: Uncoupled from Deactivation but Impacting Activation. J. Cogn. Neurosci. 16, 1484–1492.

Gu, Y., Liu, S., Fetsch, C.R., Yang, Y., Fok, S., Sunkara, A., DeAngelis, G.C., Angelaki, D.E., 2011. Perceptual learning reduces interneuronal correlations in macaque visual cortex. Neuron 71, 750–761.

Gutnisky, D.A., Dragoi, V., 2008. Adaptive coding of visual information in neural populations. Nature 452, 220–224.

Hampson, M., Peterson, B.S., Skudlarski, P., Gatenby, J.C., Gore, J.C., 2002. Detection of functional connectivity using temporal correlations in MR images. Hum. Brain Mapp. 15, 247–262.

Hansen, B.J., Chelaru, M.I., Dragoi, V., 2012. Correlated Variability in Laminar Cortical Circuits. Neuron 76, 590–602.

Harris, K.D., Thiele, A., 2011. Cortical state and attention. Nat. Rev. Neurosci. 12, 509–523.

Herrero, J.L., Gieselmann, M.A., Sanayei, M., Thiele, A., 2013. Attention-induced variance and noise correlation reduction in macaque V1 is mediated by NMDA receptors. Neuron 78, 729–739.

Herrero, J.L., Roberts, M.J., Delicato, L.S., Gieselmann, M.A., Dayan, P., Thiele, A., 2008. Acetylcholine contributes through muscarinic receptors to attentional modulation in V1. Nature 454, 1110–1114.

Huang, X., Lisberger, S.G., 2009. Noise Correlations in Cortical Area MT and Their Potential Impact on Trial-by-Trial Variation in the Direction and Speed of Smooth-Pursuit Eye Movements. J. Neurophysiol. 101, 3012–3030.

Kanitscheider, I., Coen-Cagli, R., Pouget, A., 2015. Origin of information-limiting noise correlations. Proc. Natl. Acad. Sci. U. S. A. 112, E6973-6982.

Karube, F., Kisvárday, Z.F., 2011. Axon Topography of Layer IV Spiny Cells to Orientation Map in the Cat Primary Visual Cortex (Area 18). Cereb. Cortex 21, 1443–1458.

Kenet, T., Bibitchkov, D., Tsodyks, M., Grinvald, A., Arieli, A., 2003. Spontaneously emerging cortical representations of visual attributes. Nature 425, 954–956.

Kerr, J.N.D., de Kock, C.P.J., Greenberg, D.S., Bruno, R.M., Sakmann, B., Helmchen, F., 2007. Spatial Organization of Neuronal Population Responses in Layer 2/3 of Rat Barrel Cortex. J. Neurosci. 27, 13316–13328.

Kohn, A., Smith, M.A., 2005. Stimulus Dependence of Neuronal Correlation in Primary Visual Cortex of the Macaque. J. Neurosci. 25, 3661–3673.

Kohn, A., Zandvakili, A., Smith, M.A., 2009. Correlations and brain states: from electrophysiology to functional imaging. Curr. Opin. Neurobiol. 19, 434–438.

Komiyama, T., Sato, T.R., O'Connor, D.H., Zhang, Y.-X., Huber, D., Hooks, B.M., Gabitto, M., Svoboda, K., 2010. Learning-related fine-scale specificity imaged in motor cortex circuits of behaving mice. Nature 464, 1182–1186.

Laufs, H., Krakow, K., Sterzer, P., Eger, E., Beyerle, A., Salek-Haddadi, A., Kleinschmidt, A., 2003. Electroencephalographic signatures of attentional and cognitive default modes in spontaneous brain activity fluctuations at rest. Proc. Natl. Acad. Sci. 100, 11053–11058.

Lee, D., Port, N.L., Kruse, W., Georgopoulos, A.P., Neurology, 1998. Variability and correlated noise in the discharge of neurons in motor and parietal areas of the primate cortex. J Neurosci 18:1161–1170.

Liu, X., de Zwart, J.A., Schölvinck, M.L., Chang, C., Ye, F.Q., Leopold, D.A., Duyn, J.H., 2018. Subcortical evidence for a contribution of arousal to fMRI studies of brain activity. Nat. Commun. 9.

Ly, C., Middleton, J.W., Doiron, B., 2012. Cellular and circuit mechanisms maintain low spike co-variability and enhance population coding in somatosensory cortex. Front. Comput. Neurosci. 6, 7.

Meyers, E.M., Qi, X.-L., Constantinidis, C., 2012. Incorporation of new information into prefrontal cortical activity after learning working memory tasks. Proc. Natl. Acad. Sci. U. S. A. 109, 4651–4656.

Mitchell, J.F., Sundberg, K.A., Reynolds, J.H., 2009. Spatial attention decorrelates intrinsic activity fluctuations in macaque area V4. Neuron 63, 879–888.

Moreno-Bote, R., Beck, J., Kanitscheider, I., Pitkow, X., Latham, P., Pouget, A., 2014. Information-limiting correlations. Nat. Neurosci. 17, 1410.

Muller, J.R., 1999. Rapid Adaptation in Visual Cortex to the Structure of Images. Science 285, 1405–1408.

Nandy, A.S., Nassi, J.J., Reynolds, J.H., 2017. Laminar Organization of Attentional Modulation in Macaque Visual Area V4. Neuron 93, 235–246.

Nauhaus, I., Busse, L., Carandini, M., Ringach, D.L., 2009. Stimulus contrast modulates functional connectivity in visual cortex. Nat. Neurosci. 12, 70–76.

Nevet, A., Morris, G., Saban, G., Arkadir, D., Bergman, H., 2007. Lack of Spike-Count and Spike-Time Correlations in the Substantia Nigra Reticulata Despite Overlap of Neural Responses. J. Neurophysiol. 98, 2232–2243.

Ni, A.M., Ruff, D.A., Alberts, J.J., Symmonds, J., Cohen, M.R., 2018. Learning and attention reveal a general relationship between population activity and behavior. Science 359, 463–465.

Poort, J., Roelfsema, P.R., 2009. Noise correlations have little influence on the coding of selective attention in area V1. Cereb. Cortex N. Y. N 1991 19, 543–553.

Poulet, J.F.A., Petersen, C.C.H., 2008. Internal brain state regulates membrane potential synchrony in barrel cortex of behaving mice. Nature 454, 881–885.

Raichle, M.E., 2015. The brain's default mode network. Annu. Rev. Neurosci. 38, 433–447.

Raichle, M.E., MacLeod, A.M., Snyder, A.Z., Powers, W.J., Gusnard, D.A., Shulman, G.L., 2001. A default mode of brain function. Proc. Natl. Acad. Sci. U. S. A. 98, 676–682.

Reich, D.S., 2001. Independent and Redundant Information in Nearby Cortical Neurons. Science 294, 2566–2568.

Reimer, J., Froudarakis, E., Cadwell, C.R., Yatsenko, D., Denfield, G.H., Tolias, A.S., 2014. Pupil fluctuations track fast switching of cortical states during quiet wakefulness. Neuron 84, 355–362.

Renart, A., de la Rocha, J., Bartho, P., Hollender, L., Parga, N., Reyes, A., Harris, K.D., 2010. The asynchronous state in cortical circuits. Science 327, 587–590.

Reynolds, J.H., Chelazzi, L., 2004. ATTENTIONAL MODULATION OF VISUAL PROCESSING. Annu. Rev. Neurosci. 27, 611–647.

Rosenbaum, R.J., Trousdale, J., Josić, K., 2010. Pooling and correlated neural activity. Front. Comput. Neurosci. 4, 9.

Schneidman, E., Bialek, W., Berry, M.J., 2003. Synergy, Redundancy, and Independence in Population Codes. J. Neurosci. 23, 11539–11553.

Schölvinck, M.L., Saleem, A.B., Benucci, A., Harris, K.D., Carandini, M., 2015. Cortical state determines global variability and correlations in visual cortex. J. Neurosci. Off. J. Soc. Neurosci. 35, 170–178.

Schwender, D., Rimkus, T., Haessler, R., Klasing, S., Pöppel, E., Peter, K., 1993. EFFECTS OF INCREASING DOSES OF ALFENTANIL, FENTANYL AND MORPHINE ON MID-LATENCY AUDITORY EVOKED POTENTIALS. BJA Br. J. Anaesth. 71, 622–628.

Seriès, P., Latham, P.E., Pouget, A., 2004. Tuning curve sharpening for orientation selectivity: coding efficiency and the impact of correlations. Nat. Neurosci. 7, 1129–1135.

Shadlen, M.N., Newsome, W.T., 1998. The variable discharge of cortical neurons: implications for connectivity, computation, and information coding. J. Neurosci. Off. J. Soc. Neurosci. 18, 3870–3896.

Shamir, M., Sompolinsky, H., 2004. Nonlinear Population Codes. Neural Comput. 16, 1105–1136.

Sharpee, T.O., Sugihara, H., Kurgansky, A.V., Rebrik, S.P., Stryker, M.P., Miller, K.D., 2006. Adaptive filtering enhances information transmission in visual cortex. Nature 439, 936–942.

Shulman, G.L., Fiez, J.A., Corbetta, M., Buckner, Y.L., Miezin, F.M., Raichle, M.E., Petersen, S.E., 1997. Common blood flow changes across visual tasks:, I. Increases in subcortical structures and cerebellum but not in nonvisual cortex. J. Cogn. Neurosci. 624–647.

Smith, M.A., Kohn, A., 2008. Spatial and Temporal Scales of Neuronal Correlation in Primary Visual Cortex. J. Neurosci. 28, 12591–12603.

Smith, M.A., Sommer, M.A., 2013. Spatial and temporal scales of neuronal correlation in visual area V4. J. Neurosci. Off. J. Soc. Neurosci. 33, 5422–5432.

Snippe, H.P., Koenderink, J.J., 1992. Information in channel-coded systems: correlated receivers. Biol. Cybern. 67, 183–190.

Sompolinsky, H., Yoon, H., Kang, K., Shamir, M., 2001. Population coding in neuronal systems with correlated noise. Phys. Rev. E Stat. Nonlin. Soft Matter Phys. 64, 051904.

Stark, E., Globerson, A., Asher, I., Abeles, M., 2008. Correlations between groups of premotor neurons carry information about prehension. J. Neurosci. Off. J. Soc. Neurosci. 28, 10618–10630.

Thiele, A., Hoffmann, K.-P., 2008. Neuronal firing rate, inter-neuron correlation and synchrony in area MT are correlated with directional choices during stimulus and reward expectation. Exp. Brain Res. 188, 559–577.

Tolhurst, D.J., Movshon, J.A., Dean, A.F., 1983. The statistical reliability of signals in single neurons in cat and monkey visual cortex. Vision Res. 23, 775–785.

Tremblay, S., Pieper, F., Sachs, A., Martinez-Trujillo, J., 2015. Attentional filtering of visual information by neuronal ensembles in the primate lateral prefrontal cortex. Neuron 85, 202–215.

Ts'o, D.Y., Gilbert, C.D., Wiesel, T.N., 1986. Relationships between horizontal interactions and functional architecture in cat striate cortex as revealed by cross-correlation analysis. J. Neurosci. 6, 1160–1170.

Turchi, J., Chang, C., Ye, F.Q., Russ, B.E., Yu, D.K., Cortes, C.R., Monosov, I.E., Duyn, J.H., Leopold, D.A., 2018. The Basal Forebrain Regulates Global Resting-State fMRI Fluctuations. Neuron 97, 940-952.e4.

Vaadia, E., Haalman, I., Abeles, M., Bergman, H., Prut, Y., Slovin, H., Aertsen, A., 1995. Dynamics of neuronal interactions in monkey cortex in relation to behavioural events. Nature 373, 515–518.

Van de Ville, D., Britz, J., Michel, C.M., 2010. EEG microstate sequences in healthy humans at rest reveal scale-free dynamics. Proc. Natl. Acad. Sci. U. S. A. 107, 18179–18184.

Vincent, J.L., Patel, G.H., Fox, M.D., Snyder, A.Z., Baker, J.T., Van, D.E., Zempel, J.M., Snyder, L.H., Corbetta, M., Raichle, M.E., 2007. Intrinsic functional architecture in the anaesthetized monkey brain. Nature 447, 83–86.

Vinck, M., Batista-Brito, R., Knoblich, U., Cardin, J.A., 2015. Arousal and locomotion make distinct contributions to cortical activity patterns and visual encoding. Neuron 86, 740–754.

Wilke, S.D., Eurich, C.W., 2001. Representational Accuracy of Stochastic Neural Populations.

Womelsdorf, T., Schoffelen, J.-M., Oostenveld, R., Singer, W., Desimone, R., Engel, A.K., Fries, P., 2007. Modulation of Neuronal Interactions Through Neuronal Synchronization. Science 316, 1609–1612.

Zohary, E., Shadlen, M.N., Newsome, W.T., 1994. Correlated neuronal discharge rate and its implications for psychophysical performance. Nature 370, 140–143.

Chapter II

Interneuronal correlations dynamically adjust to task demands at multiple time-scales

Interneuronal correlations dynamically adjust to task demands at multiple time-scales

Ben Hadj Hassen[1], S., Gaillard[1], C., Astrand[1,2], E., Wardak[1,3], C., Ben Hamed[1], S.

1. Institut des Sciences Cognitives Marc Jeannerod, CNRS, UMR5229, 67 Boulevard Pinel, 69675 Bron Cedex, France

2. Mälardalen University, IDT, Högskoleplan 1, 721 23 Västerås, Sweden

3. Imagerie et Cerveau (iBrain), 10 Boulevard Tonnellé 37032 Tours Cedex 1, France

Lead contact: Suliann Ben Hamed, benhamed@isc.cnrs.fr

Corresponding author: Suliann Ben Hamed, benhamed@isc.cnrs.fr; Sameh Ben Hadj Hassen, sameh.ben-hadj@isc.cnrs.fr

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Abstract

Functional neuronal correlations between pairs of neurons are thought to play an important role in neuronal information processing and optimal neuronal computations during attention, perception, decision-making and learning. Here, we report dynamic changes in prefrontal neuronal noise correlations at multiple time-scales, as a function of task contingencies. Specifically, we record neuronal activity from the macaque frontal eye fields, a cortical region at the source of spatial attention top-down control, while the animals are engaged in tasks of varying cognitive demands. First, we show that noise correlations decrease as cognitive engagement and task demands increase, both across tasks and within-trials. Second, we demonstrate, for the first time, a rhythmic modulation of noise correlations in the alpha and the beta frequency ranges that account both for overt behavioral performance and for layer specific modulations in spike-field coherence. All this taken together demonstrates a strong functional role of noise correlations in cognitive flexibility.

I. *Introduction*

Optimal behavior is the result of interactions between neurons both within and across brain areas. Identifying how these neuronal interactions flexibly adjust to the ongoing behavioral demand is key to understand the neuronal processes and computations underlying optimal behavior. Several studies have demonstrated that functional neuronal correlations between pairs of neurons, otherwise known as noise correlations, play an important role in perception and decision-making (Ts'o et al., 1986; Engel et al., 1991; Ahissar et al., 1992; Zohary et al., 1994; Vaadia et al., 1995; Narayanan et Laubach 2006; Cohen et al., 2010; Poulet et Petersen 2008; Stark et al., 2008). Specifically, several experimental and theoretical studies show that noise correlations have an impact on the amount of information that can be decoded for neuronal populations (Abbott et Dayan 1999; Zohary et al., 1994; Sompolinsky et al. 2001; Averbeck et al., 2006) as well as on overt behavioral performance (Zohary et al., 1994; Abbott et Dayan 1999; Sompolinsky et al., 2001; Averbeck et al., 2006; Ecker et al., 2011; Moreno-Bote et al., 2014; Ekstrom et al., 2008). As a result, understanding how noise correlations dynamically adjust to task demands is a key step toward clarifying how neural circuits dynamically control information transfer, thereby optimizing behavioral performance.

Several sources of noise correlations have been proposed, arising from shared connectivity (Shadlen and Newsome, 1998), global fluctuations in the excitability of cortical circuits (Ecker et al. 2014; Goris et al., 2014), feedback signals (Wimmer et al., 2015) or internal areal dynamics (Ben-Yishai et al., 1995; Litwin-Kumar et Doiron 2012; Ly et al., 2012), or bottom-up peripheral sensory processing (Kanitscheider et al., 2015). From a cognitive point of view, noise correlations have been shown to change as a function of spatial attention (Cohen et Maunsell 2009), spatial memory (Meyers et al., 2012) and learning (Gu et al., 2011; Ni et al., 2018), suggesting that they are subject both to rapid dynamic changes as well as to longer term changes, supporting optimal neuronal computations (Ni et al., 2018).

Here, we focus onto how multiple task contingencies induce dynamic changes in prefrontal neuronal noise correlations at multiple time-scales. Specifically, we record neuronal activity from the macaque frontal eye fields, a cortical region which has been shown to be at the source of spatial attention top-down control (Buschman et Miller 2007; Wardak et al., 2006; Ibos et al., 2013; Ekstrom et al., 2008) while the animals are engaged in tasks of varying cognitive demands, as assessed by their overt behavioral performance. Overall, we demonstrate that noise correlations dynamically adjust to the cognitive demand, decreasing as cognitive engagement and task demands increase. These dynamical changes take place both

across task, as a function of task demands, and within trials, as a function of the probabilistic structure of the task, demonstrating a top-down control over this neuronal process. We also demonstrate, for the first time, rhythmic modulations of noise correlation in two specific functional frequency ranges: the alpha and beta frequency ranges. Crucially, these rhythmic modulations in noise correlations account both for overt behavioral performance and for layer specific modulations in spike-field coherence. All this taken together demonstrates a strong functional role of noise correlations in cognitive flexibility. These findings are discussed in relation with previously reported functional and structural sources of variations in noise correlation and a comprehensive model of shared population neuronal variability is proposed.

II. Method

Ethical statement

All procedures were in compliance with the guidelines of European Community on animal care (Directive 2010/63/UE of the European Parliament and the Council of 22 September 2010 on the protection of animals used for scientific purposes) and authorized by the French Committee on the Ethics of Experiments in Animals (C2EA) CELYNE registered at the national level as C2EA number 42 (protocole C2EA42-13-02-0401-01).

Surgical procedure:

As in Astrand et al. (2016), two male rhesus monkeys (Macaca mulatta) weighing between 6-8 kg underwent a unique surgery during which they were implanted with two MRI compatible PEEK recording chambers placed over the left and the right FEF hemispheres respectively (figure 1a), as well as a head fixation post. Gas anesthesia was carried out using Vet-Flurane, 0.5 – 2% (Isofluranum 100%) following an induction with Zolétil 100 (Tiletamine at 50mg/ml, 15mg/kg and Zolazepam, at 50mg/ml, 15mg/kg). Post-surgery pain was controlled with a morphine pain-killer (Buprecare, buprenorphine at 0.3mg/ml, 0.01mg/kg), 3 injections at 6 hours interval (first injection at the beginning of the surgery) and a full antibiotic coverage was provided with Baytril 5% (a long action large spectrum antibiotic, Enrofloxacin 0.5mg/ml) at 2.5mg/kg, one injection during the surgery and thereafter one each day during 10 days. A 0.6mm isomorphic anatomical MRI scan was acquired post surgically on a 1.5T Siemens Sonata MRI scanner, while a high-contrast oil filled grid (mesh of holes at a resolution of 1mmx1mm) was placed in each recording chamber, in the same orientation as the final recording grid. This allowed a precise

localization of the arcuate sulcus and surrounding gray matter underneath each of the recording chambers. The FEF was defined as the anterior bank of the arcuate sulcus and we specifically targeted those sites in which a significant visual and/or oculomotor activity was observed during a memory guided saccade task at 10 to 15° of eccentricity from the fixation point (figure 1A). In order to maximize task-related neuronal information at each of the 24-contacts of the recording probes, we only recorded from sites with task-related activity observed continuously over at least 3 mm of depth.

Behavioral task:

During a given experimental session, the monkeys were placed in front of a computer screen (1920x1200 pixels and a refresh rate of 60 Hz) with their head fixed. Their water intake was controlled so that their initial daily intake was covered by their performance in the task, on a trial by trial basis. This quantity was complemented as follows. On good performance sessions, monkeys received fruit and water complements. On bad performance sessions, water complements were provided at a distance from the end of the session. Each recording session consisted of random alternations of three different tasks (see below and figure 1b), so as to control for possible time in the session or task order effects. For all tasks, to initiate a trial, the monkeys had to hold a bar in front of the animal chair, thus interrupting an infrared beam. (1) ***Fixation Task*** (figure 1B.1): A red fixation cross (0.7x0.7°), appeared in the center of the screen and the monkeys were required to hold fixation during a variable interval randomly ranging between 7000 and 9500ms, within a fixation window of 1.5x1.5°, until the color change of the central cross. At this time, the monkeys had to release the bar within 150-800 ms after color change. Success conditioned reward delivery. (2) ***Target detection Task*** (figure 1B.2): A red fixation cross (0.7x0.7°), appeared in the center of the screen and the monkeys were required to hold fixation during a variable interval ranging between 1300 and 3400 ms, within a fixation window of 1.5x1.5°, until a green squared target (0.28x0.28°) was presented for 100 ms in one of four possible positions ((10°,10°), (-10°,10°), (-10°,-10°) and (10°,-10°)) in a randomly interleaved order. At this time, the monkeys had to release the bar within 150-800 ms after target onset. Success conditioned reward delivery. (3) ***Memory-guided saccade Task*** (figure 1B.3): A red fixation cross (0.7x0.7°) appeared in the center of the screen and the monkeys were required to hold fixation for 500 msec, within a fixation window of 1.5x1.5°. A squared green cue (0.28x0.28°) was then flashed for 100ms at one of four possible locations ((10°, 10°), (-10°, 10°), (-10°,-10°) and (10°,-10°)). The monkeys had to continue maintain fixation on the central fixation point for another 700–1900

ms until the fixation point disappeared. The monkeys were then required to make a saccade towards the memorized location of the cue within 500-800ms from fixation point disappearance, and a spatial tolerance of 4°x4°. On success, a target, identical to the cue was presented at the cued location and the monkeys were required to fixate it and detect a change in its color by a bar release within 150-800 ms from color change. Success in all of these successive requirements conditioned reward delivery.

Neural recordings

On each session, bilateral simultaneous recordings in the two FEFs were carried out using two 24- contact Plexon U-probes. The contacts had an interspacing distance of 250 µm. Neural data was acquired with the Plexon Omniplex® neuronal data acquisition system. The data was amplified 400 times and digitized at 40,000 Hz. The MUA neuronal data was high-pass filtered at 300 Hz. The LFP neuronal data was filtered between 0.5 and 300 Hz. In the present paper, all analyses are performed on the multi-unit activity recorded on each of the 48 recording contacts. A threshold defining the multi-unit activity was applied independently for each recording contact and before the actual task-related recordings started. All further analyses of the data were performed in Matlab™ and using FieldTrip (Oostenveld et al., 2011) and the Wavelet Coherence Matlab Toolbox (Grinsted et al., 2004), both open source Matlab™ toolboxes.

Data Analysis

Data preprocessing. Overall, MUA recordings were collected from 48 recording channels on 26 independent recording sessions (13 for M1 and 13 for M2). We excluded from subsequent analyses all channels with less than 5 spikes per seconds. For each session, we identified the task-related channels based on a statistical change (one-way ANOVA, $p<0.05$) in the MUA neuronal activity in the memory-guided saccade task, in response to either cue presentation ([0 400] ms after cue onset) against a pre-cue baseline ([-100 0] ms relative to cue onset), or to saccade execution go signal and to saccade execution (i.e. fixation point off, [0 400] ms after go signal) against a pre-go signal baseline ([-100 0] ms relative to go signal), irrespective of the spatial configuration of the trial. In total, 671 channels were retained for further analyses out of 1248 channels.

Distance between recording sites. For each electrode, pairs of MUA recordings were classified along four possible distance categories: D1, spacing of 250 µm; D2, spacing of 500 µm; D3, spacing of 750 µm and D4, spacing of 1mm. These distances are an indirect proxy to

actual cortical distance, as the recordings were performed tangentially to cortical surface, i.e. more or less parallel to sulcal surface.

MUA spatial selectivity. FEF neurons are characterized by a strong visual, saccadic, spatial memory and spatial attention selectivity (Bruce et Goldberg 1985; Ibos et al., 2013; Astrand et al., 2015). We used a one-way ANOVA ($p<0.05$) to identify the spatially selective channels in response to cue presentation ([0 400] ms following cue onset) and to the saccade execution go signal ([0 400] ms following go signal).

Post-hoc t-tests served to further order, for each channels, the neuron's response in each visual quadrant from preferred (p1), to least preferred (p4). By convention, positive modulations were considered as preferred and negative modulations as least preferred. For example, in a given session, the MUA signal recorded on channel 1 of a probe placed in the left FEF, could have as best preferred position p1 the upper right quadrant, the next best preferred position p2 the lower right quadrant, the next preferred position p3 the upper left quadrant and the least preferred position p4 the lower left quadrant. The MUA signal recorded on channel 14 of this same probe, could have as best preferred position p1 the lower right quadrant, the next best preferred position p2 the upper right quadrant, the next preferred position p3 the lower left quadrant and the least preferred position p4 the upper left quadrant. Positions with no significant modulation in any task epoch were labeled as p0 (no selectivity for this position). Once this was done, for each electrode, pairs of MUA recordings were classified along two possible functional categories: pairs with the same spatial selectivity (SSS pairs, sharing the same p1) and pairs with different spatial selectivities (DSS pairs, such that the p1 of one MUA is a p0 for the other MUA). For the sake of clarity, we do not consider partial spatial selectivity pairs (such that the p1 of one MUA is a non-preferred, p2, p3 or p4 for the other MUA).

MUA layer attribution. As stated above, our recordings are not tangential to cortical surface. As a proxy to attribute a given recording channel to upper or lower cortical layers we proceeded as follows. For each electrode and each channel, we estimated, at the time of cue onset in the memory-guided saccade task (100ms-500ms from cue onset), the spike-field coherence in the alpha range (6 to 16 Hz) and the gamma range (40 to 60 Hz). Based on previous literature (Buffalo et al., 2011a), we used the ratio between the alpha and gamma spike field-coherence as a proxy to assign the considered LFP signals to a deep cortical layer site (high alpha / gamma spike-field coherence ratio) or to a superficial cortical layer site (low

alpha / gamma spike-field coherence ratio). We also categorized MUA signals into visual, visuo-motor and motor categories, as in Cohen et al. (2009). Briefly, average firing rates were computed in 3 epochs: [-100 0] ms before cue onset (baseline), [0 200] ms after cue onset (visual), and [0 200] ms before saccade onset (movement). Neurons with activity statistically significantly different from the baseline (Wilcoxon rank-sum test, $P < 0.05$) after cue onset were categorized as visual. Neurons with activity statistically significantly different from the baseline (Wilcoxon rank-sum test, $P < 0.05$) before saccade onset were categorized as oculomotor. Neurons that were active in both epochs were categorized as visuo-movement neurons. The LFP categorization along the alpha to gamma spike-field coherence ratio strongly coincided with the classification of the MUA signals into purely visual sites (low alpha and gamma spike-field coherence ratio, input FEF layers) and visuo-motor sites (high alpha and gamma spike-field coherence ratio, output FEF layers, figure 4).

Noise Correlations. The aim of the present work is to quantify task effects onto the spiking statistics of the FEF spiking activity during equivalent task-fixation epochs. The statistics that we discuss is that of noise correlations between the MUA activities on the different simultaneously recorded signals. For each channel, and each task, intervals of interest of 200ms were defined during the fixation epoch from 300 ms to 500 ms from eye fixation onset. Specifically, for each channel i, and each trial k, the average neuronal response $r_i(k)$ for this time interval was calculated and z-score normalized into $z_i(k)$, where $z_i(k)=r_i(k)-\mu_i/std_i$ and μ_i and std_i respectively correspond to the mean firing rate and standard deviation around this mean during the interval of interest of the channel of interest i. This z-score normalization allows to capture the changes in neuronal response variability independently of changes in mean firing rates. Noise correlations between pairs of MUA signals during the interval of interest were then defined as the Pearson correlation coefficient between the z-scored individual trial neuronal responses of each MUA signal over all trials. Only positive significant noise correlations are considered, unless stated otherwise. In any given recording session, noise correlations were calculated between MUA signals recorded from the same electrode, thus specifically targeting intra-cortical correlations. This procedure was applied independently for each task. Depending on the question being asked, noise correlations were either computed on activities aligned on fixation onset, or on activities aligned on target (Fixation and Target detection task) or saccade execution (memory guided saccade task) signals.

In order to control for the fact that the observed changes in noise correlations cannot be attributed to changes in other firing rate metrics, several statistics were also extracted, from comparable task epochs, from 300 to 500ms following trial initiation and fixation onset. None of these metrics were significantly affected by the task. Specifically, we analyzed (a) mean firing rate (ANOVA, $p>0.5$), (b) the standard error around this mean firing rate (ANOVA, $p>0.6$), and (c) the corresponding Fano factor (ANOVA, $p>0.7$). These data, reproducing previous reports (Cohen et Maunsell 2009) are not shown.

Oscillations in noise correlations. To measure oscillatory patterns in the noise correlation time-series data, we computed, for each task, and each session (N=12), noise correlations over time (over successive 200ms intervals, sliding by 10ms, running from 300ms to 1500ms following eye fixation onset for Fixation and Target detection tasks and from 300ms to 1500ms following cue offset form Memory-guided saccade task). A wavelet transform (Fieldtrip, Oostenveld et al., 2011) was then applied on each session's noise correlation time series. Statistical differences in the noise correlation power frequency spectra were assessed using a non-parametric Friedman test. When computing the noise correlations in time, we equalized the number of trials for all tasks and all conditions so as to prevent any bias that could be introduced by unequal numbers of trials. To control that oscillations in noise correlations in time cannot be attributed to changes in spiking activity, a wavelet analysis was also run onto MUA time series data (data not shown).

Spike field Coherence (SFC). In our study monkeys performed three tasks with different task engagement levels. For each selected channel, SFC spectra were calculated between the spiking activity obtained in one channel and the LFP activity from the next adjacent channel in the time interval running from 300ms to 1500ms following eye fixation onset (Fixation and Target detection task) or cue offset (Memory guided saccade task). We used a single Hanning taper and applied convolution transform to the Hanning-tapered trials. We equalized the number of trials for all tasks so as to prevent any bias that could be introduced by unequal numbers of trials. We used a 4 cycles length per frequency. The memory guided saccade task is known to involve spatial processes during the cue to target interval that bias spike field coherence. In this task, SFC was thus measured separately for trials in which the cued location matched the preferred spatial location of the channel and trials in which the cued location did not match the preferred spatial location of the channel. Statistics were computed across channels x sessions, using a non-parametric Friedman test.

Modulation of behavioral performance by phase of noise correlation alpha and beta rhythmicity. To quantify the effect of noise correlation oscillations onto behavioral performance, we used a complex wavelet transform analysis (Fieldtrip, Oostenveld et al. 2011) to compute, for each session and each task, in the noise correlations, the phase of the frequencies of interest (alpha / beta) following eye fixation onset (for the Fixation and Target detection tasks) or cue offset (for the Memory guided saccade task). For each session, we identified hit and miss trials falling at zero phase of the frequency of interest (+/- π /140) with respect to target presentation or fixation point offset time. In the fixation task, premature fixation aborts by anticipatory manual response or eye fixation failure were considered as misses. Hit rates (HR) were computed for this zero phase bin. We then shifted this phase window by π /70 steps and recalculated the HR, repeating this procedure to generate phase-detection HR functions, across all phases, for each frequency of interest (Fiebelkorn et al., 2013). For each session, the phase bin for which hit rate was maximal was considered as the optimal phase. The effect of a given frequency (alpha or beta) onto behavior corresponds to the difference between HR at this optimal phase and HR at the anti-optimal phase (optimal phase + π). To test for statistical significance, observed hit/miss phases were randomized across trials so as to shuffle the temporal relationship between phases and behavioral performance. This procedure was repeated 1000 times. 95% CI was then computed and compared to the observed behavioral data.

III. Results

Our main goal in this work is to examine how the degree of cognitive engagement and task demands impact the neuronal population state as assessed from interneuronal noise correlations. Cognitive engagement was operationalized through tasks of increasing behavioral requirements. The easiest task (***Fixation task***, figure 1B.1) was a central fixation task in which monkeys were required to detect an unpredictable change in color of the fixation point, by producing a manual response within 150 to 800ms from color change. The second task (***Target detection task***, figure 1B.2) added a spatial uncertainty on top of the temporal uncertainty of the event associated with the monkeys' response. This was a target detection task, in which the target could appear at one of four possible locations, at an unpredictable time from fixation onset. The monkeys had to respond to this target presentation by producing a manual response within 150 to 800ms from color change. In the third task (***Memory guided saccade task***, figure 1B.3), monkeys were required to hold the

position of a spatial cue in memory for 700 to 1900ms and to perform a saccade towards that memorized spatial location on the presentation of a go signal. This latter task thus involved a temporal uncertainty but no spatial uncertainty. However, in contrast with the previous tasks, it required the production of a spatially oriented oculomotor response rather than a simple manual response. Accordingly, both monkeys had higher performances on the memory guided saccade task than on the target detection task (Figure 1C, Wilcoxon rank sum test, Monkey 1, $p<0.01$, Monkey 2, $p<0.05$), and higher performances on the target detection task than on the fixation task (Wilcoxon rank sum test, $p<0.05$).

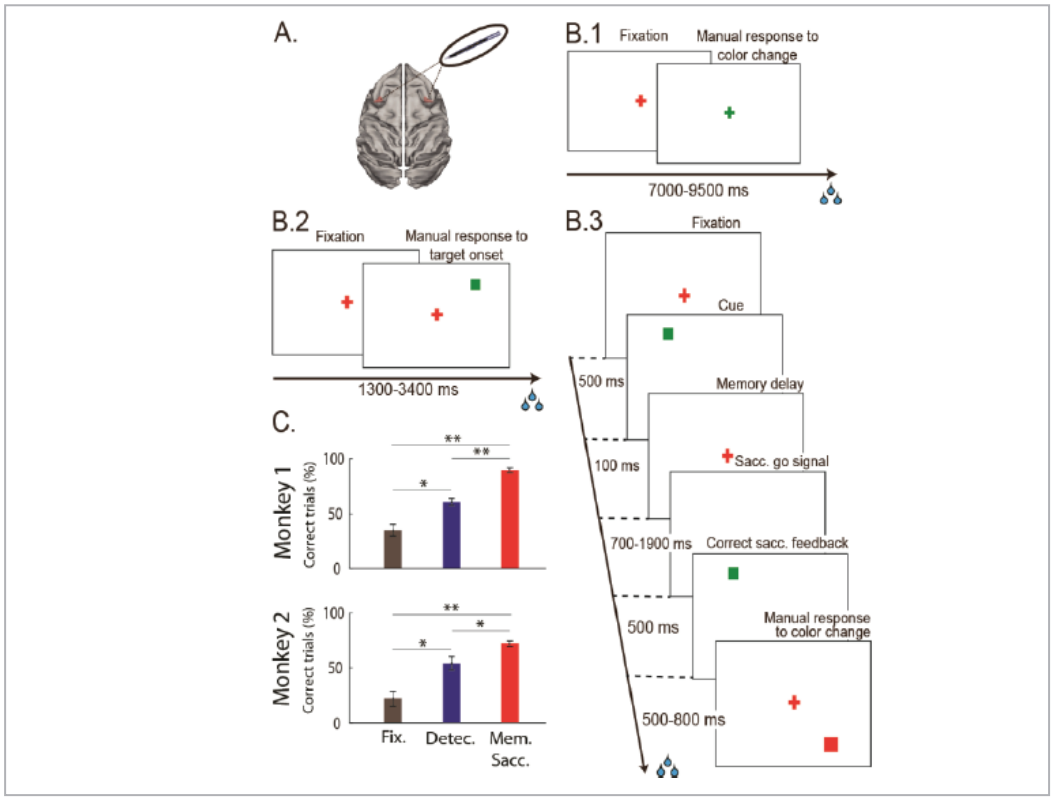

Figure 1: (A) Recordings sites. *On each session, 24-contact recording probes were placed in the left and right FEFs.* ***(B.1) Fixation task.*** *Monkeys had to fixate a red central cross and were rewarded for producing a manual response 150ms to800 ms following fixation cross color change.* ***(B.2) Target detection task.*** *Monkeys had to fixate a red central cross and were rewarded for producing a manual response 150ms to 800ms from the onset of a low luminosity target at an unpredictable location out of four possible locations on the screen.* ***(B.3) Memory-guided saccade task.*** *Monkeys had to fixate a red central cross. A visual cue was briefly flashed in one of four possible locations on the screen. Monkeys were required to hold fixation until the fixation cross disappeared and then produce a saccade to the spatial location indicated by the cue within 300ms from fixation point offset. On success, the cue re-appeared and the monkeys had to fixate it. They were then rewarded for producing a manual response 150ms to 800ms following the color change of this new fixation stimulus.* ***(C) Behavioral performance.*** *Average percentage of correct trials across sessions for each tasks and each monkey with associated standard errors.*

Neuronal recordings were performed in the prefrontal cortex, specifically in the frontal eye field (FEF, figure 1A), a structure known to play a key role in covert spatial attention (Ibos et al., 2013; Gregoriou et al., 2009,2012; Armstrong et al., 2009). In each session, multi-unit activity (MUA) and local field potential (LFP) were recorded bilaterally, while monkeys performed these three tasks. In the following, the noise correlations between the different prefrontal signals of the same hemisphere were computed on equivalent task fixation epochs, away from both sensory intervening events and motor responses. In a first step, we analyzed how these noise correlations varied both across tasks, as a function of cognitive engagement and within-tasks, as a function of the probabilistic structure of the task. In a second step, we describe the temporal oscillatory structure of noise correlations. We relate these rhythmic variations to cognitive engagement and we show that they correlate with changes in the coupling between local field potentials and MUA spiking activity, in specific functional frequency bands.

Noise correlations decrease as cognitive engagement and task requirements increase.

In order to characterize how inter-neuronal noise correlations vary as a function of cognitive engagement and task requirements, we proceeded as follows. In each session (n=26), noise correlations were computed between each pair of task-responsive channels (n=671, see Methods), over equivalent fixation task epochs, running from 300 to 500 ms after eye fixation onset. This epoch was at a distance from a possible visual or saccadic foveation response and in all three tasks, monkeys were requested to maintain fixation at this stage. It was also still early on in the trial, such that no intervening sensory event was to be expected by the monkey at this time. Importantly, fixation behavior, i.e. the distribution of eye position in within the fixation window, did not vary between the different tasks (Friedman test, $p<0.001$). As a result, and because tasks were presented in blocks, any difference in noise correlations across tasks during this "neutral" fixation epoch are to be attributed to general non-specific task effects, i.e. differences in the degree of cognitive engagement and task demands. Noise correlations were significantly different between tasks (Figure 2A, ANOVA, $p<0.001$). Specifically, they were higher in the fixation task than in the target detection task (Figure 2A, Wilcoxon rank sum test, $p<0.001$) and in the memory guided saccade task (Wilcoxon rank sum test, $p<0.001$). They were also significantly higher in the target detection task than in the memory guided saccade task (Wilcoxon rank sum test, $p<0.001$). Importantly, these significant changes in noise correlations existed in the absence of significant differences

in mean firing rate (ANOVA, p>0.5), standard error around this mean firing rate (ANOVA, p>0.6), and Fano factor (ANOVA, p>0.7, data not shwon). We thus describe that, in absence of any sensory or cognitive processing, noise correlations are strongly modulated by cognitive engagement and task demands.

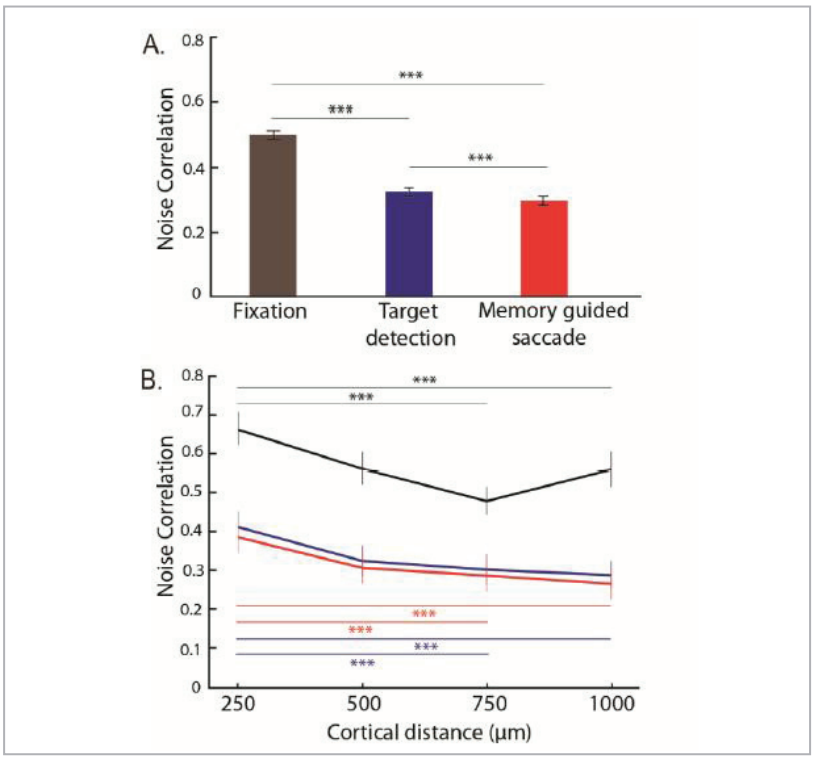

Figure2: *(A)* ***Noise correlations as a function of task****. Average noise correlations across sessions for each of the three tasks (mean +/- s.e., noise correlations calculated on the neuronal activities from 300 to 500 after eye fixation onset. Black: fixation task; blue: target detection task; red: memory guided saccade task. Stars indicate statistical significance following a one-way ANOVA; *p<0.05; **p<0.01; ***p<0.001. (B)* ***Noise correlations as a function of cortical distance.*** *Average noise correlations (mean +/- s.e.) across sessions, for each task (conventions as in (A)), from 300 ms to 500ms after eye fixation onset, as a function of distance between pairs of channels: 250µm; 500µm; 750µm; 1000µm. Stars indicate statistical significance following a two-way ANOVA and rank sum post-hoc tests; *p<0.05; **p<0.01; ***p<0.001.*

Cortical distance, spatial selectivity and cortical layer effects on noise correlations are task independent.

The task differences in noise correlations described above could reflect changes in the shared functional connectivity, within the large-scale parieto-frontal functional network the cortical region of interest belongs to (Shadlen and Newsome, 1998) or to global fluctuations in the excitability of cortical circuits (Schölvinck et al., 2015; Arieli et al., 1996). This large-scale hypothesis predicts that the observed changes in noise correlations are independent from

intrinsic connectivity as assessed by the distance, the spatial selectivity or cortical layer between the pairs of signals across which noise correlations are computed. Alternatively, these task differences in noise correlations could reflect a more complex reweighing of functional connectivity and the excitatory/inhibitory balance in the area of interest, due to local changes in the random shared fluctuations in the pre-synaptic activity of cortical neurons (Zohary et al., 1994; Bair et al., 2001; Bryant et al., 1973; Shadlen et Newsome 1998). This local hypothesis predicts that the observed changes in noise correlations depend onto intrinsic microscale connectivity. In the following, we characterize task differences in noise correlations as a function of cortical distance, spatial selectivity and cortical layer.

Cortical distance effects. Our recordings were performed as tangentially to FEF cortical surface as possible. The distance between the different recording probe contacts is thus a fair proxy to actual cortical tangential distance. Consistent with previous studies (Constantinidis et Goldman-Rakic 2002; Lee et al., 1998; Smith et Kohn 2008), noise correlations significantly decreased as the distance between the pair of signals across which noise correlations were computed increased (Figure 2B). Importantly, this distance effect was present for all tasks and expressed independently of the main task effect described above (2-way ANOVA, Task x Distance, Task effect: $p<0.001$; Distance effect: $p<0.001$, interaction: $p>0.05$). Post-hoc analyses indicate that this distance effect is statistically significant, for all tasks, beyond 500 µm (Wilcoxon rank sum test, Fixation task: $p<0.001$ for a cortical distance of 750 µm, $p<0.005$ for 1000 µm; Target detection task: $p<0.001$ for 750 µm, $p<0.001$ for 1000 µm; Memory-guided saccade task: $p<0.001$ for 750 µm, $p<0.001$ for 1000 µm).

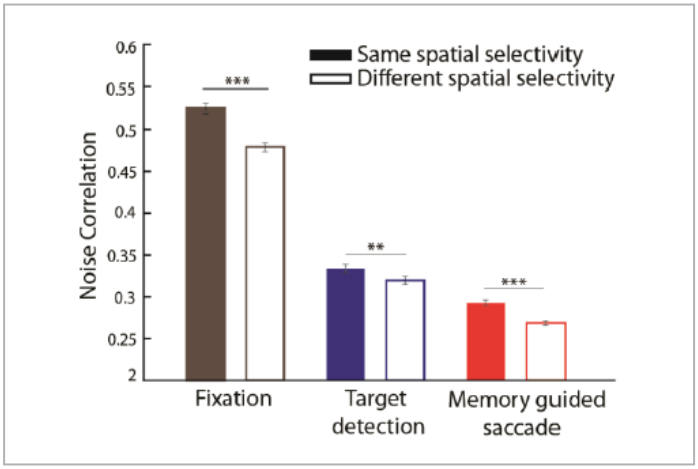

Figure3: Noise correlations as a function of spatial selectivity*. Average noise correlations (mean +/- s.e.) across sessions, for each tasks (conventions as in figure 2), from 300ms to 500ms after eye fixation onset, as a function of whether noise correlations are calculated over signals sharing the same spatial selectivity (full bars) or not (empty bars). Stars indicate statistical significance following a two-way ANOVA and rank sum post-hoc tests; *p<0.05; **p<0.01; ***p<0.001.*

Spatial selectivity effects. The spatial selectivity of each task-related MUA in response to cue presentation and saccade execution was assessed using an ANOVA (see methods). As described previously (Mohler et al., 1973; Bruce et Goldberg 1985), the receptive fields of FEF neurons are quite large and most MUA responded to cue presentation or saccade execution in more than one quadrant (94% of MUA). For each MUA, we further identified the visual quadrant that elicited maximal neuronal response to cue or saccade execution, as well as, whenever possible the visual quadrant that didn't elicit any response. In the following, and under the assumption of a higher functional connectivity between pairs of MUA sharing the same spatial selectivity, we compared noise correlations between pairs of neurons sharing the same preferred quadrant and pairs for which the preferred quadrant of one MUA matched the unresponsive quadrant of the other MUA. Consistent with previous studies (Bair et al., 2001), noise correlations were significantly lower for different spatial selectivity pairs than for same spatial selectivity pairs (Figure 3). This spatial selectivity effect was present for all tasks (2-way ANOVA, Task x Spatial selectivity, Task effect: $p<0.001$; Spatial selectivity effect: $p<0.001$). Post-hoc analyses indicate that this spatial selectivity effect is statistically significant for all tasks (Wilcoxon rank sum test, Fixation task: $p<0.001$; Target detection task: $p<0.01$; Memory-guided saccade task: $p<0.001$). However, spatial selectivity effects were not constant across tasks, possibly suggesting task-dependent functional changes in spatial selectivity based neuronal interactions (Task x Spatial selectivity interaction: $p<0.05$).

Cortical layer effects. FEF neurons are characterized by a strong visual, saccadic, spatial memory and spatial attention selectivity (Bruce et Goldberg 1985; Ibos et al., 2013; Astrand et al., 2015). Previous studies have shown that pure visual neurons are located in the input layers of the FEF while visuo-motor neurons are located in its output layers (Bruce et Goldberg 1985; Segraves et Goldberg 1987; Schall 1991; Schall et Hanes 1993; Schall et al., 1995; Schall et Thompson 1999). Independently, Buffalo et al. (2011) have shown that, in extrastriate area V4, the ratio between the alpha and gamma spike field coherence discriminated between LFP signals in deep (low alpha / gamma spike field coherence ratio) or superficial cortical layers (high alpha / gamma spike field coherence ratio). In our own data, because our recordings were performed tangentially to FEF cortical surface, we have no direct way of assigning the recorded MUAs to either superficial or deep cortical layers. However, the alpha / gamma spike field coherence ratio provides a very reliable segregation of visual

and viso-motor MUAs (figure 4A). We thus consider that, as has been described for area V4, this measure allows for a robust delineation of superficial and deep layers in area FEF. In the following, we computed inter-neuronal noise correlations between three different categories of pairs based on their assigned cortical layer: superficial/superficial pairs, superficial/deep pairs and deep/deep pairs, where superficial MUA correspond to predominantly visual, low alpha/gamma spike field coherence ratio signals and deep MUA correspond to predominantly visuo-motor, high alpha/gamma spike field coherence ratio signals. Noise correlations varied as a function of cortical layer (Figure 4B). This cortical layer effect was present for all tasks and expressed independently of the main task effect described above (2-way ANOVA, Task x Cortical layer, Task effect: $p<0.001$; Cortical layer effect: $p<0.001$). As for spatial selectivity, layer effects were not constant across tasks, possibly suggesting task-dependent functional changes in within and across layer neuronal interactions (interaction: $p<0.05$). Unexpectedly, belonging to the same layer cortical layer didn't systematically maximize noise correlations. Indeed, post-hoc analyses indicate significantly lower noise correlations between the superficial/superficial pairs as compared to the deep/deep pairs (Wilcoxon rank sum test, Fixation task: $p<0.05$; Target detection task: $p<0.05$; Memory-guided saccade task: $p<0.01$). Superficial/deep pairs sat in between these two categories and had significantly lower noise correlations than the deep/deep pairs (Wilcoxon rank sum test, Fixation task: $p<0.05$; Target detection task: $p<0.05$; Memory-guided saccade task: $p<0.01$) and higher noise correlations than the superficial/superficial pairs, though this difference was never significant.

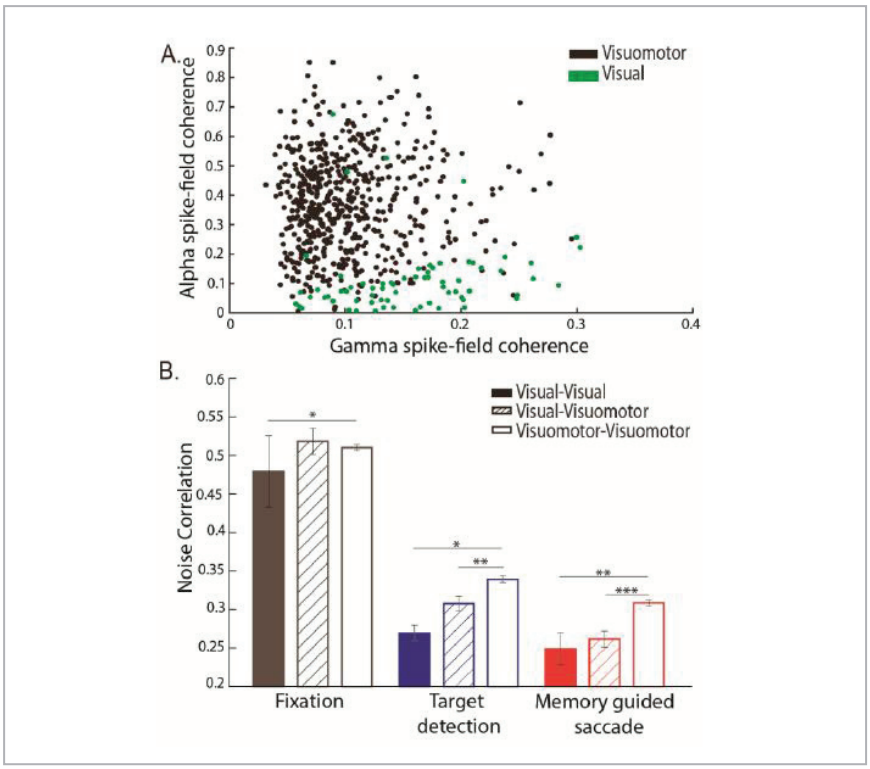

Figure 4: (A) Distribution of alpha spike-field coherence (6-16Hz) as a function of gamma (40-60Hz) spike-field coherence for visual and visuomotor frontal eye field sites. *Sites with visual selectivity but no motor selectivity (green, putative superficial sites) demonstrated stronger gamma-band spike-field coherence, whereas sites with visuomotor selectivity (black, putative deep sites) demonstrated stronger alpha-band spike-field coherence.* ***(B) Noise correlations as a function of pair functional selectivity.*** *Average of noise correlations (mean +/- s.e.) across sessions, for each task (conventions as in figure 2), from 300ms to 500ms after eye fixation onset, as a function of pair functional selectivity: visual-visual, visual-visuomotor, visuomotor-visuomotor. Stars indicate statistical significance following a two-way ANOVA and rank sum post-hoc tests; *p<0.05; **p<0.01; ***p<0.001.*

Overall, these observations support the co-existence of both a global large-scale change as well as a local change in functional connectivity. Indeed, task effects onto noise correlations build up onto cortical distance, spatial selectivity and cortical layer effects, indicating global fluctuations in the excitability of cortical circuits (Schölvinck et al., 2015; Arieli et al., 1996). On top of this global effect, we also note more complex changes as reflected from statistical interactions between Task and spatial selectivity or layer attribution effects. This points towards more local changes in neuronal interactions, based on both 1) functional neuronal properties such as spatial selectivity that may change across tasks (Womelsdorf et al., 2006,2008; Anton-Erxleben et al., 2007; Ben Hamed et al., 2002) and 2) the functional reweighing of top-down and buttom-up processes (Buschman et Miller 2007a; Ibos et al., 2013).

Impact of the probabilistic structure of the task onto noise correlations.

Up to now, we have shown that noise correlations vary as a function of cognitive engagement and task demands. This suggests an adaptive mechanism that adjusts noise correlations to the ongoing behavior. On task shifts, this mechanism probably builds up during the early trials of the new task, past trial history affecting noise correlations in the current trials. In Astrand et al. (2016) we show that, in a cued target detection task, while noise correlations are higher on miss trials than on hit trials, noise correlations are also higher on both hit and miss trials, when the previous trial was a miss as compared to when it was a hit. Here, one would expect that on the first trials of task shifts, noise correlations would be at an intermediate level between the previous and the ongoing task. Task shifts being extremely rare events in our experimental protocol, this cannot be confirmed. On top of this slow dynamics carry on effect, one can also expect faster dynamic adjustments to the probabilistic structure of the task. This is what we demonstrate below.

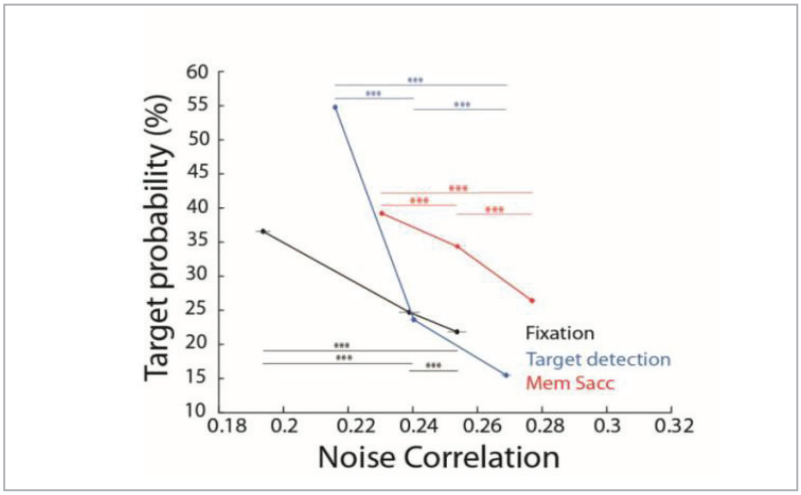

Figure 5: Noise correlations decrease as function of expected response probability. *Average noise correlations (mean +/- s.e.) across sessions, for each task (conventions as in figure 2), calculated on 200 ms before the target (Fixation and Target detection tasks) onset or saccade execution signal onset (memory guided saccade task), as a function of expected target probability. Each data point corresponds to noise correlations computed over trials of different fixation onset to event response intervals, i.e. over trials of different expected response probability. Stars indicate statistical significance following a two-way ANOVA and rank sum post-hoc tests; *p<0.05; **p<0.01; ***p<0.001.*

In each of the three tasks, target probability (saccade go signal probability in the case of the memory guided saccade task) varied as a function of time. As a result, early target onset trials had a different target probability than intermediate target onset trials than late target onset trials. Our prediction was that if monkeys had integrated the probabilistic structure of the task, this should reflect onto a dynamic adjustment of noise correlations as a

function of target probability. Figure 5 confirms this prediction. Specifically, for all tasks, noise correlations were lowest in task epochs with highest target probability (Wilcoxon non-parametric test, $p<0.001$ for all pair-wise comparisons). These variations between the highest and lowest target probability epochs were highly significant and in the order of the 15% or more (Fixation task: 15%, Target detection task: 40%, Memory-guided saccade task: 14%). This variation range was lower than the general task effect we describe above but yet quite similar across tasks. Overall, this indicates that noise correlations are dynamically adjusted to the task structure, and are lowest at the time of highest behavioral demand in the trial.

Rhythmic fluctuations in noise correlations.

Up to now, we have described within and across task-related variations in noise correlations, building up onto intrinsic connectivity influences as reflected by cortical distance, spatial selectivity and layer attribution effects. Looking at noise correlations in time (figure 6A) reveals an additional source of variation, namely rhythmic changes in noise correlation levels, phase locked to fixation onset (Fixation and target detection task) or cue presentation (Memory guided saccade task). These rhythmic fluctuations take place in two distinct frequency ranges: a high alpha frequency range (10-16 Hz) and a beta frequency range (20-30Hz), as quantified by a wavelet analysis (figure 6B). These oscillations can be described in all of the three tasks, this in spite of an overall higher background spectral power during the memory guided saccade task, both when noise correlations are calculated on trials in which spatial memory was instructed towards the preferred or the non-preferred location of the MUA signals (figure 6B, red and green curves respectively). Because spatial selective processes are at play in the memory guided saccade task, both for trials in which spatial memory is oriented towards the preferred MUA location (excitatory processes) or towards the non-preferred location (inhibitory processes), we will mostly focus on the fixation and the target detection tasks. When compensating the rhythmic modulations of noise correlations for background power levels (assuming an equal frequency power between all conditions beyond 30Hz), frequency power in the two ranges of interest are higher in the fixation task than in the target detection task (Friedman non-parametric test, all pairwise comparisons, $p<0.001$), in agreement with the proposal that cognitive flexibility coincides with lower amplitude beta oscillations (Engel et Fries 2010) and that attentional engagement coincides with lower amplitude alpha oscillations (Thut et al., 2006; Rihs et al., 2009). Importantly, these oscillations are absent from the raw MUA signals (Friedman non-parametric test, all pairwise comparisons, $p>0.2$), as well as when noise correlations are computed during the same task

epochs but from neuronal activities aligned onto target presentation (or saccade go signal in the memory guided saccade task, Friedman non-parametric test, all pairwise comparisons, $p>0.2$).

Importantly, in all of the three tasks, behavioral performance, defined as the proportion of correct trials as compared to error trials, varied as a function of alpha and beta noise correlation oscillations. Indeed, on a session by session basis, we could identify an optimal alpha (10-16Hz) phase for which the behavioral performance was maximized, in antiphase with a bad alpha phase, for which the behavioral performance was lowest (figure 6C). These effects were highest in the fixation task (34.6% variation in behavioral performance) and lowest though significant in the memory-guided saccade task (13.3% in the target detection task and 9.5% in the memory guided saccade task). Similarly, an optimal beta (20-30Hz) phase was also found to modulate behavioral performance in the same range as the observed alpha behavioral modulations (28.3% variation in behavioral performance in the fixation task, 19.2% in the target detection task and 11% in the memory guided saccade task). As a result, Alpha and beta oscillation phase in noise correlations were predictive of behavioral performance, and the strength of these effects co-varied with alpha and beta oscillation amplitude in noise correlations, being higher in the fixation task, than in the target detection task than in the memory guided saccade task.

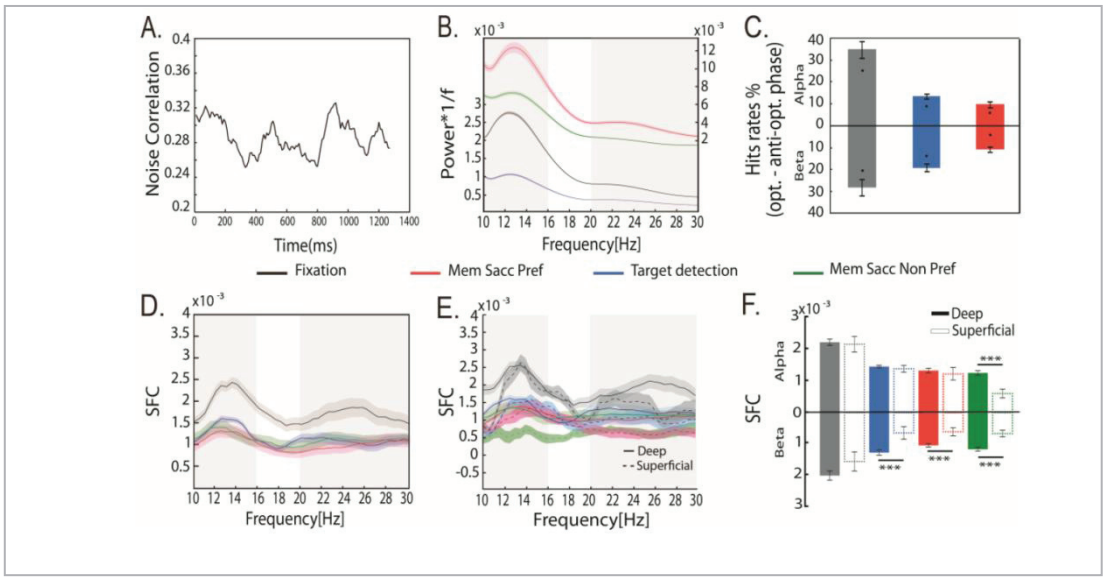

Figure 6: Rhythmic fluctuations in noise correlations modulate behavioral response and spike-field coherence in upper input cortical layers. ***(A)*** *Single memory guided saccade session example of noise correlation variations as a function of trial time.* ***(B)*** *1/f weighted power frequency spectra of noise correlation in time (average +/- s.e.m), for each task, calculated from 300ms to 1500ms from fixation onset (Fixation and Target detection tasks) or following cue offset (Memory guided saccade task).* ***(C)*** *Hit rate modulation by alpha (top histogram) and beta (bottom histogram)*

noise correlation at optimal phase as compared to anti-optimal phase for all three tasks (color as in (B), average +/- s.e., dots represent the 95% confidence interval under the assumption of absence of behavioral performance phase dependence). ***(D)*** *Spike field coherence between LFP and spike data as a function of frequency, time intervals as in (B).* ***(E)*** *Spike field coherence calculated as in (C) but as a function of the layer attribution of each signal, time intervals as in (B).* ***(F)*** *Average SFC (+/- s.e.) in alpha (10-16Hz, top histogram) and beta (20-30Hz, bottom histogram) for each task and both of superficial and deep cortical layer signals (t-test, ***: p<0.001).*

High alpha and beta oscillations in the local field potentials (LFP) are ubiquitous and are considered to reflect long-range processes. Beta oscillations have been associated with cognitive control and cognitive flexibility. On the other hand, alpha oscillations are associated with attention, anticipation (Thut et al., 2006; Rihs et al., 2009), perception (Varela et al., 1981; Mathewson et al., 2009; Busch et VanRullen 2010), and working memory (Klimesch, 1997). We hypothesized a functional link between these LFP oscillations and the rhythmic oscillatory pattern of noise correlations. Figure 6D represents spike field coherence (SFC) between spiking activity and LFP signals (see Materials and Methods) computed during a 1200ms time interval starting 300ms after either fixation onset (Fixation and Target detection task) or cue offset (Memory guided saccade task). SFC peaks at both the frequency ranges identified in the noise correlation spectra, namely the high alpha range (10-16Hz) and the beta range (20-30Hz). Importantly, this SFC modulation is highest for the fixation task as compared to the target detection task, thus matching the oscillatory power differences observed in the noise correlations. SFC are lowest in the memory guided saccade task whether considering preferred or non-preferred spatial processing. This is probably due to the fact that the cue to go signal interval of the memory guided saccade task involves memory processes that are expected to desynchronize spiking activity with respect to the LFP frequencies of interest (Buffalo et al., 2011, specifically in the 20-30Hz frequency range). This will need to be further explored.

In figure 4, we show layer specific effects onto noise correlations that build up onto the global task effects. An important question is whether these layer effects result from layer specific changes in SFC. Figure 6E represents the SFC data of figure 6D, segregated on the bases of the attribution of the MUA to either superficial or deep cortical FEF layers. While SFC modulations are observed in the same frequencies of interest as in figure 6D, clear layer specific differences can be observed (figure 6F). Specifically, beta range SFC are markedly significantly lower in the superficial layers than in the deep layers, for both the detection task and the memory guided saccade task. These, points towards a selective control of correlated noise in input, superficial FEF layers. In contrast, alpha range SFC are significantly lower in the superficial layers than in the deep layers only in the memory guided saccade, and

specifically when spatial memory is oriented towards a non-preferred location. This points towards overall weaker layer differences for alpha SFC. Alternatively, alpha SFC could result from a different mechanism than beta SFC. This will need to be further explored. Thus in spite of the fact that a comprehensive layer effect of alpha SFC is still lacking at this stage, both alpha and beta noise correlation rhythmicity co-vary with 1) selective SFC modulations in the alpha and beta frequency ranges (these latter being more pronounced in the superficial input cortical layers than in the deeper cortical layers) as well as with 2) pronounced variations in overt behavioral performance.

Overall, we thus identify a last functional oscillatory source of variations in noise correlations in the alpha and beta ranges that both have an important functional relevance, as they coincide with systematic variations in behavioral performance. These oscillations reflect selective changes in SFC, more pronounced in the superficial than in the deep cortical layers. This oscillatory source of variation in noise correlations adds up on top of the previously identified sources of variation, namely global task demands and the probabilistic structure of the task.

IV. Discussion

In this work, our main goal was to examine the impact of cognitive engagement and task demands onto the neuronal population shared variability as assessed from interneuronal noise correlations at multiple time scales. Recordings were performed in the macaque frontal eye fields, a cortical region in which neuronal noise correlations have been shown to vary as a function of spatial attention (Cohen et Maunsell 2009) and spatial memory (Constantinidis et Klingberg 2016; Meyers et al., 2012). Noise correlations were computed over equivalent behavioral task epochs, prior to response production, during a delay in which eyes were fixed and in the absence of any intervening sensory event or motor response. As a result, any observed differences in noise correlations are to be assigned to an attention source of shared neuronal variability.

Overall, we demonstrate, for the first time, that noise correlations dynamically adjust to task demands at different time scales. Specifically, we show that noise correlations decrease as cognitive engagement and task demands increase. These task-related variations in noise correlations co-exist with within-trial dynamic changes related to the probabilistic structure of the tasks as well as with long- and short-range oscillatory brain mechanisms. These findings are discussed below in relation with previously reported functional and

structural sources of variations in noise correlation and a comprehensive model of shared population neuronal variability is proposed.

Shared neuronal population response variability dynamically adjusts to the behavioral demands.

Noise correlations have been shown to vary with learning or changes in behavioral state (V1: Gutnisky et Dragoi 2008; Poort et Roelfsema 2009; Reich 2001; Smith et Kohn 2008; V4: Cohen et Maunsell 2009; Mitchell et al., 2009; Gawne et al., 1996; Gawne et Richmond 1993; MT: Cohen et Newsome 2008; Huang et Lisberger 2009; Zohary et al., 1994). For example, shared neuronal population response variability was lower in V1 in trained than in naïve monkeys (Gu et al. 2011). More recently, Ni et al. (2018) describe, within visual areas, a robust relationship between correlated variability and perceptual performance, whether changes in performance happened rapidly (attention instructed by a spatial cue) or slowly (learning). This relationship was robust even when the main effects of attention and learning were accounted for (Ni et al., 2018). Here, we question whether changes in noise correlations can be observed simultaneously at multiple time scales. We describe two different times scales at which noise correlations dynamically adjust to the task demands.

The first adjustment in noise correlations we describe is between tasks, that is between blocked contexts of varying cognitive demand, the monkeys knowing that general task requirements will be constant over a hundred of trials or more. Task performance is taken as a proxy to cognitive adjustment to the task demands and negatively correlates with noise correlations in the recorded population. Shared neuronal population variability measure is largest in the fixation task as compared to the two other tasks, by almost 30%. The difference between noise correlations in the target detection task as compared to the guided memory saccade task is in the range of 2%, closer to what has been previously reported in the context of noise correlation changes under spatial attention (Cohen et Maunsell 2009) or spatial memory manipulations. Importantly, these changes in noise correlations are observed in the absence of significant variations in individual neuronal spiking statistics (average spiking rates, spiking variability or associated Fano factor). To our knowledge, this is the first time that such task effects are described onto noise correlations. This variation in noise correlations as a function of cognitive engagement and task requirements suggests an adaptive mechanism that adjusts noise correlations to the ongoing behavior. Such a mechanism is expected to express itself at different timescales, ranging from the task level, to the across trial level to the within trial level. This is explored next.

It is unclear whether the transitions between high and low noise correlation states when changing from one task to another are fast (over one or two trials) or slow (over tens of trials). In Astrand et al. (2016), we show that noise correlations vary as a function of immediate trial past history. Specifically, noise correlations are significantly higher on error trials than on correct trials, both measures being higher if the previous trial is an error trial than if the previous trial is a correct trial. We thus predict a similar past history effect to be observed on noise correlations at transitions between tasks, and we expect for example, noise correlations to be lower in fixation trials that are preceded by a target detection trial, than in trials preceded by fixation trials. In our experimental design, task transitions are unfortunately rare events, precluding the computation of noise correlations on these transitions.

However, our experimental design affords an analysis at a much finer timescale, i.e. the description of a dynamical adjustment in noise correlations within trials. Specifically, we show that noise correlations dynamically adjust to the probability of occurrence of a behaviorally key task event associated with the reward response production (target presentation on the fixation and target detection tasks or saccade go signal on the memory guided saccade task). In other words, shared neuronal population response variability dynamically adjusts to higher demand task epochs. As expected from the general idea that low noise correlations allow for optimal signal processing (Ecker et al., 2010; Renart et al., 2010; Averbeck et al., 2006), we show that, on each of the three tasks, at any given time in the fixation epoch prior to response production, the higher the probability of having to initiate a response, the lower the noise correlations.

Overall, this supports the idea that noise correlations is a flexible physiological parameter that dynamically adjusts at multiple timescales to optimally meet ongoing behavioral demands, as has been demonstrated in multisensory integration (for example, Chandrasekaran 2017) and through learning and attention (Ni et al., 2018). The mechanisms through which this possibly takes place are discussed below.

Long-range and short-range mechanisms for noise correlation dynamics.

As described by previous studies, in all the three tasks, interneuronal noise correlations significantly decay as a function of cortical distance (Constantinidis et Goldman-Rakic 2002; Lee et al., 1998; Smith et Kohn 2008). Likewise, in all the three tasks, noise correlations are significantly higher among neurons sharing the same spatial selectivity as compared to between neurons with different spatial selectivity (Seriès et al., 2004; Zohary et al., 1994; Bair et al., 2001; Smith et Kohn 2008;. Cohen et Newsome 2008; Ecker et al., 2010, 2011),

supporting a functional role for noise correlations (Cohen and Maunsell, 2009) in the framework of biased competition models of perception (Desimone and Duncan, 1995). Last, in all three tasks, noise correlations depend on the functional selectivity of the neurons. Indeed, noise correlations were lowest for visual MUA pairs, highest for visuomotor MUA pairs and intermediate for visuo-visuomotor MUA pairs layers (Bruce et Goldberg 1985; Segraves et Goldberg 1987; Schall 1991; Schall et Hanes 1993; Schall et al., 1995; Schall et Thompson 1999). This thus points towards local layer specific noise correlation mechanisms.

Noise correlations are thought to vary due to global fluctuations in the excitability of cortical circuits at large (Schölvinck et al., 2015; Arieli et al., 1996) as well as to fluctuations specific to a given functional network (Shadlen and Newsome, 1998). Alternatively, variations in shared neuronal population response variability are also proposed to result from changes in local processes, due to a reweighing of local functional connectivity, local excitatory/inhibitory balance and/or a change in the random shared fluctuations in the pre-synaptic activity of cortical neurons (Zohary et al., 1994; Bair et al., 2001; Bryant et al., 1973; Shadlen et Newsome 1998). These two hypotheses are not mutually exclusive. The question is whether the task demand effects we describe here affect noise correlations irrespective of cortical distance, neuronal spatial selectivity and functional/layer specificity, or whether an interaction can be identified between task demand effects and cortical distance, neuronal spatial selectivity and functional/layer specificity. An absence of interactions would point towards a global noise correlation modulatory mechanism while an interaction would point towards more local noise correlation modulatory mechanism.

Our observations support the co-existence of both long-range global mechanisms and short-range local mechanisms. Indeed, we identify a very clear scaling of cortical distance, neuronal spatial selectivity and functional/layer specificity effects by general task demand, reflecting global influences onto noise correlations. On top of these global effects, we also note more complex changes in noise correlations that point towards local changes in neuronal interactions. Indeed, while task demand modulates noise correlations independently of cortical distance effects, we describe statistical interactions between task demand effects and neuronal spatial selectivity and functional/layer specificity effects. Specifically, neuronal spatial selectivity effects are more pronounced in the less demanding fixation task, than in the more demanding target detection and memory-guided saccade tasks. This suggests an active mechanism whereby noise correlations across neurons sharing the same spatial selectivity are selectively decreased under task demand, irrespectively of changes in noise correlations in the

neurons of different spatial selectivity. Alternatively these selective changes in noise correlation can result from task-related dynamic changes in the neuronal spatial selectivity (Womelsdorf et al., 2006, 2008; Anton-Erxleben et al., 2007; Ben Hamed et al., 2002). On the other hand, layer specificity effects are less pronounced in the less demanding fixation task, than in the more demanding target detection and memory-guided saccade tasks. This suggests an active mechanism whereby noise correlations across visual neuronal pairs (and to a lesser degree visuo-visuomotor neuronal pairs) are selectively decreased under task demand, irrespectively of changes in noise correlations in the visuomotor neuronal pairs, possibly relying on a dynamic functional reweighing of top-down and buttom-up processes (Buschman et Miller 2007; Ibos et al., 2013).

All this taken together indicates that changes in noise correlations in the FEF as a function of task demand both depend onto long-range global mechanisms and short-range functional and layer specific mechanisms.

Rhythmic fluctuations in noise correlations.

In the above, we describe changes in noise correlations between tasks as a function of the cognitive demand, as well as within trials, as a function of the probabilistic structure of each task. In addition to these task-related dynamics, we also observe rhythmic fluctuations in noise correlations. These fluctuations are clearly identified in the high alpha frequency range (10-16 Hz) and to a lesser extent in the low gamma frequency range (20-30Hz). To our knowledge, this is the first time that such rhythmic variations in noise correlations are reported. The question is whether these oscillations have a functional relevance or not.

From a behavioral point of view, we show that overt behavioral performance in the three tasks co-vary with both the 10-16Hz and 20-30Hz noise correlation oscillations. In other words, these oscillations account for more than 10% of the behavioral response variability, strongly supporting a functional role for these alpha and beta oscillations.

From a functional point of view, attention directed to the receptive field of neurons has been shown to both reduce noise correlations (Cohen and Maunsell, 2009a) and spike-field coherence in the gamma range (V4: Chalk et al., (2010), it is however to be noted that Engel et al., 2001 describe increased spike-field coherence in V1, the gamma range under the same conditions, hinting towards areal specific differences). In our hands, the rhythmic fluctuations in noise correlations co-exist with increased spike-field coherence in the very same 10-16Hz and 20-30Hz frequency ranges we identify in the noise correlations. This suggests that changes in shared neuronal variability possibly arise from changes in the local coupling

between neuronal spiking activity and local field potentials. Supporting such a functional coupling, both the rhythmic fluctuations in noise correlations and spike-field coherence in the frequencies of interest are highest in the fixation task as compared to the other two tasks.

Beta oscillations in the local field potentials (LFP) are considered to reflect long-range processes and have been associated with cognitive control and flexibility (Engel et al., 2001; Okazaki et al., 2008; Iversen et al., 2009; Buschman et Miller 2007, 2009; Engel et Fries 2010) as well as with motor control (Joundi et al., 2012; Lalo et al., 2007; Courtemanche et al., 2003; for review see: Engel et Fries 2010). Specifically, lower beta power LFPs has been associated with states of higher cognitive flexibility. In our hands, lower beta in noise correlations correspond to higher cognitive demands. We thus hypothesize a functional link between these two measures, LFP oscillations locally changing spiking statistics, i.e. noise correlations, by a specific spike-field coupling in this frequency range. Supporting a long-range origin of these local processes (figure 7, inset), we show that spike-field coherence in this beta range strongly decreases in the more superficial cortical layers as compared to the deeper layers, as task cognitive demand increases. On the other hand, alpha oscillations are associated with attention, anticipation (Thut et al., 2006; Rihs et al., 2009), perception (Varela et al., 1981; Mathewson et al., 2009; Busch et VanRullen 2010), and working memory (Klimesch, 1997). As for beta oscillations, lower alpha in noise correlations, and accordingly in spike-field coherence, correspond to higher cognitive demands. In contrast with what is observed for beta spike-field coherence, alpha spike-field coherence does not exhibit any layer specificity across task demands. Thus overall, alpha and beta rhythmicity account for strong fluctuations in behavioral performance, as well as for changes in spike-field coherence. However, beta processes seem to play a distinct functional role as compared to the alpha processes, as their effect is more marked in the superficial than in the deeper cortical layers. These observations coincide with recent evidence that cognition is rhythmic (Fiebelkorn et al., 2018; Fiebelkorn and Kastner, 2018) and that noise correlations play a key role in optimizing behavior to the ongoing time-varying cognitive demands (Ni et al., 2018).

We thus demonstrate that noise correlations are highly dynamic, adjusting to the ongoing behavioral demands, both across tasks and within trials. They are also rhythmic, time varying in the alpha and beta frequency ranges. These rhythmic changes account both for overt behavioral performance as well as for selective changes in spike-field coupling in prefrontal superficial input cortical layers.

These dynamic adjustments in noise correlations correspond to a top-down control (Figure 7, blue) over local neuronal processes, mediated through long-range inter-areal influences. Alpha and beta rhythmicity appear to play a major role in this process, beta rhythmicity being involved in a selective superficial SFC modulation (Figure 7, inset, (2)), and alpha rhythmicity being involved in a more global SFC modulation (Figure 7, inset, (1)). These rhythmic processes co-exist with selective changes in noise correlations as a function of neuronal selectivity (Figure 7, inset, (3)). These top-down dynamic adjustments in noise correlations are expected to add up onto state-related changes in noise correlations (Figure 7, black), possibly mediated through neuromodulatory mechanisms, and sensory bottom-up induced changes in noise correlations (Figure 7, red).

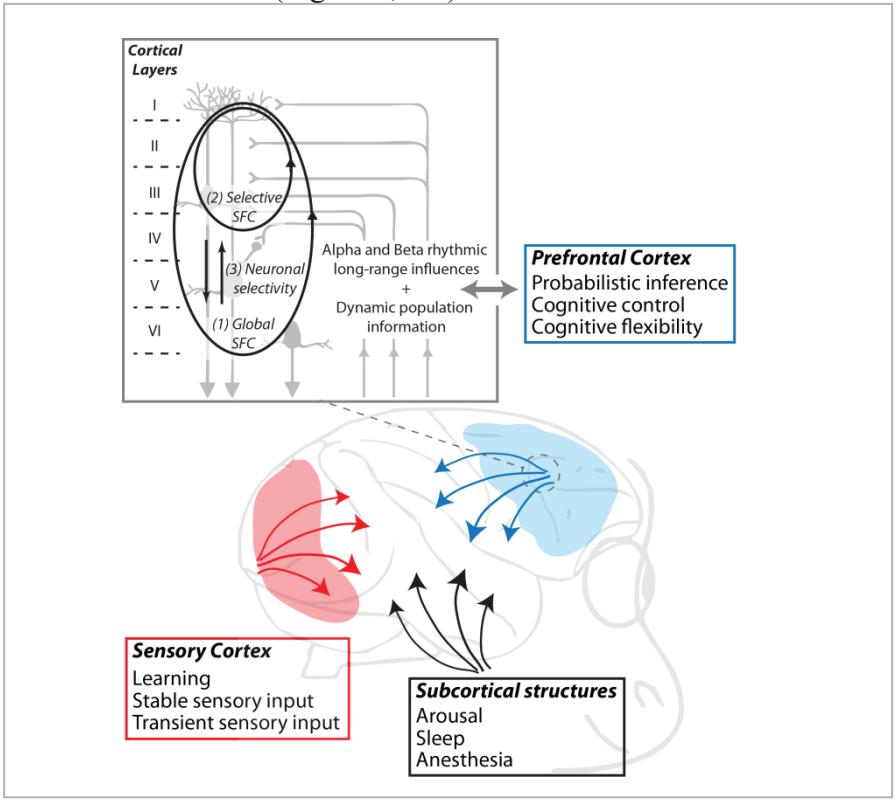

Figure7

Overall, neuronal correlations are to be considered as a key neuronal mechanism through which top-down and bottom-up neuronal influences are integrated to optimize behavioral performance, along the same integrative rules as described for other neuronal activity statistics.

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V. References

Abbott, L.F., Dayan, P., 1999. The Effect of Correlated Variability on the Accuracy of a Population Code. Neural Comput. 11(1):91-101.

Ahissar, E., Vaadia, E., Ahissar, M., Bergman, H., Arieli, A., Abeles, M., 1992. Dependence of Cortical Plasticity on Correlated Activity of Single Neurons and on Behavioral Context. Science 257, 1412–1415.

Anton-Erxleben, K., Henrich, C., Treue, S., 2007. Attention changes perceived size of moving visual patterns. J Vis 7, 5.1-9.

Arieli, A., Sterkin, A., Grinvald, A., Aertsen, A., 1996. Dynamics of ongoing activity: explanation of the large variability in evoked cortical responses. Science 273, 1868–1871.

Armstrong, K.M., Chang, M.H., Moore, T., 2009. Selection and maintenance of spatial information by frontal eye field neurons. J. Neurosci. 29, 15621–15629.

Astrand, E., Ibos, G., Duhamel, J.-R., Ben Hamed, S., 2015. Differential dynamics of spatial attention, position, and color coding within the parietofrontal network. J. Neurosci. 35, 3174–3189.

Astrand, E., Wardak, C., Baraduc, P., Ben Hamed, S., 2016. Direct Two-Dimensional Access to the Spatial Location of Covert Attention in Macaque Prefrontal Cortex. Curr. Biol. 26, 1699–1704.

Averbeck, B.B., Latham, P.E., Pouget, A., 2006. Neural correlations, population coding and computation. Nat Rev Neurosci 7, 358–366.

Bair, W., Zohary, E., Newsome, W.T., 2001. Correlated firing in macaque visual area MT: time scales and relationship to behavior. J. Neurosci. 21, 1676–1697.

Ben Hamed, S., Duhamel, J.-R., Bremmer, F., Graf, W., 2002. Visual receptive field modulation in the lateral intraparietal area during attentive fixation and free gaze. Cereb. Cortex 12, 234–245.

Ben-Yishai, R., Bar-Or, R.L., Sompolinsky, H., 1995. Theory of orientation tuning in visual cortex. Proc. Natl. Acad. Sci. U.S.A. 92, 3844–3848.

Bruce, C.J., Goldberg, M.E., 1985. Primate frontal eye fields: I. Single neurons discharging before saccades. Journal of Neurophysiology. 53(3):603-35.

Bryant, H.L., Marcos, A.R., Segundo, J.P., 1973. Correlations of neuronal spike discharges produced by monosynaptic connections and by common inputs. Journal of Neurophysiology 36, 205–225.

Buffalo, E.A., Fries, P., Landman, R., Buschman, T.J., Desimone, R., 2011a. Laminar differences in gamma and alpha coherence in the ventral stream. Proc. Natl. Acad. Sci. U.S.A. 108, 11262–11267.

Buffalo, E.A., Fries, P., Landman, R., Buschman, T.J., Desimone, R., 2011b. Laminar differences in gamma and alpha coherence in the ventral stream. Proc. Natl. Acad. Sci. U.S.A. 108, 11262–11267.

Busch, N.A., VanRullen, R., 2010. Spontaneous EEG oscillations reveal periodic sampling of visual attention. Proc. Natl. Acad. Sci. U.S.A. 107, 16048–16053.

Buschman, T.J., Miller, E.K., 2009. Serial, covert shifts of attention during visual search are reflected by the frontal eye fields and correlated with population oscillations. Neuron 63, 386–396.

Buschman, T.J., Miller, E.K., 2007. Top-down versus bottom-up control of attention in the prefrontal and posterior parietal cortices. Science 315, 1860–1862.

Chalk, M., Herrero, J.L., Gieselmann, M.A., Delicato, L.S., Gotthardt, S., Thiele, A., 2010. Attention Reduces Stimulus-Driven Gamma Frequency Oscillations and Spike Field Coherence in V1. Neuron 66, 114.

Chandrasekaran, C., 2017. Computational principles and models of multisensory integration. Curr. Opin. Neurobiol. 43, 25–34.

Cohen, J.Y., Crowder, E.A., Heitz, R.P., Subraveti, C.R., Thompson, K.G., Woodman, G.F., Schall, J.D., 2010. Cooperation and competition among frontal eye field neurons during visual target selection. J. Neurosci. 30, 3227–3238.

Cohen, M.R., Maunsell, J.H.R., 2009a. Attention improves performance primarily by reducing interneuronal correlations. Nat Neurosci 12, 1594–1600.

Cohen, M.R., Maunsell, J.H.R., 2009b. Attention improves performance primarily by reducing interneuronal correlations. Nat. Neurosci. 12, 1594–1600.

Cohen, M.R., Newsome, W.T., 2008. Context-dependent changes in functional circuitry in visual area MT. Neuron 60, 162–173.

Constantinidis, C., Goldman-Rakic, P.S., 2002a. Correlated discharges among putative pyramidal neurons and interneurons in the primate prefrontal cortex. J. Neurophysiol. 88, 3487–3497.

Constantinidis, C., Goldman-Rakic, P.S., 2002b. Correlated discharges among putative pyramidal neurons and interneurons in the primate prefrontal cortex. J. Neurophysiol. 88, 3487–3497.

Constantinidis, C., Klingberg, T., 2016. The neuroscience of working memory capacity and training. Nat. Rev. Neurosci. 17, 438–449.

Courtemanche, R., Fujii, N., Graybiel, A.M., 2003. Synchronous, focally modulated beta-band oscillations characterize local field potential activity in the striatum of awake behaving monkeys. J. Neurosci. 23, 11741–11752.

Desimone, R., Duncan, J., 1995. Neural Mechanisms of Selective Visual Attention. Annual Review of Neuroscience 18, 193–222.

Ecker, A.S., Berens, P., Cotton, R.J., Subramaniyan, M., Denfield, G.H., Cadwell, C.R., Smirnakis, S.M., Bethge, M., Tolias, A.S., 2014. State Dependence of Noise Correlations in Macaque Primary Visual Cortex. Neuron 82, 235–248.

Ecker, A.S., Berens, P., Keliris, G.A., Bethge, M., Logothetis, N.K., Tolias, A.S., 2010. Decorrelated Neuronal Firing in Cortical Microcircuits. Science 327, 584–587.

Ecker, A.S., Berens, P., Tolias, A.S., Bethge, M., 2011. The effect of noise correlations in populations of diversely tuned neurons. J Neurosci. 31(40):14272-83.

Ekstrom, L.B., Roelfsema, P.R., Arsenault, J.T., Bonmassar, G., Vanduffel, W., 2008. Bottom-up dependent gating of frontal signals in early visual cortex. Science 321, 414–417.

Engel, A.K., Fries, P., 2010. Beta-band oscillations--signalling the status quo? Curr. Opin. Neurobiol. 20, 156–165.

Engel, A.K., Fries, P., Singer, W., 2001. Dynamic predictions: oscillations and synchrony in top-down processing. Nat. Rev. Neurosci. 2, 704–716.

Engel, A.K., König, P., Kreiter, A.K., Singer, W., 1991. Interhemispheric Synchronization of Oscillatory Neuronal Responses in Cat Visual Cortex. Science 252, 1177–1179.

Fiebelkorn, I.C., Snyder, A.C., Mercier, M.R., Butler, J.S., Molholm, S., Foxe, J.J., 2013. Cortical cross-frequency coupling predicts perceptual outcomes. Neuroimage 69, 126–137.

Gawne, T.J., Kjaer, T.W., Hertz, J.A., Richmond, B.J., 1996. Adjacent visual cortical complex cells share about 20% of their stimulus-related information. Cereb. Cortex 6, 482–489.

Gawne, T.J., Richmond, B.J., 1993. How independent are the messages carried by adjacent inferior temporal cortical neurons? J. Neurosci. 13, 2758–2771.

Goris, R.L.T., Movshon, J.A., Simoncelli, E.P., 2014. Partitioning neuronal variability. Nat Neurosci 17, 858–865.

Gregoriou, G.G., Gotts, S.J., Desimone, R., 2012. Cell-type-specific synchronization of neural activity in FEF with V4 during attention. Neuron 73, 581–594.

Gregoriou, G.G., Gotts, S.J., Zhou, H., Desimone, R., 2009. High-frequency, long-range coupling between prefrontal and visual cortex during attention. Science 324, 1207–1210.

Grinsted, A., Moore, J.C., Jevrejeva, S., 2004. Application of the cross wavelet transform and wavelet coherence to geophysical time series. Nonlinear Processes in Geophysics 11, 561–566.

Gu, Y., Liu, S., Fetsch, C.R., Yang, Y., Fok, S., Sunkara, A., DeAngelis, G.C., Angelaki, D.E., 2011. Perceptual learning reduces interneuronal correlations in macaque visual cortex. Neuron 71, 750–761.

Gutnisky, D.A., Dragoi, V., 2008. Adaptive coding of visual information in neural populations. Nature 452, 220–224.

Huang, X., Lisberger, S.G., 2009. Noise Correlations in Cortical Area MT and Their Potential Impact on Trial-by-Trial Variation in the Direction and Speed of Smooth-Pursuit Eye Movements. Journal of Neurophysiology 101, 3012–3030.

Ibos, G., Duhamel, J.-R., Ben Hamed, S., 2013. A functional hierarchy within the parietofrontal network in stimulus selection and attention control. J. Neurosci. 33, 8359–8369.

Iversen, J.R., Repp, B.H., Patel, A.D., 2009. Top-down control of rhythm perception modulates early auditory responses. Ann. N. Y. Acad. Sci. 1169, 58–73.

Joundi, R.A., Jenkinson, N., Brittain, J.-S., Aziz, T.Z., Brown, P., 2012. Driving oscillatory activity in the human cortex enhances motor performance. Curr. Biol. 22, 403–407.

Kanitscheider, I., Coen-Cagli, R., Pouget, A., 2015. Origin of information-limiting noise correlations. Proc. Natl. Acad. Sci. U.S.A. 112, E6973-6982.

Klimesch, W., 1997. EEG-alpha rhythms and memory processes. Int J Psychophysiol 26, 319–340.

Lalo, E., Gilbertson, T., Doyle, L., Di Lazzaro, V., Cioni, B., Brown, P., 2007. Phasic increases in cortical beta activity are associated with alterations in sensory processing in the human. Exp Brain Res 177, 137–145.

Lee, D., Port, N.L., Kruse, W., Georgopoulos, A.P., Neurology, 1998a. Variability and correlated noise in the discharge of neurons in motor and parietal areas of the primate cortex. J Neurosci 18:1161–1170.

Lee, D., Port, N.L., Kruse, W., Georgopoulos, A.P., Neurology, 1998b. Variability and correlated noise in the discharge of neurons in motor and parietal areas of the primate cortex. J Neurosci 18:1161–1170.

Litwin-Kumar, A., Doiron, B., 2012. Slow dynamics and high variability in balanced cortical networks with clustered connections. Nat Neurosci 15, 1498–1505.

Ly, C., Middleton, J.W., Doiron, B., 2012. Cellular and circuit mechanisms maintain low spike co-variability and enhance population coding in somatosensory cortex. Front Comput Neurosci 6, 7.

Mathewson, K.E., Gratton, G., Fabiani, M., Beck, D.M., Ro, T., 2009. To See or Not to See: Prestimulus α Phase Predicts Visual Awareness. J. Neurosci. 29, 2725–2732.

Meyers, E.M., Qi, X.-L., Constantinidis, C., 2012. Incorporation of new information into prefrontal cortical activity after learning working memory tasks. Proc Natl Acad Sci U S A 109, 4651–4656.

Mitchell, J.F., Sundberg, K.A., Reynolds, J.H., 2009. Spatial attention decorrelates intrinsic activity fluctuations in macaque area V4. Neuron 63, 879–888.

Mohler, C.W., Goldberg, M.E., Wurtz, R.H., 1973. Visual receptive fields of frontal eye field neurons. Brain Res. 61, 385–389.

Moreno-Bote, R., Beck, J., Kanitscheider, I., Pitkow, X., Latham, P., Pouget, A., 2014. Information-limiting correlations. Nature neuroscience 17, 1410.

Narayanan, N.S., Laubach, M., 2006. Top-down control of motor cortex ensembles by dorsomedial prefrontal cortex. Neuron 52, 921–931.

Ni, A.M., Ruff, D.A., Alberts, J.J., Symmonds, J., Cohen, M.R., 2018. Learning and attention reveal a general relationship between population activity and behavior. Science 359, 463–465.

Okazaki, M., Kaneko, Y., Yumoto, M., Arima, K., 2008. Perceptual change in response to a bistable picture increases neuromagnetic beta-band activities. Neurosci. Res. 61, 319–328.

Oostenveld, R., Fries, P., Maris, E., Schoffelen, J.-M., 2011. FieldTrip: Open Source Software for Advanced Analysis of MEG, EEG, and Invasive Electrophysiological Data. Intell. Neuroscience 2011, 1:1–1:9.

Poort, J., Roelfsema, P.R., 2009. Noise correlations have little influence on the coding of selective attention in area V1. Cereb. Cortex 19, 543–553.

Poulet, J.F.A., Petersen, C.C.H., 2008. Internal brain state regulates membrane potential synchrony in barrel cortex of behaving mice. Nature 454, 881–885.

Reich, D.S., 2001. Independent and Redundant Information in Nearby Cortical Neurons. Science 294, 2566–2568.

Renart, A., de la Rocha, J., Bartho, P., Hollender, L., Parga, N., Reyes, A., Harris, K.D., 2010. The asynchronous state in cortical circuits. Science 327, 587–590.

Rihs, T.A., Michel, C.M., Thut, G., 2009. A bias for posterior alpha-band power suppression versus enhancement during shifting versus maintenance of spatial attention. Neuroimage 44, 190–199.

Schall, J.D., 1991. Neuronal activity related to visually guided saccades in the frontal eye fields of rhesus monkeys: comparison with supplementary eye fields. J. Neurophysiol. 66, 559–579.

Schall, J.D., Hanes, D.P., 1993. Neural basis of saccade target selection in frontal eye field during visual search. Nature 366, 467–469.

Schall, J.D., Hanes, D.P., Thompson, K.G., King, D.J., 1995. Saccade target selection in frontal eye field of macaque. I. Visual and premovement activation. J. Neurosci. 15, 6905–6918.

Schall, J.D., Thompson, K.G., 1999. Neural selection and control of visually guided eye movements. Annu. Rev. Neurosci. 22, 241–259.

Schölvinck, M.L., Saleem, A.B., Benucci, A., Harris, K.D., Carandini, M., 2015. Cortical state determines global variability and correlations in visual cortex. J. Neurosci. 35, 170–178.

Segraves, M.A., Goldberg, M.E., 1987. Functional properties of corticotectal neurons in the monkey's frontal eye field. J. Neurophysiol. 58, 1387–1419.

Seriès, P., Latham, P.E., Pouget, A., 2004. Tuning curve sharpening for orientation selectivity: coding efficiency and the impact of correlations. Nat. Neurosci. 7, 1129–1135.

Shadlen, M.N., Newsome, W.T., 1998. The variable discharge of cortical neurons: implications for connectivity, computation, and information coding. J. Neurosci. 18, 3870–3896.

Smith, M.A., Kohn, A., 2008. Spatial and Temporal Scales of Neuronal Correlation in Primary Visual Cortex. J. Neurosci. 28, 12591–12603.

Sompolinsky, H., Yoon, H., Kang, K., Shamir, M., 2001. Population coding in neuronal systems with correlated noise. Phys Rev E Stat Nonlin Soft Matter Phys 64, 051904.

Stark, E., Globerson, A., Asher, I., Abeles, M., 2008. Correlations between groups of premotor neurons carry information about prehension. J. Neurosci. 28, 10618–10630.

Thut, G., Nietzel, A., Brandt, S.A., Pascual-Leone, A., 2006. Alpha-band electroencephalographic activity over occipital cortex indexes visuospatial attention bias and predicts visual target detection. J. Neurosci. 26, 9494–9502.

Ts'o, D.Y., Gilbert, C.D., Wiesel, T.N., 1986. Relationships between horizontal interactions and functional architecture in cat striate cortex as revealed by cross-correlation analysis. J. Neurosci. 6, 1160–1170.

Vaadia, E., Haalman, I., Abeles, M., Bergman, H., Prut, Y., Slovin, H., Aertsen, A., 1995. Dynamics of neuronal interactions in monkey cortex in relation to behavioural events. Nature 373, 515–518.

Varela, F.J., Toro, A., John, E.R., Schwartz, E.L., 1981. Perceptual framing and cortical alpha rhythm. Neuropsychologia 19, 675–686.

Wardak, C., Ibos, G., Duhamel, J.-R., Olivier, E., 2006. Contribution of the monkey frontal eye field to covert visual attention. J. Neurosci. 26, 4228–4235.

Wimmer, K., Compte, A., Roxin, A., Peixoto, D., Renart, A., de la Rocha, J., 2015. Sensory integration dynamics in a hierarchical network explains choice probabilities in cortical area MT. Nat Commun 6, 6177.

Womelsdorf, T., Anton-Erxleben, K., Treue, S., 2008. Receptive field shift and shrinkage in macaque middle temporal area through attentional gain modulation. J. Neurosci. 28, 8934–8944.

Womelsdorf, T., Fries, P., Mitra, P.P., Desimone, R., 2006. Gamma-band synchronization in visual cortex predicts speed of change detection. Nature 439, 733–736.

Zohary, E., Shadlen, M.N., Newsome, W.T., 1994. Correlated neuronal discharge rate and its implications for psychophysical performance. Nature 370, 140–143.

Chapter III

Neurophysiology of Noradrenaline

I. Noradrenergic neuro-modulation

Neuromodulators are released by brainstem neurons to control the state and the functionality of neural networks and their synaptic transmission (Marder, 2012). The main neuromodulators in the brain are serotonin, acetylcholine, catecholamines, dopamine and noradrenaline. The cell bodies of neuromodulatory neurons are grouped in specific nuclei in the brainstem, the midbrain and the basal forebrain. Through their wide spread projections they influence many brain regions and functions. For example, noradrenergic neurons are grouped in the locus coeruleus (LC). The noradrenaline, also called norepinephrine (NE) is implicated in several brain functions such as sensory signal detection (Devilbiss et al., 2006) and general arousal and alertness in the waking state (Berridge et Waterhouse 2003). More recent evidences suggest that NE plays an important role in behavior and cognition, such as attention (Rachel E. Cain et al., 2011; J. McGaughy et al., 2008; Navarra et al., 2017; Rachel L. Navarra et al., 2013; Lori A. Newman et al., 2008), behavioral flexibility (Bouret et Sara 2005; Aston-Jones et Cohen 2005b; Sara 2009; Sara et Bouret 2012), and learning and memory (Hagena et al., 2016; Hansen and Manahan-Vaughan, 2015; Schutsky et al., 2011). Importantly, many studies have demonstrated that altering the noradrenergic system is a source of many psychiatric disorders like depression (Zhao et al., 2009), anxiety (Adamec et al., 2004; Janitzky et al., 2015), attention-deficit hyperactivity disorder (ADHD)(Arnsten 2006, 2007; Agster et al. 2011), schizophrenia (Brown et al., 2012; Shoja Shafti et al., 2015), autism (Genestine et al., 2015), Parkinson's disease (Delaville et al., 2012; Gesi et al., 2000), and Alzheimer's disease (Weinshenker, 2008). A large body of information has been stored regarding the LC-noradrenergic system as reviewed in many excellent reviews (Amaral and Sinnamon, 1977; Bast et al., 2018; Berridge and Waterhouse, 2003; Foote et al., 1983).

In this review, we will first summarize physiological and behavioral data describing the LC-NE system as a major source of NE then we will describe the implication of NE in attention and we will review the models proposed for LC-NE activity. Last we will confront these models to NE neuronal modulation based on the existent literature.

II. Origin of central and peripheral norepinephrine

NE was one of the first neurotransmitters identified in the central nervous system by the swedish physiologist Ulf von Euler during the 1940s, but it was the experiments of Dahlström and Fuxe that identified LC as the main source of norepinephrine in the brain. It's now established that LC is the principal source of NE (Robertson et al., 2013). Briefly, LC is composed of a densely packed population of cells (1600 cells per LC in the rodent) with a common embryonic origin, all of which produce norepinephrine (Robertson et al., 2013). The activity of LC neurons is closely linked to the sleep-wake cycle and its involvement in the induction and regulation of cortical arousal has been intensively documented (for a review, see Berridge, 2008, see also recent studies using ontogenetic manipulation: Carter et al., 2010 a; 2012). LC neurons have two modes of discharge activities, figure 1(B.): **1) A tonic discharge mode**, during which neurons display a sustained and highly regular discharge pattern (Foote et al., Bloom 1980; Aston-Jones et Bloom 1981a). It's important to know that this tonic mode is state-dependent as demonstrated by (Hobson et al., 1975). For example, LC neurons activity has a lower discharge rate during slow-wave sleep (1< Hz) and higher rates of discharge during wake (2> Hz) (Foote et al., 1980). **2) A phasic discharge mode,** during which neurons display phasic alterations in discharge rate. This mode is associated with waking, sustained attention, alertness and arousal (Aston-Jones et al., 1994; Aston-Jones and Bloom, 1981a; Foote et al., 1980). NE effects take place within the target cortical regions through different types of adrenoceptors. Globally nine noradrenergics receptors were identified ; three α1-adrenoceptors (α1A, α1B,α1D), three α2-subtypes (α2A,α2B,α2C), and three β-adrenoceptors (β1,β2,β3) (Bylund et al., 1994). Hein (2006) reviews in details information about adrenoreceptor signaling neurons, receptor-associated proteins, receptor dimerization, subcellular trafficking, and fluorescence optical methods for the study of the kinetics of adrenergic signaling. It has been demonstrated that the effects of NE are different, depending on the activated receptor (reviewed in Berridge & Waterhouse 2003 and Foote et al. 1983). For example, α1- adrenoceptor activation is often linked with excitation, and α-2 adrenoceptor activation with inhibition (Rogawski & Aghajanian 1982, Williams et al., 1985).

The fiber projections from LC give rise to three pathways (Figure1(A.)): **1) The ascending pathway** innervates structures in the midbrain (periaqueductal grey substance, nucleus raphe dorsalis, colliculi), thalamus, limbic system (amygdala, hippocampus, cingulate and parahippocampal gyri), and all neocortical areas (Gatter and Powell, 1977). **2) The cerebellar pathway** projects to the cerebellar nuclei and cerebellar cortex via the superior

cerebellar peduncle (Szabadi, 2013). **3) The descending pathway** sends collaterals to motor nuclei in the lower brainstem (dorsal nucleus of the vagus, inferior olivary complex), and then descends to the spinal cord (coeruleo-spinal pathway), innervating spinal neurons in all three nuclear columns (Moore et Bloom 1979). In fact, the multitude of LC characteristics as topographical organization, molecular composition (Schwarz et al., 2015) and subtle differences in anatomical connectivity suggest that the LC-NE system does not perform completely homogenously in its target regions and his neurons could affect differentially the physiology of their targets by several mechanisms.

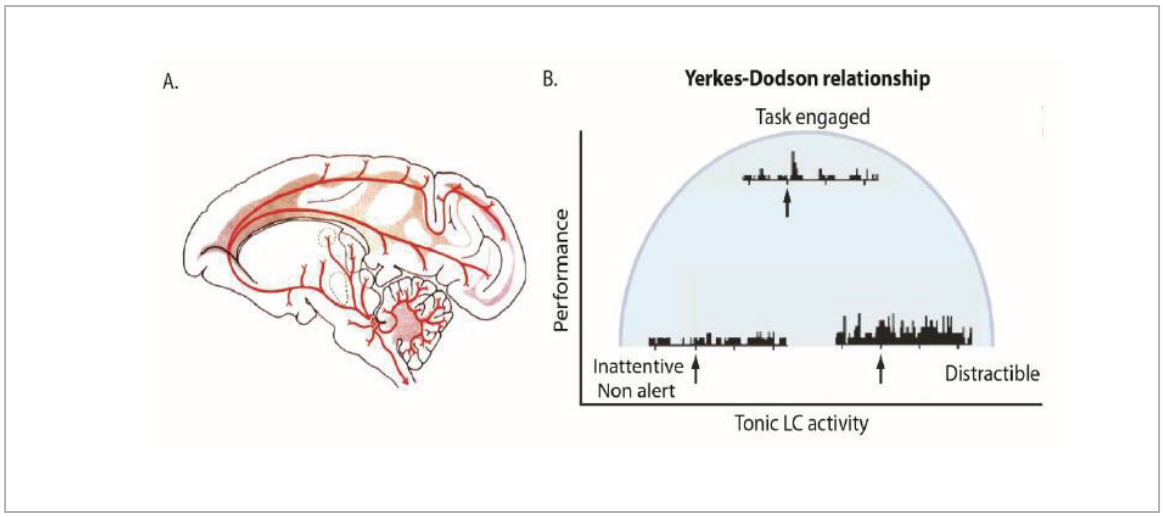

Figure1: ***(A)*** *Illustration of projections of the LC system. Saggital view of a monkey brain showing LC neurons located in the pons with efferent projections throughout the central nervous system. Note that only few areas do not receive LC innervation (e.g., hypothalamus and caudate-putamen).* ***(B)*** *Inverted-U relationship between LC activity and performance on tasks that require focused attention. Performance is poor at very low levels of LC tonic discharge because animals are drowsy and non-alert. Performance is optimal with moderate LC tonic activity and prominent phasic LC activation following goal-relevant stimuli (phasic LC mode). Performance is poor at high levels of tonic LC activity (tonic mode, lacking phasic LC activity). This resembles the classical Yerkes-Dodson relationship between arousal and performance. From Aston-Jones et al. 2005.*

It has been demonstrated that NE plays important roles in different cognitive function such as working memory and attention. Given the focus of the present dissertation on the prefrontal cortex and specifically the frontal eye fields, a cortical regions which has been shown to play a crucial role in attention orientation and processing (Moore and Scheaffer, Wardak et al., 2006, Ibos et al., 2013, Astrand et al., 2016), in the next section, I will focus only in the role of NE in attention.

III. Norepinephrine and attention

Attention is the process that enables us, at any given moment, to select some information for further processing, while setting aside other information (Desimone and Duncan, 1995). Without attention, which is a complex multi-faceted function, higher cognitive functions such as perception, decision making and learning cannot operate properly. Posner et colleagues have proposed a human model in which attention is divided into three subsystems: **1) An alerting system**, that achieves and maintains a state of high sensitivity to incoming stimuli. This component is proposed to be associated with frontal, parietal and thalamic activity and with noradrenaline. **2) An orientation system** that helps select relevant sensory information, and which is proposed to be associated with activity of the inferior parietal lobes, frontal eye field, superior colliculus, pulvinar, and with acethylcholine. As a result, spatial attention is proposed to be directed to peripheral visual events in two ways: 1) An overt shift of attention, or 'top down attention', during which head and eye movements can be employed to gaze directly at an item, and 2) A covert shift of attention, during which spatial attention can be directed towards the relevant stimulus without any movement of the eyes(Corbetta and Shulman, 2002). These two kinds of attentional orienting are also referred to as exogenous and attention attentional controls (Corbetta and Shulman, 2002; Desimone and Duncan, 1995) **3) An executive control system** that detects and resolves internal conflicts and produces accurate behavioral responses, and which is associated with activity in the anterior cingulate cortex (ACC), medial frontal cortex (MFC), and lateral prefrontal cortex (LPFC), and with dopamine (Petersen and Posner, 2012). The implication of PFC (Astrand et al., 2016, 2015; Ibos et al., 2013; Moore et al., 2003; Moore and Fallah, 2004) and the parietal cortex (Corbetta and Shulman, 2002; Herrington and Assad, 2009; Ibos et al., 2013; Yantis et al., 2002) in visuospatial attention is well established. Several studies have identified neuronal correlates of both bottom-up and top-down attention in the lateral intraparietal area (LIP) (Bisley and Goldberg, 2003; Gottlieb et al., 1998, Ibos et al., 2013) and in the frontal eye field (FEF) (Armstrong et al., 2009; Monosov and Thompson, 2009; Thompson et al., 2005, Ibos et al., 2013).

NE effects on attention are proposed to take place both on temporal attention or on spatial attention. To characterize the effect of NA on **attention in time**, researchers often use a discrimination task during which subjects have to detect the target by responding or by inhibit their response. This task is known as the continuous performance task or CPT. For example, Coull et al (1995) have found that in humans, clonidine, which decreases NE in the synaptic

cleft, decreases subject's sensitivity to detect the target. However, Decamp et al 2011, have found that guanfancine, which has the same mechanism of action as clonidine, improves monkeys' performance by reducing errors of omission without affecting errors of comission. In other tasks in which subjects have to inhibit the response as soon as possible when they see the ('stop-signal'), ATX, which is a NA reuptake inhibitor, reduces the impulsivity by reducing the reaction time in stop trials (Robinson et al 2008, chamberlain et al 2009) and improves the number of correct trials in 'go' trials (Bari et al 2009). Overall NA has an effect on subjects' performances in tasks involving attention in time.

On the other hand, many studies have characterized the link between LC-NA and spatial attention but they are not conclusive. Two kinds of tasks have been used: visuospatial search tasks or Posner tasks. Nieuwenhuis et al. (2007) have used **visuospatial search** tasks and have found an increase of reaction time after clonidine administration, but no effect on performance. Overall, with this type of task there is no study that has succeeded to find an effect of NA on performances of healthy subject. In **Posner task**, subjects have to detect a cued target. The cue could predict target position (valid cue) or not (invalid cue). Two cues could appear (neutral cue) to indicate the appearance of the target without any spatial indication and only temporal information. Spatial orientation by the cue induces shorter reaction times when the target is preceded by a valid cue as compared to an invalid cue. Attention displacement is thus represented by the cost in reaction time of invalid cue over valid cue. Spatially non-specific alert by the cue induce shorter reaction times when the target is preceded by a neutral cue as compared to non cued targets. Non-specific alertness effects are thus represented by the cost in reaction times of uncued trials over neutrally cued trials. Studies that have used this task have found that clonidine reduces the cost of invalid cue but Witte and Marrocco didn't find any significant effect (Witte and Marrocco, 1997). It has been suggested that NE could play a role in attention reorientation. There are two kind of tasks that could be used to characterize this type of attention ('task-set shifting') or ('reversal-learning tasks'). Within the same task, stimulus feature or dimension changes (horizontal to vertical) and what is tracked is the time required for subject adaptation to the change of the cue. It has been found that the increase of NE transmission reduces the number of trials required to achieve the number of correct trials (Lapiz et Morilak 2006; Lapiz, et al., 2007; Kehagia et al., 2010). A recent fMRI study has demonstrated the activation of both fronto-parietal network, in regions that receives a dense LC-NE innervations (Foote & Morrison 1987) and LC region when subjects are required to adapt continuously their behavior as a function of

randomized changes of the association of the response and the stimulus (von der Gablentz et al., 2015). All together, this is evidence of a link between LC-NE and attention, though the exact neuronal mechanisms through which this takes place are yet to be described. This is further discussed in experimental ***Chapter IV*** and **V** of the present dissertation. In the next section we will describe the proposed models of LC-NE activity.

IV. Models of LC-NE function

The current prevailing models of NE function are that LC neurons affect target regions through two different models.

1. ***The neuronal gain model:*** Based on behavioral and electrophysiological evidence, Aston-Jones et Cohen (The Adaptive Gain Theory, 2005) propose a model of LC-NE activity, called gain model (figure 2), within which the LC activity modes are adjusted to facilitate or disengage from task-specific processes. This model thus links LC-NE function both to arousal and to the optimization of reward-seeking behaviors.

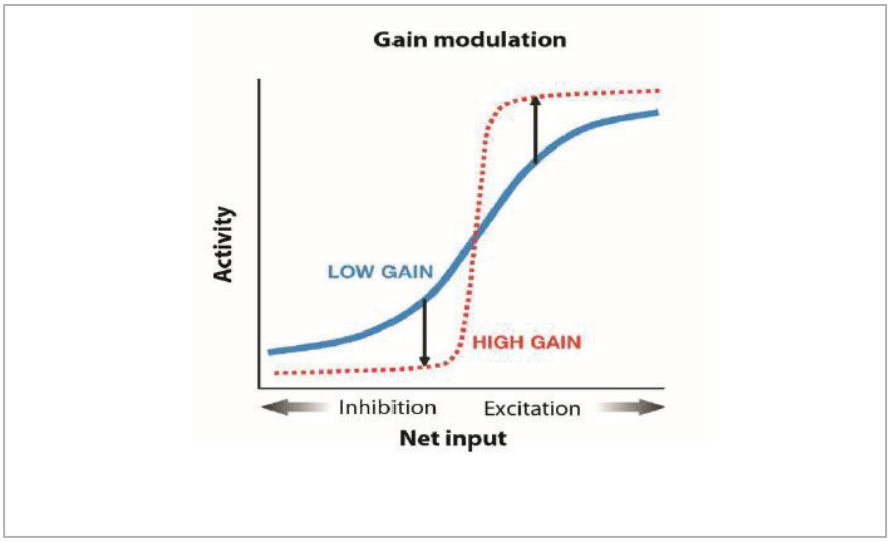

Figure2: *Effect of gain modulation on nonlinear activation function. The activation (or transfer) function relates the net input of a unit to its activity state (e.g., the firing rate of a single neuron or the mean firing rate of a population). The function illustrated here is given by*

$$\text{Activation} = \frac{1}{1 + e^{(\text{gain} * \text{net input})}}$$

An increase in gain (dotted line) increases theactivity of units receiving excitatory input (upward arrow on right) and decreases the activity of units receiving inhibitory input (downward arrow on left), thus increasing the contrast between activated and inhibited units and driving them toward more binary function. From Servan-Schreiberet al.(1990).

In their model Aston-Jones et Cohen proposed that LC-NE system optimizes behavior through a phasic mode that acts like a temporal filtering and regulates the balance between exploitation and exploration behavior (Aston-Jones and Cohen, 2005b). Specifically, Aston-Jones et Cohen (2005) hypothesize that the noradrenergic system guides the transitions between different types of behavior: exploiting of known sources of reward against exploring the environment to find more interesting opportunities. Overall, the two modes of activity of LC adjust the balance between these two fundamental states of the behavior: exploitation versus exploration (Aston-Jones et Cohen 2005a; Gilzenrat et al. 2010; Jepma et Nieuwenhuis 2011). This theory is built on two key observations: one concerning the modes of LC functions, and the other concerning the influence of NE release on cortical processing. This theory is supported by the study of Aston-Jones (1997) which demonstrates that reversal reward decreases phasic mode and increases tonic mode within LC-NE system. More recently, Gilzenrat et al (2010) confirmed this theory by measuring the pupil diameter as an index of locus coeruleus activity; low tonic LC activity are accompanied by a reduced baseline pupil diameter (Hou et al., 2005; Rajkowski et al., 1994a) and increased tonic LC activity increase baseline pupil diameter (Phillips et al., 2000). More precisely, pupil diameter decrease is associated with good performances, whereas, an increase of the pupil diameter is associated with poor performances. These results completely support the results found on the effect of LC-NE system activity on performances on selective attention tasks (see ***Chapter IV*** of present dissertation). To summarize, the neuronal gain model proposes that the LC tonic mode supports optimization on a broader scale, favoring exploration when task-related utility is below an acceptable value while LC phasic mode supports optimization of current task performance as long as task-related utility is enough high. In order to support their model, Aston-Jones et Cohen suggest that the effect of LC-NE system through gain model takes place in link with the orbito-frontal cortex (OFC) and the anterior cingulate cortex (ACC). In fact, a growing body of evidence suggests that OFC plays a critical role in evaluating rewards (Roesch and Olson, 2004; Rolls, 2004; Tremblay and Schultz, 1999; Wallis and Miller, 2003) and that ACC play critical roles in evaluating costs (Eisenberger et al., 2003; Falkenstein et al., 1991; Holroyd et al., 2004a, 2004b, ; Kiehl et al., 2000; Yeung, 2004; Yeung et al., 2004). To inform LC-NE system about reward utility and the level of the cost, it is proposed that OFC and ACC send the necessary information through strong convergent projections (for review, see Aston-Jones and Harris, 2004) (Aston-Jones et al., 2000; Gilzenrat et al., 2002). Aston-Jones and Cohen proposed that

OFC and ACC guide LC-NE activity toward phasic mode when the reward of the current task is sufficient so promote exploitation and guide LC activity toward tonic mode if the current reward is insufficient so promote the exploration of another environment to look for a new reward.

2. ***The neuronal network reorganization model:*** It's known that LC firing rate varies with the level of attentiveness and arousal: when stimuli are novel and salient LC neurons respond phasically, but they show low activity during low vigilance behavioral states such as eating or grooming (Jouvet 1969; Foote et al., 1980; Aston-Jones et Bloom 1981a, 1981b). Furthermore, it has been suggested that LC neurons of primates are involved in maintaining ongoing focused attention (Aston-Jones et al., 1994, 1991). On the other hand, several studies have shown that LC signals are important for learning and adapting to new contingencies (Sara et al., 1994; Sara et Segal 1991; Vankov et al., 1995; Aston-Jones et al., 1997; Devauges et Sara 1990). Based on these results and on the fact that LC is the primary source of NE transmitted to the rest of the brain (Jones et al., 1977; Aston-Jones et Cohen 2005a), Bouret et Sara (2005) have proposed a model to the effect that LC-NE signals have a general reset function that facilitates changes in widespread forebrain networks that are mediating specific cognitive functions. In their model LC phasic activity plays a role of "reset signal' that facilitates transitions between different behaviors. They have tested their hypothesis by using a 'Go-NoGo' task, an odor discrimination task. They describe an LC phasic response when the first light is flashed to indicate the trial onset to the animal. They refer to this task period before the Go-NoGo signal to an expectancy situation. Several studies have shown that during this period, the animal is engaged in the task and it corresponds to the expectancy mode of attention in which LC low activity (phasic mode) prevents behavioral shifts (Delagrange et al., 1993, 1989; Rougeul-Buser and Buser, 1997; Wiest and Nicolelis, 2003). Buser et al, (1997) have defined the 'expectancy' mode of attention as the state during which the LC activity is low (phasic mode) to prevent spurious behavioral distraction by irrelevant stimuli when the animal is actively engaged and waiting to process the cues. In this model, Bouret et Sara (2005) suggest that during behavioral tasks, the activation of LC neurons is related to stimulus-induced cognitive shifts and is triggered by the recognition of an awaited stimulus that is not predicted with a high reliability. They suggested that the reset signal sent by LC-NE system generates a network functional reorganization within the medial frontal cortex (mFCx) and the central nucleus of the amygdala (CeA) that have similar roles in cognitive function then LC (Birrell and Brown, 2000; Bockstaele et al.,1996.; Bouret et al., 2003; Bussey et al., 1997; Gisquet-Verrier et al., 2000.; Jodoj et al., 1998; Mantz et al., 1988)

V. Which model is more adapted to real neuronal mechanisms?

These two models discuss LC-NE activity during normal brain states. Overall the first model, the gain model offers clear schemas of how the LC-NE system plays a key role during arousal. In this context, LC-NE acts like a balance between continuous exploitation of the available reward in the environment because it has high utility value and transient exploration of a new environment, in order to discover higher utility rewards. OFC and ACC are proposed to guide this alternation in synergy, evaluating the cost and benefit of each type of reward dynamically. If the amount of the available reward in the current environment is higher than the cost associating with its retrieval, LC-NE balance shifts it favor of its exploitation. However if the amount of the current reward is lower than its associated cost, LC-NE balance shifts in favor of the exploration of another environment in order to find higher benefit and utile rewards. This balance serves to optimize 'reward-seeking behavior' during arousal, an important state associated with to attention, anxiety, stress and motivation.

In the second model, the 'reset signal model', proposes a clear schema of how the LC-NE system plays a key role during the expectancy mode of attention, thus preventing behavioral distraction by irrelevant stimuli. In this model, when a relevant stimulus is presented, LC-NE generate network reorganization, due to the reset signal, generates a cognitive shift to the benefit of the relevant stimulus. The organized network is thus more adapted to the ongoing task demands and thus allows optimal behavior.

Both models involve attentional processes. The existing literature doesn't provide enough information to decide between these two models. An important approach to disambiguate between these two models would be to study the contribution of LC-NE both to normal and pathological attentional states. It has been shown that in many neuropsychiatric disorders, patients suffer from attention deficit. Furthermore, it has been suggested that LC–noradrenergic system may result in deficits in a variety of cognitive and affective processes that are, in turn, associated with numerous neuropsychiatric and neurodegenerative disorders such as attention deficit/hyperactivity disorder (ADHD) (Agster et al. 2011; Arnsten 2001; Swanson 1976), depression (McMillan et al., 2011; Zhao et al., 2009), schizophrenia(Brown et al., 2012; Shoja Shafti et al., 2015) and Alzheimer's disease (Hammerschmidt et al., 2013; Rey et al., 2015). The most related pathologies to LC-noradrenergic system dysfunction are those linked with stress and sustained attention disorders such as ADHD.

ADHD is a neurobehavioral developmental disorder in children and adults characterized by inappropriate levels of impulsive and inattentive behaviors, sometimes associated with hyperactivity. While the cause of ADHD is unknown, several mechanisms have been proposed to explain this disease. For example, it has been suggested that ADHD is connected to imbalance between dopaminergic and noradrenergic monoamine systems. This perturbation arises from a lack of phosphoinositide 3-kinase PI3Kγ which cause an increase in the levels of cAMP and subsequent stimulation of the transcription factor CREB, which regulates the ratio of NA to DA in PFC and striatum (Arnsten, 2009; Biederman, 2005; D'Andrea et al., 2015; Darcq and Kieffer, 2015; Kim et al., 2011). Another proposed mechanism for ADHD is impaired NE transporter (NET) function, however, and quite surprisingly, human studies that used PET have shown that availability and distribution of NET doesn't change in ADHD patients (Vanicek et al., 2014). Furthermore, drugs that inhibit NET such as methylphenidate and atomoxetine improve behavioral outcomes and sensory signal processing in animals performing flexible and sustained tasks (Caetano et al., 2013; Rachel L. Navarra et al., 2013; Lori A. Newman et al., 2008). Several imaging and neuropsychological studies have found a link between PFC impairment and ADHD. For example, PFC size is remarkably reduced in ADHD patients, particularly in the right hemisphere (Hill et al., 2003; Sowell et al., 2003). In addition, a reduced metabolism in the PFC is found in ADHD patients with imaging studies (Yeo et al., 2000). Another group of study have shown that patients with ADHD could not perform tasks that involve PFC function such as working memory, behavioral inhibition and reward reversal (Bedard et al., 2003; McLean et al., 2004). A recent fMRI study has shown an increase of fronto-parietal network activation in ADHD patient after administration of NET inhibitor called atomoxetine (Bush et al., 2013). Another recent study has shown that methylphenidate, a psychostimulant used in the treatment of ADHD, which enhances NA and DA signaling, improves sustained attention (Dockree et al., 2017). Thus, all these results show a clear link between ADHD, LC-NE system and prefrontal cortex (PFC). Prefrontal FEF is proposed to be the source of spatial attention top-down control (Buschman et Miller 2007; Wardak et al., 2006; Ibos et al., 2013; Ekstrom et al., 2008). Given the evident link between ADHD, LC-NE system and FEF, the behavioral (***Chapter IV***) and FEF neural correlates (***Chapter V***) of noradrenergic modulation will be investigated and discussed in relation with the two above described models of LC-NE function.

VI. References

Adamec, R., Walling, S., Burton, P., 2004. Long-lasting, selective, anxiogenic effects of feline predator stress in mice. Physiol. Behav. 83, 401–410.

Agster, K.L., Clark, B.D., Gao, W.-J., Shumsky, J.S., Wang, H.X., Berridge, C.W., Waterhouse, B.D., 2011. Experimental strategies for investigating psychostimulant drug actions and prefrontal cortical function in ADHD and related attention disorders. Anat. Rec. Hoboken NJ 2007 294, 1698–1712.

Armstrong, K.M., Chang, M.H., Moore, T., 2009. Selection and maintenance of spatial information by frontal eye field neurons. J. Neurosci. Off. J. Soc. Neurosci. 29, 15621–15629.

Arnsten, A.F., 2001. Modulation of prefrontal cortical-striatal circuits: relevance to therapeutic treatments for Tourette syndrome and attention-deficit hyperactivity disorder. Adv. Neurol. 85, 333–341.

Arnsten, A.F.T., 2009. Toward a new understanding of attention-deficit hyperactivity disorder pathophysiology: an important role for prefrontal cortex dysfunction. CNS Drugs 23 Suppl 1, 33–41.

Arnsten, A.F.T., 2007. Catecholamine and second messenger influences on prefrontal cortical networks of "representational knowledge": a rational bridge between genetics and the symptoms of mental illness. Cereb. Cortex N. Y. N 1991 17 Suppl 1, i6-15.

Arnsten, A.F.T., 2006. Fundamentals of attention-deficit/hyperactivity disorder: circuits and pathways. J. Clin. Psychiatry 67 Suppl 8, 7–12.

Aston-Jones, G., Bloom, F.E., 1981a. Activity of norepinephrine-containing locus coeruleus neurons in behaving rats anticipates fluctuations in the sleep-waking cycle. J. Neurosci. Off. J. Soc. Neurosci. 1, 876–886.

Aston-Jones, G., Bloom, F.E., 1981b. Norepinephrine-containing locus coeruleus neurons in behaving rats exhibit pronounced responses to non-noxious environmental stimuli. J. Neurosci. Off. J. Soc. Neurosci. 1, 887–900.

Aston-Jones, G., Chiang, C., Alexinsky, T., 1991. Discharge of noradrenergic locus coeruleus neurons in behaving rats and monkeys suggests a role in vigilance. Prog. Brain Res. 88, 501–520.

Aston-Jones, G., Cohen, J.D., 2005a. Adaptive gain and the role of the locus coeruleus-norepinephrine system in optimal performance. J. Comp. Neurol. 493, 99–110.

Aston-Jones, G., Cohen, J.D., 2005b. An integrative theory of locus coeruleus-norepinephrine function: adaptive gain and optimal performance. Annu. Rev. Neurosci. 28, 403–450.

Aston-Jones, G., Harris, G.C., 2004. Brain substrates for increased drug seeking during protracted withdrawal. Neuropharmacology 47, 167–179.

Aston-Jones, G., Rajkowski, J., Cohen, J., 2000. Locus coeruleus and regulation of behavioral flexibility and attention, in: Progress in Brain Research. Elsevier, pp. 165–182.

Aston-Jones, G., Rajkowski, J., Kubiak, P., 1997. Conditioned responses of monkey locus coeruleus neurons anticipate acquisition of discriminative behavior in a vigilance task. Neuroscience 80, 697–715.

Aston-Jones, G., Rajkowski, J., Kubiak, P., Alexinsky, T., 1994. Locus coeruleus neurons in monkey are selectively activated by attended cues in a vigilance task. J. Neurosci. Off. J. Soc. Neurosci. 14, 4467–4480.

Astrand, E., Ibos, G., Duhamel, J.-R., Ben Hamed, S., 2015. Differential dynamics of spatial attention, position, and color coding within the parietofrontal network. J. Neurosci. Off. J. Soc. Neurosci. 35, 3174–3189.

Astrand, E., Wardak, C., Baraduc, P., Ben Hamed, S., 2016. Direct Two-Dimensional Access to the Spatial Location of Covert Attention in Macaque Prefrontal Cortex. Curr. Biol. CB 26, 1699–1704.

Bedard, A.-C., Ickowicz, A., Logan, G.D., Hogg-Johnson, S., Schachar, R., Tannock, R., 2003. Selective inhibition in children with attention-deficit hyperactivity disorder off and on stimulant medication. J. Abnorm. Child Psychol. 31, 315–327.

Berridge, C.W., Waterhouse, B.D., 2003. The locus coeruleus-noradrenergic system: modulation of behavioral state and state-dependent cognitive processes. Brain Res. Brain Res. Rev. 42, 33–84.

Biederman, J., 2005. Attention-deficit/hyperactivity disorder: a selective overview. Biol. Psychiatry 57, 1215–1220.

Birrell, J.M., Brown, V.J., 2000. Medial Frontal Cortex Mediates Perceptual Attentional Set Shifting in the Rat. J. Neurosci. 20, 4320–4324.

Bisley, J.W., Goldberg, M.E., 2003. Neuronal activity in the lateral intraparietal area and spatial attention. Science 299, 81–86.

Bockstaele, E.J.V., Chan, J., Pickel, V.M., n.d. Input from central nucleus of the amygdala efferents to pericoerulear dendrites, some of which contain tyrosine hydroxylase immunoreactivity 14.

Bouret, S., Duvel, A., Onat, S., Sara, S.J., 2003. Phasic Activation of Locus Ceruleus Neurons by the Central Nucleus of the Amygdala. J. Neurosci. 23, 3491–3497.

Bouret, S., Sara, S.J., 2005. Network reset: a simplified overarching theory of locus coeruleus noradrenaline function. Trends Neurosci. 28, 574–582.

Brown, D.C., Co, M.S., Wolff, R.C., Atzori, M., 2012. α-Adrenergic receptors in auditory cue detection: α2 receptor blockade suppresses false alarm responding in the rat. Neuropharmacology 62, 2178–2183.

Buschman, T.J., Miller, E.K., 2007. Top-down versus bottom-up control of attention in the prefrontal and posterior parietal cortices. Science 315, 1860–1862.

Bush, G., Holmes, J., Shin, L.M., Surman, C., Makris, N., Mick, E., Seidman, L.J., Biederman, J., 2013. Atomoxetine increases fronto-parietal functional MRI activation in attention-deficit/hyperactivity disorder: a pilot study. Psychiatry Res. 211, 88–91.

Bussey, T.J., Everitt, B.J., Robbins, T.W., 1997. Dissociable effects of cingulate and medial frontal cortex lesions on stimulus-reward learning using a novel Pavlovian autoshaping procedure for the rat: Implications for the neurobiology of emotion. Behav. Neurosci. 111, 908–919.

Bylund, D.B., Eikenberg, D.C., Hieble, J.P., Langer, S.Z., Lefkowitz, R.J., Minneman, K.P., Molinoff, P.B., Ruffolo, R.R., Trendelenburg, U., 1994. International Union of Pharmacology nomenclature of adrenoceptors. Pharmacol. Rev. 46, 121–136.

Caetano, M.S., Jin, L.E., Harenberg, L., Stachenfeld, K.L., Arnsten, A.F.T., Laubach, M., 2013. Noradrenergic control of error perseveration in medial prefrontal cortex. Front. Integr. Neurosci. 6.

Cain, R.E., Wasserman, M.C., Waterhouse, B.D., McGaughy, J.A., 2011. Atomoxetine facilitates attentional set shifting in adolescent rats. Dev. Cogn. Neurosci. 1, 552–559.

Corbetta, M., Shulman, G.L., 2002. Control of goal-directed and stimulus-driven attention in the brain. Nat. Rev. Neurosci. 3, 201–215.

D'Andrea, I., Fardella, V., Fardella, S., Pallante, F., Ghigo, A., Iacobucci, R., Maffei, A., Hirsch, E., Lembo, G., Carnevale, D., 2015. Lack of kinase-independent activity of PI3Kγ in locus coeruleus induces ADHD symptoms through increased CREB signaling. EMBO Mol. Med. 7, 904–917. 7

Darcq, E., Kieffer, B.L., 2015. PI3K signaling in the locus coeruleus: a new molecular pathway for ADHD research. EMBO Mol. Med. 7, 859–861.

Delagrange, P., Canu, M.H., Rougeul, A., Buser, P., Bouyer, J.J., 1993. Effects of locus coeruleus lesions on vigilance and attentive behaviour in cat. Behav. Brain Res. 53, 155–165.

Delagrange, P., Tadjer, D., Bouyer, J.J., Rougeul, A., Conrath, M., 1989. Effect of DSP4, a neurotoxic agent, on attentive behaviour and related electrocortical activity in cat. Behav. Brain Res. 33, 33–43.

Delaville, C., Navailles, S., Benazzouz, A., 2012. Effects of noradrenaline and serotonin depletions on the neuronal activity of globus pallidus and substantia nigra pars reticulata in experimental parkinsonism. Neuroscience 202, 424–433.

Desimone, R., Duncan, J., 1995. Neural Mechanisms of Selective Visual Attention. Annu. Rev. Neurosci. 18, 193–222.

Devauges, V., Sara, S.J., 1990. Activation of the noradrenergic system facilitates an attentional shift in the rat. Behav. Brain Res. 39, 19–28.

Devilbiss, D.M., Page, M.E., Waterhouse, B.D., 2006. Locus ceruleus regulates sensory encoding by neurons and networks in waking animals. J. Neurosci. Off. J. Soc. Neurosci. 26, 9860–9872.

Eisenberger, N.I., Lieberman, M.D., Williams, K.D., 2003. Does Rejection Hurt? An fMRI Study of Social Exclusion. Science 302, 290–292.

Ekstrom, L.B., Roelfsema, P.R., Arsenault, J.T., Bonmassar, G., Vanduffel, W., 2008. Bottom-up dependent gating of frontal signals in early visual cortex. Science 321, 414–417.

Falkenstein, M., Hohnsbein, J., Hoormann, J., Blanke, L., 1991. Effects of crossmodal divided attention on late ERP components. II. Error processing in choice reaction tasks. Electroencephalogr. Clin. Neurophysiol. 78, 447–455.

Foote, S.L., Aston-Jones, G., Bloom, F.E., 1980. Impulse activity of locus coeruleus neurons in awake rats and monkeys is a function of sensory stimulation and arousal. Proc. Natl. Acad. Sci. U. S. A. 77, 3033–3037.

Gatter, K.C., Powell, T.P., 1977. The projection of the locus coeruleus upon the neocortex in the macaque monkey. Neuroscience 2, 441–445.

Genestine, M., Lin, L., Durens, M., Yan, Y., Jiang, Y., Prem, S., Bailoor, K., Kelly, B., Sonsalla, P.K., Matteson, P.G., Silverman, J., Crawley, J.N., Millonig, J.H., DiCicco-Bloom, E., 2015. Engrailed-2 (En2) deletion produces multiple neurodevelopmental defects in monoamine systems, forebrain structures and neurogenesis and behavior. Hum. Mol. Genet. 24, 5805–5827.

Gesi, M., Soldani, P., Giorgi, F.S., Santinami, A., Bonaccorsi, I., Fornai, F., 2000. The role of the locus coeruleus in the development of Parkinson's disease. Neurosci. Biobehav. Rev. 24, 655–668.

Gilzenrat, M.S., Holmes, B.D., Rajkowski, J., Aston-Jones, G., Cohen, J.D., 2002. Simplified dynamics in a model of noradrenergic modulation of cognitive performance. Neural Netw. Off. J. Int. Neural Netw. Soc. 15, 647–663.

Gilzenrat, M.S., Nieuwenhuis, S., Jepma, M., Cohen, J.D., 2010. Pupil diameter tracks changes in control state predicted by the adaptive gain theory of locus coeruleus function. Cogn. Affect. Behav. Neurosci. 10, 252–269.

Gisquet-Verrier, P., Winocur, G., Delatour, Beno., n.d. Functional dissociation between dorsal and ventral regions of the medial prefrontal cortex in rats 13.

Gottlieb, J.P., Kusunoki, M., Goldberg, M.E., 1998. The representation of visual salience in monkey parietal cortex. Nature 391, 481–484.

Hagena, H., Hansen, N., Manahan-Vaughan, D., 2016. β-Adrenergic Control of Hippocampal Function: Subserving the Choreography of Synaptic Information Storage and Memory. Cereb. Cortex N. Y. N 1991 26, 1349–1364.

Hammerschmidt, T., Kummer, M.P., Terwel, D., Martinez, A., Gorji, A., Pape, H.-C., Rommelfanger, K.S., Schroeder, J.P., Stoll, M., Schultze, J., Weinshenker, D., Heneka, M.T., 2013. Selective loss of noradrenaline exacerbates early cognitive dysfunction and synaptic deficits in APP/PS1 mice. Biol. Psychiatry 73, 454–463.

Hansen, N., Manahan-Vaughan, D., 2015. Hippocampal long-term potentiation that is elicited by perforant path stimulation or that occurs in conjunction with spatial learning is tightly controlled by beta-adrenoreceptors and the locus coeruleus. Hippocampus 25, 1285–1298.

Hein, L., 2006. Adrenoceptors and signal transduction in neurons. Cell Tissue Res. 326, 541–551.

Herrington, T.M., Assad, J.A., 2009. Neural activity in the middle temporal area and lateral intraparietal area during attentionly cued shifts of attention. J. Neurosci. Off. J. Soc. Neurosci. 29, 14160–14176.

Hill, D.E., Yeo, R.A., Campbell, R.A., Hart, B., Vigil, J., Brooks, W., 2003. Magnetic resonance imaging correlates of attention-deficit/hyperactivity disorder in children. Neuropsychology 17, 496–506.

Hobson, J.A., McCarley, R.W., Wyzinski, P.W., 1975. Sleep cycle oscillation: reciprocal discharge by two brainstem neuronal groups. Science 189, 55–58.

Holroyd, C.B., Larsen, J.T., Cohen, J.D., 2004a. Context dependence of the event-related brain potential associated with reward and punishment. Psychophysiology 41, 245–253.

Holroyd, C.B., Nieuwenhuis, S., Yeung, N., Cohen, J.D., n.d. Errors in reward prediction are re£ected in the event-related brain potential 4.

Holroyd, C.B., Nieuwenhuis, S., Yeung, N., Nystrom, L., Mars, R.B., Coles, M.G.H., Cohen, J.D., 2004b. Dorsal anterior cingulate cortex shows fMRI response to internal and external error signals. Nat. Neurosci. 7, 497–498.

Hou, R.H., Freeman, C., Langley, R.W., Szabadi, E., Bradshaw, C.M., 2005. Does modafinil activate the locus coeruleus in man? Comparison of modafinil and clonidine on arousal and autonomic functions in human volunteers. Psychopharmacology (Berl.) 181, 537–549.

Ibos, G., Duhamel, J.-R., Ben Hamed, S., 2013. A functional hierarchy within the parietofrontal network in stimulus selection and attention control. J. Neurosci. Off. J. Soc. Neurosci. 33, 8359–8369.

Janitzky, K., D'Hanis, W., Kröber, A., Schwegler, H., 2015. TMT predator odor activated neural circuit in C57BL/6J mice indicates TMT-stress as a suitable model for uncontrollable intense stress. Brain Res. 1599, 1–8.

Jepma, M., Nieuwenhuis, S., 2011. Pupil diameter predicts changes in the exploration-exploitation trade-off: evidence for the adaptive gain theory. J. Cogn. Neurosci. 23, 1587–1596.

Jodoj, E., Chiang, C., Aston-Jones, G., 1998. Potent excitatory influence of prefrontal cortex activity on noradrenergic locus coeruleus neurons. Neuroscience 83, 63–79.

Jones, B.E., Harper, S.T., Halaris, A.E., 1977. Effects of locus coeruleus lesions upon cerebral monoamine content, sleep-wakefulness states and the response to amphetamine in the cat. Brain Res. 124, 473–496.

Jouvet, M., 1969. Biogenic amines and the states of sleep. Science 163, 32–41.

Kehagia, A.A., Murray, G.K., Robbins, T.W., 2010. Learning and cognitive flexibility: frontostriatal function and monoaminergic modulation. Curr. Opin. Neurobiol. 20, 199–204.

Kiehl, K.A., Liddle, P.F., Hopfinger, J.B., 2000. Error processing and the rostral anterior cingulate: an event-related fMRI study. Psychophysiology 37, 216–223.

Kim, J.-I., Lee, H.-R., Sim, S., Baek, J., Yu, N.-K., Choi, J.-H., Ko, H.-G., Lee, Y.-S., Park, S.-W., Kwak, C., Ahn, S.-J., Choi, S.Y., Kim, H., Kim, K.-H., Backx, P.H., Bradley, C.A., Kim, E., Jang, D.-J., Lee, K., Kim, S.J., Zhuo, M., Collingridge, G.L., Kaang, B.-K., 2011. PI3Kγ is required for NMDA receptor-dependent long-term depression and behavioral flexibility. Nat. Neurosci. 14, 1447–1454.

Lapiz, M.D.S., Bondi, C.O., Morilak, D.A., 2007. Chronic treatment with desipramine improves cognitive performance of rats in an attentional set-shifting test. Neuropsychopharmacol. Off. Publ. Am. Coll. Neuropsychopharmacol. 32, 1000–1010.

Lapiz, M.D.S., Morilak, D.A., 2006. Noradrenergic modulation of cognitive function in rat medial prefrontal cortex as measured by attentional set shifting capability. Neuroscience 137, 1039–1049.

Mantz, J., Milla, C., Glowinski, J., Thierry, A.M., 1988. Differential effects of ascending neurons containing dopamine and noradrenaline in the control of spontaneous activity and of evoked responses in the rat prefrontal cortex. Neuroscience 27, 517–526.

Marder, E., 2012. Neuromodulation of neuronal circuits: back to the future. Neuron 76, 1–11.

McGaughy, J., Ross, R.S., Eichenbaum, H., 2008. Noradrenergic, but not cholinergic, deafferentation of prefrontal cortex impairs attentional set-shifting. Neuroscience 153, 63–71.

McLean, A., Dowson, J., Toone, B., Young, S., Bazanis, E., Robbins, T.W., Sahakian, B.J., 2004. Characteristic neurocognitive profile associated with adult attention-deficit/hyperactivity disorder. Psychol. Med. 34, 681–692.

McMillan, P.J., White, S.S., Franklin, A., Greenup, J.L., Leverenz, J.B., Raskind, M.A., Szot, P., 2011. Differential response of the central noradrenergic nervous system to the loss of locus coeruleus neurons in Parkinson's disease and Alzheimer's disease. Brain Res. 1373, 240–252.

Monosov, I.E., Thompson, K.G., 2009. Frontal eye field activity enhances object identification during covert visual search. J. Neurophysiol. 102, 3656–3672.

Moore, R.Y., Bloom, F.E., 1979. Central catecholamine neuron systems: anatomy and physiology of the norepinephrine and epinephrine systems. Annu. Rev. Neurosci. 2, 113–168.

Moore, T., Armstrong, K.M., Fallah, M., 2003. Visuomotor origins of covert spatial attention. Neuron 40, 671–683.

Moore, T., Fallah, M., 2004. Microstimulation of the frontal eye field and its effects on covert spatial attention. J. Neurophysiol. 91, 152–162.

Navarra, R.L., Clark, B.D., Gargiulo, A.T., Waterhouse, B.D., 2017. Methylphenidate Enhances Early-Stage Sensory Processing and Rodent Performance of a Visual Signal Detection Task. Neuropsychopharmacol. Off. Publ. Am. Coll. Neuropsychopharmacol. 42, 1326–1337.

Navarra, R.L., Clark, B.D., Zitnik, G.A., Waterhouse, B.D., 2013. Methylphenidate and atomoxetine enhance sensory-evoked neuronal activity in the visual thalamus of male rats. Exp. Clin. Psychopharmacol. 21, 363–374.

Newman, L.A., Darling, J., McGaughy, J., 2008. Atomoxetine reverses attentional deficits produced by noradrenergic deafferentation of medial prefrontal cortex. Psychopharmacology (Berl.) 200, 39–50.

Nieuwenhuis, S., van Nieuwpoort, I.C., Veltman, D.J., Drent, M.L., 2007. Effects of the noradrenergic agonist clonidine on temporal and spatial attention. Psychopharmacology (Berl.) 193, 261–269.

Petersen, S.E., Posner, M.I., 2012. The attention system of the human brain: 20 years after. Annu. Rev. Neurosci. 35, 73–89.

Phillips, M.A., Szabadi, E., Bradshaw, C.M., 2000. Comparison of the effects of clonidine and yohimbine on pupillary diameter at different illumination levels. Br. J. Clin. Pharmacol. 50, 65–68.

Rajkowski, J., Kubiak, P., Aston-Jones, G., 1994. Locus coeruleus activity in monkey: phasic and tonic changes are associated with altered vigilance. Brain Res. Bull. 35, 607–616.

Rey, H.G., Pedreira, C., Quian Quiroga, R., 2015. Past, present and future of spike sorting techniques. Brain Res. Bull. 119, 106–117.

Robertson, S.D., Plummer, N.W., de Marchena, J., Jensen, P., 2013. Developmental origins of central norepinephrine neuron diversity. Nat. Neurosci. 16, 1016–1023.

Roesch, M.R., Olson, C.R., 2004. Neuronal activity related to reward value and motivation in primate frontal cortex. Science 304, 307–310.

Rolls, E.T., 2004. Smell, Taste, Texture, and Temperature Multimodal Representations in the Brain, and Their Relevance to the Control of Appetite. Nutr. Rev. 62, S193–S204.

Rougeul-Buser, A., Buser, P., 1997. Rhythms in the alpha band in cats and their behavioural correlates. Int. J. Psychophysiol. Off. J. Int. Organ. Psychophysiol. 26, 191–203.

Sara, S.J., 2009. The locus coeruleus and noradrenergic modulation of cognition. Nat. Rev. Neurosci. 10, 211–223.

Sara, S.J., Bouret, S., 2012. Orienting and reorienting: the locus coeruleus mediates cognition through arousal. Neuron 76, 130–141.

Sara, S.J., Segal, M., 1991. Plasticity of sensory responses of locus coeruleus neurons in the behaving rat: implications for cognition. Prog. Brain Res. 88, 571–585.

Sara, S.J., Vankov, A., Hervé, A., 1994. Locus coeruleus-evoked responses in behaving rats: a clue to the role of noradrenaline in memory. Brain Res. Bull. 35, 457–465.

Schutsky, K., Ouyang, M., Castelino, C.B., Zhang, L., Thomas, S.A., 2011. Stress and glucocorticoids impair memory retrieval via β2-adrenergic, Gi/o-coupled suppression of cAMP signaling. J. Neurosci. Off. J. Soc. Neurosci. 31, 14172–14181.

Schwarz, L.A., Miyamichi, K., Gao, X.J., Beier, K.T., Weissbourd, B., DeLoach, K.E., Ren, J., Ibanes, S., Malenka, R.C., Kremer, E.J., Luo, L., 2015. Viral-genetic tracing of the input–output organization of a central noradrenaline circuit. Nature 524, 88–92.

Shoja Shafti, S., Jafarabad, M.S., Azizi, R., 2015. Amelioration of deficit syndrome of schizophrenia by norepinephrine reuptake inhibitor. Ther. Adv. Psychopharmacol. 5, 263–270.

Sowell, E.R., Thompson, P.M., Welcome, S.E., Henkenius, A.L., Toga, A.W., Peterson, B.S., 2003. Cortical abnormalities in children and adolescents with attention-deficit hyperactivity disorder. Lancet Lond. Engl. 362, 1699–1707.

Swanson, L.W., 1976. The locus coeruleus: A cytoarchitectonic, golgi and immunohistochemical study in the albino rat. Brain Res. 110, 39–56.

Szabadi, E., 2013. Functional neuroanatomy of the central noradrenergic system. J. Psychopharmacol. Oxf. Engl. 27, 659–693.

Thompson, K.G., Bichot, N.P., Sato, T.R., 2005. Frontal eye field activity before visual search errors reveals the integration of bottom-up and top-down salience. J. Neurophysiol. 93, 337–351.

Tremblay, L., Schultz, W., 1999. Relative reward preference in primate orbitofrontal cortex. Nature 398, 704–708.

Vanicek, T., Spies, M., Rami-Mark, C., Savli, M., Höflich, A., Kranz, G.S., Hahn, A., Kutzelnigg, A., Traub-Weidinger, T., Mitterhauser, M., Wadsak, W., Hacker, M., Volkow, N.D., Kasper, S., Lanzenberger, R., 2014. The norepinephrine transporter in attention-deficit/hyperactivity disorder investigated with positron emission tomography. JAMA Psychiatry 71, 1340–1349.

Vankov, A., Hervé-Minvielle, A., Sara, S.J., 1995. Response to novelty and its rapid habituation in locus coeruleus neurons of the freely exploring rat. Eur. J. Neurosci. 7, 1180–1187.

Vazey, E.M., Aston-Jones, G., 2014. Designer receptor manipulations reveal a role of the locus coeruleus noradrenergic system in isoflurane general anesthesia. Proc. Natl. Acad. Sci. U. S. A. 111, 3859–3864.

von der Gablentz, J., Tempelmann, C., Münte, T.F., Heldmann, M., 2015. Performance monitoring and behavioral adaptation during task switching: an fMRI study. Neuroscience 285, 227–235.

Wallis, J.D., Miller, E.K., 2003. Neuronal activity in primate dorsolateral and orbital prefrontal cortex during performance of a reward preference task. Eur. J. Neurosci. 18, 2069–2081.

Wardak, C., Ibos, G., Duhamel, J.-R., Olivier, E., 2006. Contribution of the monkey frontal eye field to covert visual attention. J. Neurosci. Off. J. Soc. Neurosci. 26, 4228–4235.

Weinshenker, D., 2008. Functional consequences of locus coeruleus degeneration in Alzheimer's disease. Curr. Alzheimer Res. 5, 342–345.

Wiest, M.C., Nicolelis, M.A.L., 2003. Behavioral detection of tactile stimuli during 7-12 Hz cortical oscillations in awake rats. Nat. Neurosci. 6, 913–914.

Witte, E.A., Marrocco, R.T., 1997. Alteration of brain noradrenergic activity in rhesus monkeys affects the alerting component of covert orienting. Psychopharmacology (Berl.) 132, 315–323.

Yantis, S., Schwarzbach, J., Serences, J.T., Carlson, R.L., Steinmetz, M.A., Pekar, J.J., Courtney, S.M., 2002. Transient neural activity in human parietal cortex during spatial attention shifts. Nat. Neurosci. 5, 995–1002.

Yeo, R.A., Hill, D., Campbell, R., Vigil, J., Brooks, W.M., 2000. Developmental instability and working memory ability in children: a magnetic resonance spectroscopy investigation. Dev. Neuropsychol. 17, 143–159.

Yeung, N., 2004. Independent Coding of Reward Magnitude and Valence in the Human Brain. J. Neurosci. 24, 6258–6264.

Yeung, N., Botvinick, M.M., Cohen, J.D., 2004. The neural basis of error detection: Conflict monitoring and the error-related negativity. Psychol. Rev. 931–959.

Zhao, Z., Zhang, H.-T., Bootzin, E., Millan, M.J., O'Donnell, J.M., 2009. Association of changes in norepinephrine and serotonin transporter expression with the long-term behavioral effects of antidepressant drugs. Neuropsychopharmacol. Off. Publ. Am. Coll. Neuropsychopharmacol. 34, 1467–1481.

Chapter IV

Norepinephrine improves attentional orienting in a predictive context

Norepinephrine improves attentional orienting in a predictive context

Abbreviated title: Norepinephrine improves spatial attention

Amelie J. Reynaud*[1, 2], Mathilda Froesel *[2,3], Carole Guedj[1, 2], Sameh Ben Hadj Hassen[2,3], Justine Clery[2,3], Martine Meunier [1, 2], Suliann Ben Hamed†[2,3], Fadila Hadj-Bouziane†[1, 2]

*†*These authors equally contributed to this work.*

[1] INSERM, U1028, CNRS UMR5292, Lyon Neuroscience Research Center, ImpAct Team, Lyon, F-69000, France;
[2] University UCBL Lyon 1, F-69000, France
[3] CNRS, UMR5229, Institut des Sciences Cognitives Marc Jeannerod

Corresponding authors: Amelie Reynaud, amelie.reynaud@inserm.fr and Fadila Hadj-Bouziane, fadila.hadj-bouziane@inserm.fr - INSERM U1028, CNRS UMR5292, Lyon Neuroscience Research Center, ImpAct Team, 16 avenue Doyen Lépine 69500 BRON, France.

Keywords: Atomoxetine, monkey, LATER, visuo-spatial attention, reaction time

Abstract

The role of norepinephrine (NE) in visuo-spatial attention remains poorly understood. Our goal was to identify the attentional processes influenced by atomoxetine (ATX) injections, a NE-reuptake inhibitor that boosts the level of NE in the brain, and to characterize these influences. We tested the effects of ATX injections, on seven monkeys performing a saccadic cued task in which cues and distractors were used to manipulate spatial attention. We found that when the cue accurately predicted the location of the upcoming cue in 80% of the trials, ATX consistently improved attentional orienting, as measured from reaction times (RTs). These effects were best accounted for by a faster accumulation rate in the valid trials, rather than by a change in the decision threshold. By contrast, the effect of ATX on alerting and distractor interference was more inconsistent. Finally, we also found that, under ATX, RTs to non-cued targets were longer when these were presented separately from cued targets. This suggests that the impact of NE on visuo-spatial attention depends on the context, such that the adaptive changes elicited by the highly informative value of the cues in the most frequent trials were accompanied by a cost in the less frequent trials.

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Atomoxetine improves attentional orienting in a predictive context

Amélie J. Reynaud[a,b,*,1], Mathilda Froesel[b,c,1], Carole Guedj[a,b], Sameh Ben Hadj Hassen[b,c], Justine Cléry[b,c], Martine Meunier[a,b], Suliann Ben Hamed[b,c,2], Fadila Hadj-Bouziane[a,b,**,2]

[a] INSERM, U1028, CNRS UMR5292, Lyon Neuroscience Research Center, ImpAct Team, Lyon, F-69000, France
[b] University UCBL, Lyon 1, F-69000, France
[c] CNRS, UMR5229, Institut des Sciences Cognitives Marc Jeannerod, France

HIGHLIGHTS

- Atomoxetine decreases reaction time of the most prevalent trials.
- Atomoxetine modulates the accumulation rate of sensory information.
- Atomoxetine adapts the response strategy to the context.

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ABSTRACT

The role of norepinephrine (NE) in visuo-spatial attention remains poorly understood. Our goal was to identify the attentional processes influenced by atomoxetine (ATX) injections, a NE-reuptake inhibitor that boosts the level of NE in the brain, and to characterize these influences. We tested the effects of ATX injections, on seven monkeys performing a saccadic cued task in which cues and distractors were used to manipulate spatial attention. We found that when the cue accurately predicted the location of the upcoming cue in 80% of the trials, ATX consistently improved attentional orienting, as measured from reaction times (RTs). These effects were best accounted for by a faster accumulation rate in the valid trials, rather than by a change in the decision threshold. By contrast, the effect of ATX on alerting and distractor interference was more inconsistent. Finally, we also found that, under ATX, RTs to non-cued targets were longer when these were presented separately from cued targets. This suggests that the impact of NE on visuo-spatial attention depends on the context, such that the adaptive changes elicited by the highly informative value of the cues in the most frequent trials were accompanied by a cost in the less frequent trials.

1. Introduction

Visuo-spatial attention is a pervasive function that enables us to selectively process visual information through prioritization of a spatial location while setting aside other locations. It depends on the fronto-parietal network and is under the influence of several neuromodulators including dopamine (DA), acetylcholine (ACh) and norepinephrine (NE) (see Noudoost and Moore, 2011). While a systematic approach to understand the role of DA and ACh in visual-spatial attention has been carried out over the years, the role of NE is currently less understood (see Noudoost and Moore, 2011).

In particular, only a handful of studies have addressed the role of NE transmission in visuo-spatial attention and its sub-components (alerting, orientating and executive control; Posner, 1980, Petersen and Posner, 2012), and the results are inconsistent. Petersen and Posner (2012) suggest a specific role of NE in the maintenance of high sensitivity to incoming stimuli i.e. the alerting sub-component (Petersen and Posner, 2012). At least two studies provide evidence in support of this (Witte and Marrocco, 1997; Coull et al., 2001). Evidence of the contribution of NE to spatial orienting is more inconsistent (Clark et al., 1989; Coull et al., 2001; Witte and Marrocco, 1997). As to attentional executive control, the third attentional sub-component, reaction times to identical external events have been shown to be affected by general task context, and to be much faster in highly predictive contexts than in

* Corresponding author. INSERM, U1028, CNRS UMR5292, Lyon Neuroscience Research Center, ImpAct Team, 16 avenue Doyen, Lépine, 69500, Bron, France.
** Corresponding author. INSERM U1028, CNRS UMR5292, Lyon Neuroscience Research Center, ImpAct Team, 16 avenue Doyen, Lépine, 69500, Bron, France.
E-mail addresses: amelie.reynaud@inserm.fr (A.J. Reynaud), fadila.hadj-bouziane@inserm.fr (F. Hadj-Bouziane).
[1] These authors equally contributed to this work.
[2] These authors equally contributed to this work.

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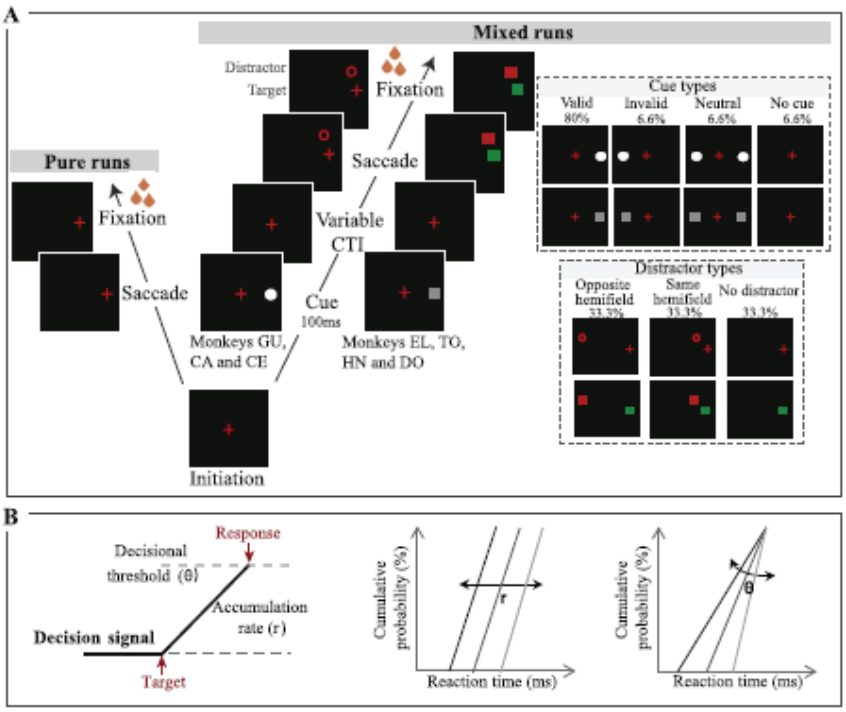

Fig. 1. Behavioral task and LATER model. A: In the mixed runs (spatial attention cued task), monkeys initiated the trial by fixating the red cross. Then, a cue was flashed and the monkey was required to keep his gaze on the red cross. The cue could either be valid, invalid, neutral or absent. After a cue-target interval (CTI), the target appeared on one side of the screen. Simultaneously, a distractor could appear in the same or opposite hemifield of the target location. The monkey had to ignore the distractor and saccade to the new target location to successfully complete the trial and receive a reward. The pure runs did not include any cue nor any distractor and monkey had to saccade to the target location to successfully complete the trial and receive a reward. **B:** According to the LATER model, RT is the culmination of a decisional signal which starts at the apparition of the target, rises in response with a constant linear rate (r) and ends with the initiation of a response at the decision threshold (θ) (left panel). Cumulative RT distributions are plotted as reciprobit plots, so that each distribution corresponds to a line. On this plot, the change of accumulation rate is embodied by a shift of the lines (middle panel) and the change of the decisional threshold by a swivel of the lines (right panel).

less predictive contexts (Los, 1996; Los et al., 2001; Albares et al., 2011; Wardak et al., 2012). While there is, to our knowledge, no direct evidence for an effect of NE onto this attentional sub-component, a recent study shows a selective increase in pupil size, an indirect index of NE activity, in the presence of highly predictive cues (Dragone et al., 2018). In addition, the involvement of the NE system in the ability to shift attentional set was reported in several studies (McGaughy et al., 2008; Newman et al., 2008; Cain et al., 2011; Berridge et al., 2012; Bradshaw et al., 2016). This, thus, suggests a possible interaction between NE and attentional executive control.

Here, we focused onto these three specific attentional components, namely alerting, spatial orienting and executive control and we aimed at 1) clarifying the components that are under the influence of NE availability and 2) characterizing the specific action of NE availability onto them.

We thus tested seven monkeys in a saccadic cued task derived from the attentional network task (Posner, 1980). This task allows manipulating the focus of attention by using cues that precede the appearance of the target. We used a context where the cue accurately predicted the spatial location of the upcoming target in 80% of the trials. A distractor could also appear simultaneously with the target to examine the subjects' ability to filter distractors out when planning their saccadic movement. We tested the monkeys under two pharmacological conditions: after saline administration used as the control condition and after atomoxetine (ATX) administration, a NE reuptake inhibitor.

To investigate whether alerting and orienting were affected by ATX, we computed attentional network scores from the reaction times (Fan et al., 2002). To identify changes driven by task context and executive control, we compared RTs in same type of trial in two different context. To investigate how these attentional processes were affected by ATX, we used the LATER model (linear approach to threshold with ergodic rate; Carpenter and Williams, 1995) to test whether changes in RT distributions following NE modulation were better accounted for by a change in signal accumulation rate, signing a perceptual process, or a change in decision threshold, signing a top-down process (Noorani and Carpenter, 2016). Following ATX injections, one could expect either 1) a global non-specific effect onto all three attentional components; 2) an effect specific to the alerting non-selective attentional component or 3) an effect specific to the dynamic/flexible components of attention, namely orienting and executive control. Our observations speak in favor of the last prediction.

2. Methods

2.1. Subjects

Seven rhesus monkeys (*Macaca mulatta*) aged 5–14 years participated to this study, three females (monkeys CA, GU and CE) and four males (monkeys EL, TO, HN and DO). Animals had free access to water (CE, CA and GU) or food (EL, TO, HN and DO) and were maintained on a food (CE, CA and GU) or water (EL, TO, HN and DO) regulation schedule, individually optimized to maintain stable motivation and performance. This study was conducted in strict accordance with Directive 2010/63/UE of the European Parliament and the Council of 22 September 2010 on the protection of animals used for scientific purposes and approved by the French Committee on the Ethics of Experiments in Animals (C2EA) CELYNE registered at the national level as C2EA number 42.

2.2. Experimental set-up

Monkeys were seated in a primate chair in a sphinx position, with the head immobilized via a surgically implanted plastic MRI-compatible head post (CE, TO, EL, HN, DO) or a non-invasive head restraint helmet (CA and GU) (Hadj-Bouziane et al., 2013), in front of a computer screen (distance: 57 cm for CE, CA and GU; 78 cm for EL, TO, HN and DO). Gaze location was sampled at 120 Hz using an infrared pupil tracking system (ISCAN Raw Eye Movement Data Acquisition Software) interfaced with a program for stimulus delivery and experimental control (Presentation®).

2.3. Behavioral task

A testing session consisted of alternations of two types of runs: mixed runs and pure runs. In both types of runs, monkeys were required to fixate a central cross to initiate the trial. Then, the target appeared randomly in the left or right side of the screen (10 degrees of eccentricity), and monkeys had to saccade as fast as possible to the target location and hold fixation during 300 ms (EL, TO, HN and DO) or 500 ms (GU, CA and CE) to receive a reward (fruit juice or water). In the mixed runs, derived from the attentional network task (Posner, 1980), several conditions were intermixed, while in the pure runs, only one condition was presented to the animals. For 4 monkeys (EL, TO, HN and DO), the color of the central cross changed across the type of runs (red or yellow cross for mixed and pure runs, respectively).

In the mixed runs (Fig. 1A), for 80% of the trials, a peripheral cue, a white dot or a grey square, was flashed for 100 ms prior to the target onset on one side of the screen, accurately predicting the upcoming target location ('*valid* cue'). In the remaining 20% of the trials, the cue was either absent ('*no* cue'), or presented on the opposite side of target location ('*invalid* cue'), or two cues were simultaneously presented ('*neutral* cue'). In addition, a distractor, a red circle or a red square, could appear simultaneously with the target onset, either in the same or in the opposite hemifield as the target (distance target-distractor: 4.5° for GU, CA and CE and between 2.1° and 3.2° for EL, TO, HN and DO). The *'no distractor'*, *'same hemifield'* and *'opposite hemifield'* conditions were intermixed and equally distributed across trials. Monkeys were required to fixate the target and ignore the distractor. In the majority of the animals (except CE), the cue-target interval (CTI) varied across trials to prevent anticipatory responses. CTIs were optimized for each monkey in order to maximize cue validity/invalidity effects, which were key in quantifying the attention orientation effects (200-300-400 ms for GU and CA, 100 ms for CE, 150-200-250 ms for EL and TO, 200-250-300 ms for HN, 140-180-240 ms for DO). The pure runs did not include any cue nor any distractor. These runs served to quantify the effect of NE on task context by comparing RTs on these trials to the same trials performed in the mixed runs (i.e. taking place in a context in which cued trials were most frequent). The mixed runs included ~90 trials for monkeys CE, CA, GU, ~150 trials for monkeys EL, TO, ~300 trials for monkey HN and ~400 trials for monkey DO. Pure runs included ~20 trials for monkeys CA, GU, ~50 trials for monkeys EL, TO, ~100 trials for monkey HN and ~150 trials for monkey DO. Note that only mixed runs were presented to monkey CE.

The overall structure of the task was similar for all animals. Only the physical characteristics of the stimuli (cues, target and distractors) and the timings varied across animals depending on their previous experience with the task and their overt behavior (Fig. 1A).

2.4. Drug administration

Once the animals reached stable performance and were accustomed to intramuscular injections, atomoxetine (ATX, Tocris Bioscience, Ellisville, MO) and saline (control) administration sessions began. As shown in previous studies (Bymaster et al., 2002; Koda et al., 2010), ATX is a potent NE reuptake inhibitor. In prefrontal cortex of mice, injection of 1 mg/kg of ATX induced a significant increase of the extracellular levels of NE and DA. Yet, the concentration of NE was 4 times larger than that of DA. Based on previous studies conducted in monkeys (in particular Gamo et al. 2010,) we chose the smallest efficient doses that corresponded to the recommended doses by the U.S. Food and Drug Administration in children with attention deficits (0.5–1.2 mg/kg). Each experiment started with one or two weeks of saline administration, followed by 3–4 weeks of testing with different doses of ATX: 0,1 mg/kg, 0,5 mg/kg, 1 mg/kg and 1,5 mg/kg. For a given week, the same dose of ATX was administered every day to the animals. Note that the dose of 1,5 mg/kg was tested only in the two younger monkeys (GU and CA). ATX or saline was administered intramuscularly 30 min prior to testing (Gamo et al., 2010). In total, for each animal, we collected 4 to 6 sessions with each dose of ATX and 1 to 5 sessions of saline condition.

2.5. Data analysis

The data were analyzed separately for each monkey. Eye movements were visually inspected with a customized toolbox implemented in MATLAB.

2.5.1. Pupil diameter

We computed the averaged normalized pupil diameter, in the trial initiation period (500 ms before the cue onset), for each animal and each pharmacological condition. In each trial, the mean pupil diameter across this 500 ms window was divided by the root mean square separately for each animal. These measures were compared across runs and pharmacological conditions.

2.5.2. Number of trials

We examined the number of initiated trials (i.e. Fig. 1A: completion of the first step: initiation) and the number of correct trials. A trial was considered correct after the animal reached and fixated the correct target location within the imparted time (270 ms for DO, 300 ms for EL and HN, 350 ms for TO or 500 ms for CA, GU and CE). Incorrect trials corresponded to either incomplete trials, anticipations (RT < 80 ms), saccades with artifacts related to blink or trials where saccades were made to the wrong target location or to the distractor location.

2.5.3. Reaction times (RTs)

2.5.3.1. Attentional scores in mixed runs. To assess the effect of cues and distractors on RTs in mixed runs, we computed four scores derived from the attentional network scores (Fan et al., 2002) and integrating the effect of distractors (Walker and Benson, 2013): alerting score, orienting score, remote distractor score and proximal distractor score. Given that these different conditions were randomly presented within runs, these scores were calculated for each run. Runs where the number of trials per cue type was under-represented (i.e. less than 3 trials) were excluded.

$$Orienting\ score = \frac{RT_{valid} - median\ RT_{Invalid}}{|median\ RT_{Invalid}|} \times 100$$

$$Alerting\ score = \frac{RT_{neutral} - median\ RT_{nocue}}{|median\ RT_{nocue}|} \times 100$$

$$Remote\ distractor\ score = \frac{RT_{different\ hemifield} - median\ RT_{no\ distractor}}{|median\ RT_{no\ distractor}|} \times 100$$

$$Proximal\ distractor\ score = \frac{RT_{same\ hemifield} - median\ RT_{no\ distractor}}{|median\ RT_{no\ distractor}|} \times 100$$

2.5.3.2. RT distributions in mixed runs. We used the LATER model (linear Approach to Threshold with Ergodic Rate) to examine changes in RT distribution for each attentional process (Noorani and Carpenter, 2016). This model proposes that RT is the culmination of a decisional process which starts at the onset of the target, rises in response with a constant linear rate (r) and ends with the initiation of a response at the decision threshold (θ) (Fig. 1B left panel). According to this model, a change in RT distribution can be explained by a change in the accumulation rate or in the decision threshold. Cumulative RT distributions are plotted as reciprobit plots, so that each distribution corresponds to a line. On this plot, the change of accumulation rate is embodied by a shift of the lines and the change of the decision threshold by a swivel between them (Fig. 1B right panel). To characterize how RT distribution was affected by trial type (i.e. to characterize a given attentional process or NE effect), we calculated the log likelihood ratio that the difference between one RT distribution and

the other is accounted for by a shift or by a swivel. A negative log likelihood ratio represents a change in accumulation rate between the two distributions (i.e. a shift) and a positive log likelihood ratio represents a change in decisional threshold (i.e. a swivel).

2.5.3.3. Non-cued trials in pure versus mixed runs. We compared RTs of correct trials in non-cued trials presented in the pure and in the mixed runs. We also used the LATER model to examine the changes in RT distribution between the types of runs.

2.6. Statistical analysis

First, we used one-sample *t*-test to determine whether the changes in the attentional scores differed significantly from 0 in the saline condition, i.e. to determine the influence of the different cues and distractors condition in the saline condition. Then, we used linear mixed models (using the 'lme4' package for R, Bates et al., 2014) to examine the effect of ATX on the different variables computed above, for each monkey. As a first step, we defined a model containing the most appropriate random effects (i.e. factors of non-interest). Random effects were thus introduced sequentially, and their effect on model fit was assessed through Likelihood Ratio Tests (LRT): residuals of each model were compared, and the one with significantly lower deviance as assessed by a chi-squared test was chosen (Table 1). We then tested the effect of pharmacological condition as fixed factor to evaluate the effect of ATX on pupil diameter, number of initiated and correct trials and the different attentional scores. To evaluate the effect of ATX on RTs in the different cue conditions, we tested the effect of pharmacological condition and cue condition as fixed factors. Finally, post-hoc comparisons were carried out using pairwise comparisons through the 'lsmeans' package for R (p-adjusted with false discovery rate method, Lenth, 2016) to assess the effect of the different doses of ATX (and the different cue conditions when assessing their effects on RTs).

In order to assess the relationship between the effect of ATX on pupil diameter (mean normalized pupil diameter) and on the different attentional scores, we computed the difference in pupil diameter and in attentional scores between saline and ATX conditions (for highest dose of ATX, i.e. 1.0 mg/kg for monkeys CE, EL, TO, HN, DO and 1.5 mg/kg for monkeys GU and CA). We then tested the relationship between these two variables using a Spearman's correlation test.

To determine whether a particular strategy was used between the different conditions (different cue conditions, distractor conditions or types of runs), LATER model log likelihood ratio tests were performed for each subject. To evaluate the effect of ATX on the strategy, we performed a wilcoxon non-parametric paired test on the group of subjects.

3. Results

In the results section below, the ATX dose-response curves are provided for pupil diameter (Fig. 2) and attentional orienting effect (Fig. 3). Other results are detailed for the highest, and most effective, dose of ATX (1.0 mg/kg for monkeys CE, EL, TO, HN, DO and 1.5 mg/kg for monkeys GU and CA).

3.1. Effect of ATX in the mixed runs

3.1.1. ATX effect on pupil size (Fig. 2)

We found a significant main effect of pharmacological condition on pupil diameter in all monkeys ($\chi^2_{(4)} = 12675$, $p < 0.001$ for GU; $\chi^2_{(4)} = 10196$, $p < 0.001$ for CA; $\chi^2_{(3)} = 9231.8$, $p < 0.001$ for CE; $\chi^2_{(3)} = 14905$, $p < 0.001$ for EL; $\chi^2_{(3)} = 2838$, $p < 0.001$ for TO; $\chi^2_{(3)} = 47527$, $p < 0.001$ for HN; $\chi^2_{(3)} = 18776$, $p < 0.001$ for DO). For all monkeys except DO, the highest dose of ATX increased the pupil diameter compared to the saline condition ($|z| = -94.3$, $p < 0.001$ for GU, $|z| = -71.6$, $p < 0.001$ for CA, $|z| = -60.7$, $p < 0.001$ for CE,

Table 1
Linear mixed models in statistical analysis. For each variable, we defined a model containing the most appropriate random effects (i.e. factors of non-interest) and we tested the effect of fixed factor (i.e. factor of interest). Random effects were sequentially introduced, and their effect on model fit was assessed through Likelihood Ratio Tests (see methods).

	Variables	Family of linear mixed model	Random factors	Fixed factors
Mixed run	Pupil diameter	Gaussian	Runs nested in sessions	Pharmacological condition
	Number of initiated trials	Binomial	Runs nested in sessions	Pharmacological condition
	Number of correct trials	Binomial	CTI; Target position; Cue condition; Distractor condition; Runs nested in sessions	Pharmacological condition
	RTs	Gaussian	Target position; Cue condition; Distractor condition; Runs nested in sessions	Pharmacological condition; Cue condition
	Alerting score	Gaussian	CTI; Target position; Distractor condition; Runs nested in sessions	Pharmacological condition
	Orienting score	Gaussian	CTI; Target position; Distractor condition; Runs nested in sessions	Pharmacological condition
	Remote distractor score	Gaussian	CTI; Target position; Cue condition; Runs nested in sessions	Pharmacological condition
	Proximal distractor score	Gaussian	CTI; Target position; Cue condition; Runs nested in sessions	Pharmacological condition
Pure run	Number of initiated trials	Binomial	Runs nested in sessions	Pharmacological condition
	Number of correct trials	Binomial	Target position; Runs nested in sessions	Pharmacological condition
	RTs	Gaussian	Target position; Runs nested in sessions	Pharmacological condition

Table 2
Attentional scores in mixed runs for the highest dose of ATX (1.0 mg/kg for CE, EL, TO, HN, DO and 1.5 mg/kg for GU and CA). *p-values reflects pairwise comparisons between the saline and the highest dose of ATX with corrections for multiple comparisons. *: significant effect in the saline condition ($p < 0.05$). ↗ or ↘: significant increase or decrease, respectively, after ATX administration. -: no difference between saline and ATX conditions.* Overall, ATX modulates all attentional scores but the most consistent effect was found for the orienting score.

Monkeys	Alerting score				Orienting score				Remote distractor score				Proximal distractor score			
	Saline	ATX	p value	ATX effect	saline	ATX	p value	ATX effect	saline	ATX	p value	ATX effect	saline	ATX	p value	ATX effect
GU	−4.2	−2.7	–	–	−6.2*	6.6	< 0.001	↗	−12.7*	−11.4	0.17	–	3.18*	1.8	–	–
CA	−3.4	−4.5	–	–	−4.5*	3	< 0.001	↗	−7.5*	−5.5	0.04	↘	1	−0.4	–	–
CE	6.4*	14	0.05	–	3.3*	8.9	< 0.001	↗	−3.1*	−8.4	< 0.001	↗	15.8*	12.6	< 0.001	↘
EL	19.1*	24.7	0.003	↗	31.7*	34.8	< 0.001	↗	−16.5*	−22.9	< 0.001	↗	−4.7*	−14.1	< 0.001	↗
TO	5.5*	2.9	0.007	↘	4.3*	6.7	0.015	↗	−2.3*	−1.4	–	–	2.4*	3.4	–	–
HN	24.7*	28.5	0.21	–	38.2*	40.3	< 0.001	↗	−14.7*	−14.3	–	–	−10.3*	−13.2	0.005	↗
DO	27.5*	23.2	0.02	↘	9.9*	−0.3	< 0.001	↘	−4.5*	−3.4	0.56	–	−2.9*	−3	0.79	–

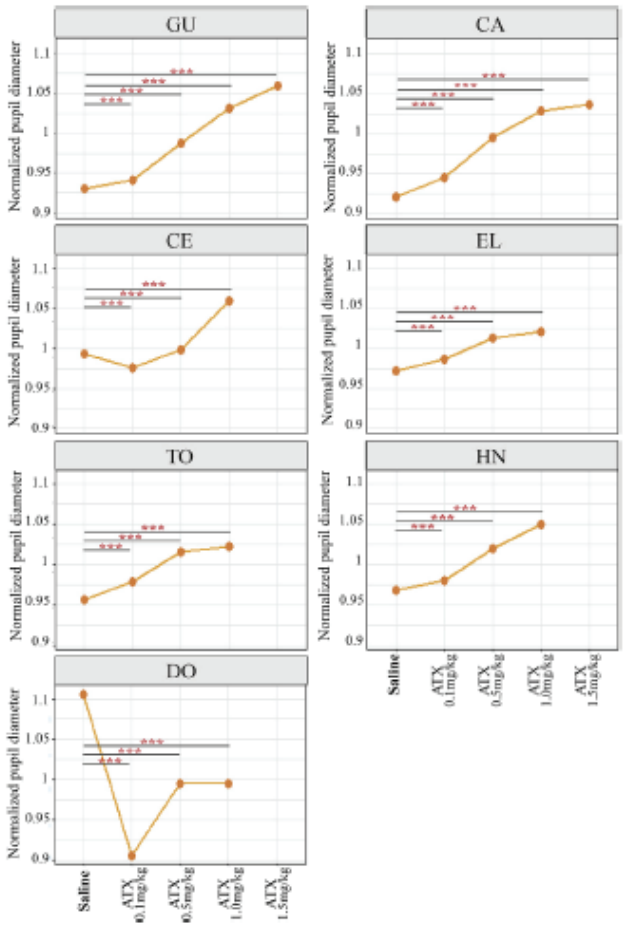

Fig. 2. ATX effect on pupil size. For each animal and each pharmacological condition, we computed normalized averaged pupil diameter (mean ± s.e) during the initiation period (fixation cross). ATX significantly increased pupil diameter as a function of the dose, in most of the monkeys, during the initiation period. ****:p-value < 0.001.*

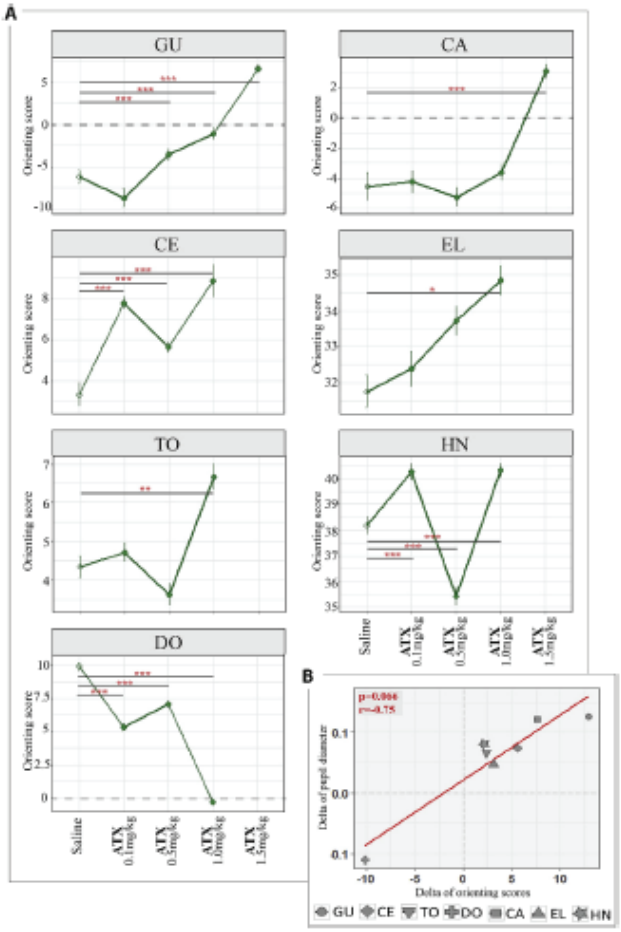

Fig. 3. ATX effect on attentional orienting. A: For each animal and each pharmacological condition, we computed the normalized averaged orienting scores across runs in the different pharmacological conditions (mean ± s.e). Our results show that ATX enhanced the orienting score in most monkeys. **p-value < 0.05; **p-value < 0.01; ***:p-value < 0.001.* **B**: For each animal, we computed the effect of ATX on pupil diameter and on the orienting score as the difference between saline and ATX conditions (highest dose of ATX, i.e. 1.0 mg/kg for monkeys CE, EL, TO, HN, DO and 1.5 mg/kg for monkeys GU and CA). Our results show that ATX-mediated changes in pupil diameter tended to be correlated with changes in attentional orienting scores.

|z| = -107, p < 0.001 for EL, |z| = -146.4, p = 0.015 for TO, |z| = -182.5, p < 0.001 for HN). For DO, the highest dose of ATX (1.0 mg/kg) significantly decreased the pupil diameter compared to the saline condition (|z| = 76.8, p < 0.001).

3.1.2. ATX effect on attentional scores (Table 2)

As predicted (Posner, 1980), in the saline condition, 5 out of 7 monkeys exhibited a significant alerting effect, i.e. shorter RTs in neutral trials compared to non-cued trials, and a significant orienting effect, i.e. shorter RTs in valid trials compared to invalid trials (*alerting effect*: $t_{(808)} = 5.6$, $p = 0.002$ for CE, $t_{(155)} = 12.3$, $p < 0.001$ for EL,

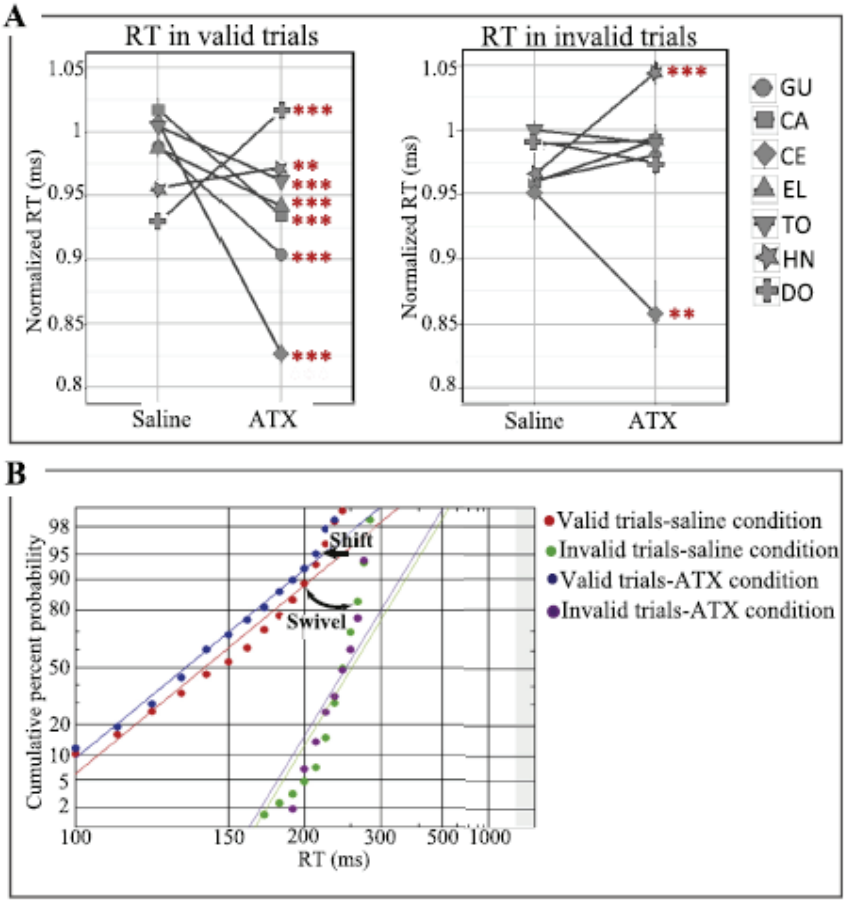

Fig. 4. ATX effect on RTs in valid and invalid trials for the highest dose of ATX (1.0 mg/kg for CE, EL, TO, HN, DO and 1.5 mg/kg for GU and CA). **A:** For each animal and each pharmacological condition, we computed the normalized RTs in valid (left panel) and invalid (right panel) trials across runs (mean ± s.e) by dividing RTs by the root mean square separately for each type of trial (valid and invalid) and each monkey. **B:** Example of reciprobit plot in valid and invalid trials in the saline and ATX conditions for monkey EL. ***:p-value < 0.01; ***:p-value < 0.001.*

$t^{(179)} = 8.5$, $p < 0.001$ for TO, $t_{(173)} = 20.7$, $p < 0.001$ for HN, $t_{(380)} = 33.5$, $p < 0.001$ for DO - *orienting effect*: $t_{(808)} = 5.6$, $p < 0.001$ for CE, $t_{(1363)} = 71.8$, $p < 0.001$ for EL, $t_{(1693)} = 15.2$, $p < 0.001$ for TO, $t_{(1999)} = 103.9$, $p < 0.001$ for HN, $t_{(4850)} = 36.8$, $p < 0.001$ for DO). For all monkeys, the remote distractor led to longer RTs ($t_{(290)} = -10.9$, $p < 0.001$ for GU, $t_{(205)} = -5.9$, $p < 0.001$ for CA, $t_{(331)} = -4.3$, $p < 0.001$ for CE, $t_{(432)} = -13$, $p < 0.001$ for EL, $t_{(557)} = -4.8$, $p < 0.001$ for TO, $t_{(596)} = -11.2$, $p < 0.001$ for HN, $t_{(1426)} = -7.8$, $p < 0.001$ for DO) whereas the proximal distractor had different effects depending on monkeys. The proximal distractor either reduced RTs ($t_{(291)} = 3.8$, $p < 0.001$ for GU, $t_{(342)} = 24.2$, $p < 0.001$ for CE, $t_{(558)} = 5.1$, $p < 0.001$ for TO) or increased RTs ($t_{(523)} = -4.7$, $p < 0.001$ for EL, $t_{(652)} = -8.1$, $p < 0.001$ for HN, $t_{(1502)} = -5.3$, $p < 0.001$ for DO).

ATX differentially modulated these attentional scores. Table 2 summarizes the effect of the highest dose of ATX (1.0 mg/kg for monkeys CE, EL, TO, HN, DO and 1.5 mg/kg for monkeys GU and CA). Specifically, ATX more consistently affected the orienting process as compared to the alerting and distractor filtering processes (see also Fig. 3A). Indeed, ATX injection significantly modified the orienting scores in all monkeys ($\chi^2_{(4)} = 383.5$, $p < 0.001$ for GU, $\chi^2_{(4)} = 166.9$, $p < 0.001$ for CA, $\chi^2_{(3)} = 49$, $p < 0.001$ for CE, $\chi^2_{(3)} = 39.7$, $p < 0.001$ for EL, $\chi^2_{(3)} = 61.7$, $p < 0.001$ for TO, $\chi^2_{(3)} = 305.5$, $p < 0.001$ for HN, $\chi^2_{(3)} = 1771.1$, $p < 0.001$ for DO) regardless of the pattern observed in the saline condition. Post-hoc tests revealed that ATX enhanced the orienting effect in 6 out of 7 monkeys ($|z| = -14$, $p < 0.001$ for GU, $|z| = -8.1$, $p < 0.001$ for CA, $|z| = -3.8$, $p < 0.001$ for CE, $|z| = -3.4$, $p < 0.001$ for EL, $|z| = -2.5$, $p = 0.015$ for TO, $|z| = -2.1$, $p < 0.001$ for HN). The enhancement of the orienting effect increased as a function of the ATX dose in 5 out of 7 monkeys (Fig. 3A). One monkey (monkey DO) had a reversed modulation, the orienting effect decreasing as a function of the ATX dose ($|z| = 10.7$, $p < 0.001$). By comparison, our results showed that ATX either decreased or increased the alerting scores and the remote or proximal distractor scores depending on the animal. Moreover, as illustrated in Fig. 3B, the effect of ATX on pupil diameter tended to be correlated with the effect of ATX on attentional orienting ($p = 0.066$, $r = 0.75$) but not with the other attentional scores (alerting scores: $p = 0.66$, $r = 0.21$; remote distractor scores: $p = 0.26$, $r = 0.5$; proximal distractor scores: $p = 0.96$, $r = -0.3$).

3.1.3. ATX effect on attentional orienting

The most consistent effect of ATX on the attentional scores across animals was an improvement of the orienting effect, i.e. shorter RTs on valid than on invalid trials. To identify whether this was driven by a change in sensory accumulation or a change in decision threshold, we compared the response strategy, as assessed from RT distributions, in the saline and ATX conditions, using the LATER model. In the saline condition, in 3 out of the 5 animals exhibiting an orienting effect, this effect resulted from a lower decisional threshold in the valid compared

to the invalid trials (Log likelihood (LL): 2365.5, Log likelihood ratio (LLR): 65.950, $p < 0.001$ for EL, LL: 3294.1, LLR: 23.693, $p < 0.001$ for HN and LL: 6725.6, LLR: 15.692, $p < 0.001$, for DO). The two other monkeys did not exhibit any specific strategy. Under ATX, in all animals except monkey DO, the improvement of the orienting effect corresponded to a reinforcement of this decision threshold-based strategy in valid compared to invalid trials ($|z| = 2.201$, $p = 0.028$). For the one animal whose orienting score was significantly deteriorated under ATX (monkey DO), ATX induced the opposite effect, i.e. a switch in the strategy, from a change in the decisional threshold in the saline condition (LL: 6725.6, LLR: 15.692, $p < 0.001$) toward a change of the accumulation rate in the ATX condition (LL: 9508, LLR: −11.55, $p < 0.001$).

The enhancement of the orienting effect under ATX could result from faster RTs in both valid and invalid trials. Alternatively, it could be that ATX affects in only one type of trials. We thus examined the effect of ATX on the RTs in valid and invalid trials. All animals, with the exception of EL, exhibited a significant two-way interaction between pharmacological conditions (Saline and 3 or 4 doses of ATX) and cue type (Valid, Invalid, Neutral and No cue) ($\chi^2_{(8)} = 41.6$, $p < 0.001$ for GU, $\chi^2_{(8)} = 28.3$, $p < 0.001$ for CA, $\chi^2_{(9)} = 70.9$, $p < 0.001$ for CE, $\chi^2_{(6)} = 29.8$, $p < 0.001$ for TO, $\chi^2_{(6)} = 87.2$, $p < 0.001$ for HN, $\chi^2_{(} = 106.3$, $p < 0.001$ for DO, and $\chi^2_{(6)} = 7.9$, $p = 0.25$ for EL). As shown in Fig. 4A, for the majority of monkeys, this effect was driven by shorter RTs in the valid trials ($|z| = 11.2$, $p < 0.001$ for GU, $|z| = 9.6$, $p < 0.001$ for CA, $|z| = 21.8$, $p < 0.001$ for CE, $|z| = 8.3$, $p < 0.001$ for TO, $|z| = 6.5$, $p < 0.001$ for EL). RTs in the invalid trials were only marginally affected by ATX. The analysis of the RT distributions with the LATER model further demonstrated a faster accumulation rate for the valid trials in the ATX condition compared to the saline condition for 4 monkeys (LL: 4150.2, LLR: −3.246, p 0.039, for EL, LL: 15148, LLR: −3.763, $p < 0.023$ for DO, LL: 4777, LLR: −6.116, $p < 0.002$ for GU and LL: 5053, LLR: −5.299, $p < 0.005$ for CA, data not shown). For the invalid trials, ATX had no systematic impact on the RT distributions. This effect is exemplified in Fig. 4B for monkey EL. Overall, this indicates that the improvement of orienting induced by ATX injection is driven by faster accumulation rates following the presentation of a valid cue as compared to the saline condition.

3.2. Pure versus mixed runs: ATX enhances task context effects

3.2.1. ATX effect on number of trials

Table 3 summarizes the effect of the highest dose of ATX (1.0 mg/kg for monkeys CE, EL, TO, HN, DO and 1.5 mg/kg for monkeys GU and CA) on animals' performance in pure and mixed runs. For 3 out of 7 monkeys, ATX increased the number of initiated trials in both types of runs (mixed runs: $|z| = -15.4$, $p < 0.001$ for GU, $|z| = -17.6$, $p < 0.001$ for CA, $|z| = -2.7$, $p = 0.04$ for EL; pure runs: $|z| = -8.9$, $p < 0.001$ for GU, $|z| = -2.6$, $p = 0.02$ for CA, $|z| = -2.8$, $p = 0.01$ for EL). By contrast, it increased the number of correct trials in only one animal ($|z| = -4.3$, $p = 0.001$ for TO) in the pure runs compared to 5 in the mixed runs ($|z| = -3.5$, $p = 0.001$ for CA, $|z| = 0.4$, $p = 0.004$ for EL, $|z| = -7.8$, $p < 0.001$ for TO, $|z| = -5.6$, $p < 0.001$ for HN, $|z| = -10.5$, $p < 0.001$for DO). In other words, ATX equally increased the number of initiated trials in half of the animals in both mixed and pure runs while its effect on accuracy, measured as the number of correct trials, was more pronounced in the mixed runs as compared to the pure runs.

3.2.2. ATX effect on RTs

We then focused on RTs on the non-cued trials in the pure versus the mixed runs (Table 3, Fig. 5A). We found that ATX increased RTs in pure runs in the majority of monkeys ($|z| = -4.5$, $p < 0.001$ for EL, $|z| = -4.9$, $p < 0.001$ for TO, $|z| = -13.1$, $p < 0.001$ for HN, $|z| = -21.6$, $p < 0.001$for DO), whereas its effect was subtler in mixed runs where it increased RTs in only two animals ($|z| = -3.1$, $p = 0.01$ for EL, $|z| = -8.1$, $p < 0.001$ for DO). The analysis of the RT distributions with the LATER model further demonstrated a slower accumulation rate in the pure ATX runs compared to the pure saline runs for 3 monkeys (LL: 4561.2, LLR: −88.993, $p < 0.001$ for EL, LL: 15730.7, LLR: −9.599, $p < 0.001$ DO and LL: 10253, LLR: −3.412, $p < 0.033$ HN) as well as compared to the mixed ATX runs for 3 monkeys (LL: 4561.2, LLR: −88.993, $p < 0.001$ for EL, LL: 7404.9, LLR: −168.680, $p < 0.001$ for HN and LL: 11252.8, LLR: −12.273, $p < 0.001$ for DO). This effect is exemplified in Fig. 5B for monkey EL.

4. Discussion

We tested the impact of ATX, a NE reuptake inhibitor that increases NE availability in the brain, on visuo-spatial attention, in seven monkeys performing a predictive saccadic cued task. We report two new findings. First, we found that ATX differentially impacted the three attentional scores measured in the mixed runs, namely alerting, orienting and the distractor interference effects, most consistently improving the orienting process across the animals. Second, we found that the animals were slower to detect non-cued targets, specifically in pure runs, in the ATX compared to the saline condition. Our results suggest that the NE influences specific processes of visuo-spatial attention, and that this influence depends on the context.

4.1. Boosting NE transmission most consistently modulates attentional orienting in a predictive context

We assessed the impact of ATX on attentional processes in mixed runs. In these runs, the cue accurately predicted the upcoming target location in 80% of the trials rendering the context highly predictive. We found that ATX affected, though not equally, all attentional processes tested in the present work, namely alerting, orienting and the distractor interference effect. Specifically, ATX changed, in a dose-dependent manner, the orienting process in all animals; deterioration did occur (1/7 monkeys), but the typical effect was an improvement (6/7 monkeys). Difference in behavioral responses to ATX between individuals has been previously reported. Such difference could reflect genetic determinants differences, in particular in a NE transporter gene (Kim et al., 2006; Greene et al., 2009; Hart et al., 2012; Whelan et al., 2012), or could be due to variability in neuronal and synaptic properties in response to neuromodulators (Hamood and Marder, 2014). The ATX-dependent improvement of the orienting process resulted from faster RTs in the trials where the cue accurately predicted the location of the target (valid trials), i.e. the most prevalent trials in our task. This result is in line with two previous studies that reported that clonidine, which decreases NE transmission, attenuated the orienting process in humans (Coull et al., 2001; Clark et al., 1989) in a predictive context. In another study, Witte and Marrocco, (1997) failed to reveal such an effect using a task in which valid trials constituted 57% of the total trials, i.e. in a task, in which the spatial cues were much less predictive than in the present study or the Coull et al. (2001) and Clark et al. (1989) studies. As a result, in the absence of a highly predictive context, monkeys probably had to rely more heavily on stimulus-driven processes as opposed to both stimulus-driven and goal-directed processes elicited by informative peripheral cues (Chica et al., 2014). This suggests that the impact of NE modulating agents might depend on the predictability of the cue and in more general terms on the context. In line with this idea, a recent study reported larger diameter of the pupil, often considered as a proxy of the LC-NE activity, in highly predictive contexts (in which the cue accurately predicted the location of the upcoming target in 80% of the trials) as compared to none predictive contexts (50%, chance level, Dragone et al., 2018). Our results also show that ATX modulated pupil diameter in a dose-dependent manner as found by Larsen and Waters (2018). Interestingly, the effect of ATX on pupil diameter tended to be correlated with the improvement (or deterioration for monkey DO) in attentional orienting and not with the other attentional scores,

Table 3
Number of trials and RTs to non-cued targets in mixed and pure runs for the highest dose of ATX (1.0 mg/kg for CE, EL, TO, HN, DO and 1.5 mg/kg for GU and CA). ↗ or ↘: *significant increase or decrease, respectively, after ATX administration. -: no difference between saline and ATX conditions. NA: not applicable, note that CE did not perform the pure run condition.* Overall, ATX tended to increase the number of initiated trials in both types of runs while it tended to improve accuracy only in mixed runs. In addition, ATX increased RTs in pure runs in the majority of monkeys whereas its effect on RTs was subtler in mixed runs.

Monkeys	Number of initiated trials							
	pure runs			mixed runs			ATX Effect	
	saline	ATX	P values	saline	ATX	P values	pure runs	mixed runs
GU	167	283	< 0.001	1067	1663	< 0.001	↗	↗
CA	122	381	0.01	813	1846	< 0.001	↗	↗
CE	*NA*	*NA*	*NA*	1113	2240	< 0.001	*NA*	↘
EL	1048	1528	0.01	3323	4225	0.04	↗	↗
TO	1095	1208	–	3531	4742	0.99	–	–
HN	1504	3058	< 0.001	3757	6435	–	↗	–
DO	3459	3898	–	8820	11678	< 0.001	–	–
Monkeys	**Number of correct trials**							
	pure runs			mixed runs			ATX Effect	
	saline	ATX	P values	saline	ATX	P values	pure runs	mixed runs
GU	166	278	0.45	1002	1514	0.31	–	–
CA	116	359	–	755	1781	0.001	–	↗
CE	*NA*	*NA*	*NA*	1070	1618	< 0.001	NA	↘
EL	710	697	< 0.001	1980	2283	0.004	↘	↗
TO	760	966	< 0.001	2271	3352	< 0.001	↗	↗
HN	1176	2054	< 0.001	2601	4697	< 0.001	↘	↗
DO	2917	3232	0.09	6418	8938	< 0.001	–	↗
Monkeys	**RT (ms) in no cued trials** (mean RT ± S.E.)							
	pure runs			mixed runs			ATX Effect	
	saline	ATX	P values	saline	ATX	P values	pure runs	mixed runs
GU	156 ± 1.4	158 ± 1.2	0.32	165.5 ± 2.9	163.1 ± 2	0.54	–	–
CA	201 ± 3.7	198 ± 1.7	0.36	203.7 ± 5.7	208.5 ± 3.1	–	–	–
CE	*NA*	*NA*	NA	231.2 ± 4.5	212.8 ± 5.5	0.06	*NA*	–
EL	226.2 ± 1.2	245.8 ± 1.1	< 0.001	231.5 ± 2.3	240.7 ± 1.3	0.01	↗	↗
TO	243.2 ± 1.2	244.4 ± 1	< 0.001	261.1 ± 2.4	259.9 ± 2	–	↗	–
HN	225.1 ± 1.3	244.2 ± 1	< 0.001	245.9 ± 1.9	246 ± 1.5	–	↗	–
DO	217.9 ± 0.4	231.6 ± 0.4	< 0.001	227.6 ± 1	236.6 ± 0.7	< 0.001	↗	↗

which suggest a link between pupil size and attentional orienting. This result nicely fits with previous reports revealing a link between pupil diameter and cognitive load or attentional performance (Murphy et al., 2014; Brink et al., 2016; Irons et al., 2017). All these results suggest that the impact of a boost in NE availability on visuo-spatial attention can be predicted from the pupil size and might depend on the level of prediction provided by the context. This effect might be more pronounced when attentional orienting involves highly informative and reliable cues.

In addition, our results show a different effect of ATX in pure *versus* mixed runs, the former being devoid of spatial cues and distractors as opposed to the latter one. First, ATX more consistently affected the rate of success (i.e. number of correct trials) across animals in the mixed runs compared to the pure runs. Second, when focusing on the non-cued trials in both types of runs, it appears that ATX more consistently increased RTs for these trials in pure runs while it only marginally affected RTs for these particular trials in mixed runs. In our experimental design, the monkeys performed about 3 times more mixed runs trials compared to pure runs trials. It is thus possible that the impact of ATX on performance was biased toward the most prevalent type of runs (i.e. mixed runs) and more specifically toward the most prevalent type of trials (i.e. valid trials that represented 80% of the trials, with a spatial cue accurately predicting the location of the target). At the time of testing, all the animals had extensive experience with the task and the alternations between the pure and mixed runs. We thus suggest that the difference of ATX effect on pure *versus* mixed runs might be interpreted in terms of a trade-off in performance that depended on the context. This finding is in line with the idea that the LC-NE system facilitates the mobilization of sensory and attentional resources to process information of the environment (Varazzani et al., 2015) and to provide behavioral flexibility, notably in the ability to shift attentional set (Lapiz and Morilak, 2006; McGaughy et al., 2008; Newman et al., 2008; Seu et al., 2009; Cain et al., 2011; Bradshaw et al., 2016). NE-dependent improvement in performance has been reported in other tasks involving working memory (Gamo et al., 2010), cognitive control (Faraone et al., 2005), sustained attention (Berridge et al., 2012) or sensory discrimination (Gelbard-sagiv et al., 2018). Our results further suggest that, beyond a global adjustment of the behavior to the context, ATX

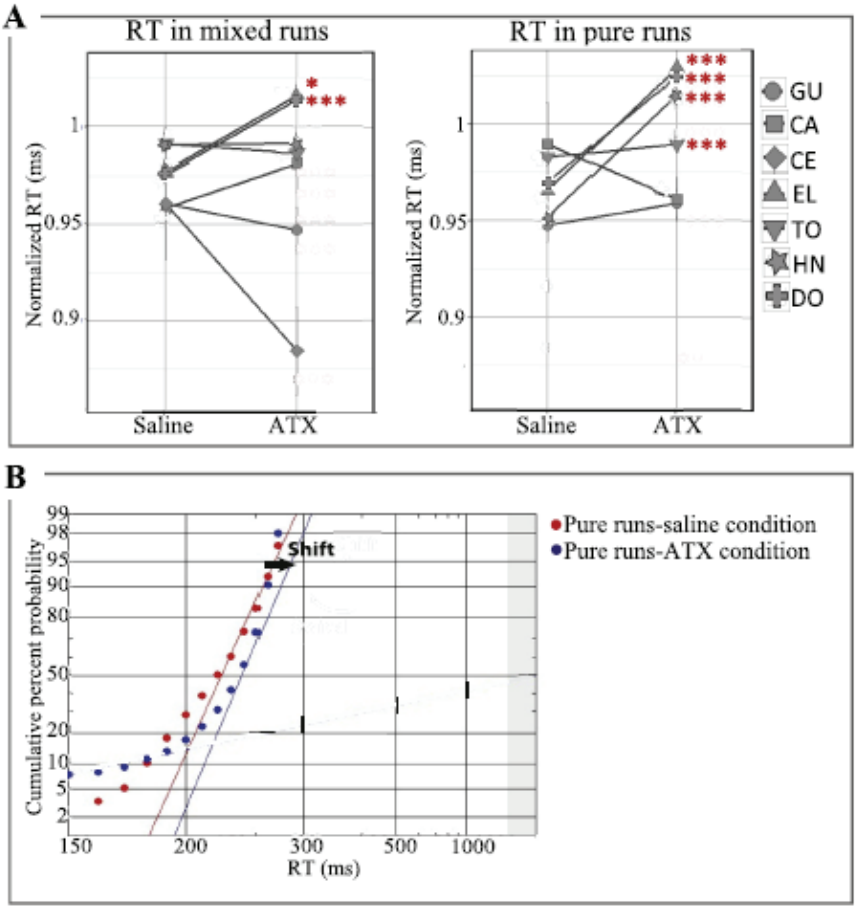

Fig. 5. ATX effect on RTs in non-cued trials in mixed and pure runs for the highest dose of ATX (1.0 mg/kg for CE, EL, TO, HN, DO and 1.5 mg/kg for GU and CA). **A:** For each animal and each pharmacological condition, we computed the normalized RTs in non-cued trials in mixed (left panel) and pure (right panel) runs across runs (mean ± s.e) by dividing RTs by the root mean square separately for each type of runs (pure and mixed) and each monkey. B: Example of reciprobit plot in non-cued trials in mixed and pure runs in the saline and ATX conditions for monkey EL. **p-value < 0.05; ***:p-value < 0.001.*

fine-tunes the behavior at the level of the trial to maximize reward rate, leading to a trade-off in the infrequent trials (Aston-Jones and Cohen, 2005; Bouret and Sara, 2005; Corbetta et al., 2008; Fazlali et al., 2016).

Thus, to answer our first question as to which components of visuo-spatial attention are under the influence of NE availability, our results points towards a specific effect onto the dynamic and flexible components of attention, namely spatial orienting and executive control when the context is highly predictive. Note that the effect of ATX, at the highest dose used in the present study, might have also influenced the dopamine transmission in the brain and in particular in the prefrontal cortex (Bymaster et al., 2002; Upadhyaya et al., 2013). At this stage, one cannot rule out this possibility and future studies should tackle this difficult challenge to tease apart the specificity of each of these two major neuromodulators onto attentional processes.

4.2. ATX-boosting effect on spatial orienting reflects changes on both sensory accumulation rate and decision threshold

The detection of a target involves both a perceptual process that can be modelled by an accumulation of information, and a decision-making step more related to top-down processes, that can be modelled by the application of a decision threshold (Noorani and Carpenter, 2016). Thus, in addition to measuring the impact of ATX on attentional scores using median reaction times, we also sought to identify ATX-driven variations in accumulation rate and decision threshold by comparing RT distributions using LATER model statistics. First, the LATER model revealed that the adaptation to the context observed under ATX condition, highlighted by a specific improvement of attentional orienting, is explained by a lower decisional threshold in ATX condition compared to saline condition. Second, we found a faster accumulation rate specifically for the trials in which the target was preceded by a predictive spatial cue (validly cued trials) under ATX with respect to saline. In other words, under high NE availability, monkeys both accumulated the available sensory evidence faster and needed less sensory information to take their decision to saccade toward the target, specifically in the prevalent valid trials. On the contrary, we observed a slower accumulation rate in the ATX condition compared to the saline condition in the pure runs. This finding is in line with an increasing number of studies showing that NE influences bottom-up processes, even at very early-stages of sensory signal processing improving the signal-noise ratio in sensory cortex in response to incoming stimuli, to shape the behavior according to the environment (see Navarra and Waterhouse, 2018; Waterhouse and Navarra, 2018). For example, it has been shown that following a systemic injection of ATX, neuronal responses to light stimuli was enhanced in dorsal lateral geniculate nucleus (i.e. the primary sensory relay for visual information from the retina to the visual cortex) in anesthetized rats (Navarra et al., 2013). A recent study showed that manipulating the NE level in humans modulates the perceptual sensitivity to detect a visual target and this effect reflected changes in evoked potentials and fMRI signals in visual cortex (Gelbard-sagiv

et al., 2018). At rest, ATX was also found to reduce the functional correlation strength within sensory networks and to modify the functional connectivity between the LC and the fronto-parietal attention network (Guedj et al., 2016, 2017), involved in visuo-spatial orienting (Corbetta et al., 2008).

Thus, to get to our second aim that was to characterize the action of NE availability onto the visuo-spatial components, our results points toward two complementary actions of NE, on both bottom-up and top-down processes. Our results bring new evidence to the role of NE on attentional processes. We highlight, in particular, the impact of the context on its effect on attentional processes. We also pinpoint its complex mechanism of action on spatial attention, exerted at different levels, likely reflecting changes within sensory cortex leading to faster accumulation rate to incoming stimuli as well as the adjustment of the decisional threshold via an action of NE within prefrontal regions (Robbins and Arnsten, 2009; Arnsten, 2011; Arnsten and Pliszka, 2011).

Conflict of Interest

The authors declare no competing financial interests.

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References

Albares, M., Criaud, M., Wardak, C., Nguyen, S.C.T., Ben Hamed, S., Boulinguez, P., 2011. Attention to baseline: does orienting visuospatial attention really facilitate target detection? J. Neurophysiol. 106.

Arnsten, A.F.T., 2011. Catecholamine influences on dorsolateral prefrontal cortical networks. Biol. Psychiatry 69, e89–e99.

Arnsten, A.F.T., Pliszka, S.R., 2011. Catecholamine influences on prefrontal cortical function: relevance to treatment of attention deficit/hyperactivity disorder and related disorders. Pharmacol. Biochem. Behav. 99, 211–216.

Aston-Jones, G., Cohen, J.D., 2005. An integrative theory of locus coeruleus-norepinephrine function: adaptive gain and optimal performance. Annu. Rev. Neurosci. 28, 403–450.

Bates, D., Mächler, M., Bolker, B., Walker, S., 2014. Fitting Linear Mixed-Effects Models using lme4.ArXiv14065823 Stat.

Berridge, C.W., Shumsky, J.S., Andrzejewski, M.E., McGaughy, J.A., Spencer, R.C., Devilbiss, D.M., Waterhouse, B.D., 2012. Differential sensitivity to psychostimulants across prefrontal cognitive tasks: differential involvement of noradrenergic α_1- and α_2-receptors. Biol. Psychiatry 71, 467–473.

Bouret, S., Sara, S.J., 2005. Network reset: a simplified overarching theory of locus coeruleus noradrenaline function. Trends Neurosci. 28, 574–582.

Bradshaw, S.E., Agster, K.L., Waterhouse, B.D., Mcgaughy, J.A., 2016. Age-related changes in prefrontal norepinephrine transporter density: the basis for improved cognitive flexibility after low doses of atomoxetine in adolescent rats. Brain Res. 1641, 245–257.

Brink, RL Van Den, Murphy, P.R., Nieuwenhuis, S., 2016. Pupil Diameter Tracks Lapses of Attention 1–16.

Bymaster, F.P., Katner, J.S., Nelson, D.L., Hemrick-Luecke, S.K., Threlkeld, P.G., Heiligenstein, J.H., Morin, S.M., Gehlert, D.R., Perry, K.W., 2002. Atomoxetine increases extracellular levels of norepinephrine and dopamine in prefrontal cortex of rat: a potential mechanism for efficacy in attention deficit/hyperactivity disorder. Neuropsychopharmacology 27, 699–711.

Cain, R.E., Wasserman, M.C., Waterhouse, B.D., McGaughy, J.A., 2011. Atomoxetine facilitates attentional set shifting in adolescent rats. Dev Cogn Neurosci 1, 552–559.

Carpenter, R.H., Williams, M.L., 1995. Neural computation of log likelihood in control of saccadic eye movements. Nature 377, 59–62.

Chica, A.B., Martín-Arévalo, E., Botta, F., Lupiáñez, J., 2014. The Spatial Orienting paradigm: how to design and interpret spatial attention experiments. Neurosci. Biobehav. Rev. 40, 35–51.

Clark, C.R., Geffen, G.M., Geffen, L.B., 1989. Catecholamines and the covert orientation of attention in humans. Neuropsychologia 27, 131–139.

Corbetta, M., Patel, G., Shulman, G.L., 2008. The reorienting system of the human brain: from environment to theory of mind. Neuron 58, 306–324.

Coull, J.T., Nobre, A.C., Frith, C.D., 2001. The noradrenergic 2 agonist clonidine modulates behavioural and neuroanatomical correlates of human attentional orienting and alerting. Cerebr. Cortex 11, 73–84.

Dragone, A., Lasaponara, S., Pinto, M., Rotondaro, F., Luca, M De, Doricchi, F., 2018. Expectancy modulates pupil size during endogenous orienting of spatial attention. Cortex 102, 57–66.

Fan, J., McCandliss, B.D., Sommer, T., Raz, A., Posner, M.I., 2002. Testing the efficiency and independence of attentional networks. J. Cogn. Neurosci. 14, 340–347.

Faraone, S.V., Biederman, J., Spencer, T., Michelson, D., Adler, L., Reimherr, F., Seidman, L., 2005. Atomoxetine and stroop task performance in adult attention-deficit/hyperactivity disorder. J. Child Adolesc. Psychopharmacol. 15, 664–670.

Fazlali, Z., Ranjbar-Slamloo, Y., Adibi, M., Arabzadeh, E., 2016. Correlation between cortical state and locus coeruleus activity: implications for sensory coding in rat barrel cortex. Front. Neural Circuits 10, 14.

Gamo, N.J., Wang, M., Arnsten, A.F.T., 2010. Methylphenidate and atomoxetine enhance prefrontal function through α2-adrenergic and dopamine D1 receptors. J. Am. Acad. Child Adolesc. Psychiatry 49, 1011–1023.

Gelbard-sagiv, H., Magidov, E., Gelbard-sagiv, H., Magidov, E., Sharon, H., Hendler, T., Nir, Y., 2018. Noradrenaline modulates visual perception and late article noradrenaline modulates visual perception and late visually evoked activity. Curr. Biol. 28, 2239–2249 e5.

Greene, C.M., Bellgrove, M.A., Gill, M., Robertson, I.H., 2009. Noradrenergic genotype predicts lapses in sustained attention. Neuropsychologia 47, 591–594.

Guedj, C., Meunier, D., Meunier, M., Hadj-Bouziane, F., 2017. Could LC-NE-dependent adjustment of neural gain drive functional brain network reorganization? Neural Plast. 2017, 4328015.

Guedj, C., Monfardini, E., Reynaud, A.J., Farnè, A., Meunier, M., Hadj-Bouziane, F., 2017. Boosting norepinephrine transmission triggers flexible reconfiguration of brain networks at rest. Cerebr. Cortex 27 (10), 4691–4700.

Hadj-Bouziane, F., Monfardini, E., Guedj, C., Gardechaux, G., Hynaux, C., Farnè, A., Meunier, M., 2014. The helmet head restraint system: a viable solution for resting state fMRI in awake monkeys. Neuroimage 86, 536–543.

Hamood, A.W., Marder, E., 2014. Animal-to-Animal variability in neuromodulation and circuit function. Cold Spring Harbor Symp. Quant. Biol. 79, 21–28.

Hart, A.B., de Wit, H., Palmer, A.A., 2012. Genetic factors modulating the response to stimulant drugs in humans. Curr Top Behav Neurosci 12, 537–577.

Irons, J.L., Jeon, M., Leber, A.B., 2017. Pre-stimulus pupil dilation and the preparatory control of attention. PLoS One 12, 1–21.

Kim, C.-H., Hahn, M.K., Joung, Y., Anderson, S.L., Steele, A.H., Mazei-Robinson, M.S., Gizer, I., Teicher, M.H., Cohen, B.M., Robertson, D., Waldman, I.D., Blakely, R.D., Kim, K.-S., 2006. A polymorphism in the norepinephrine transporter gene alters promoter activity and is associated with attention-deficit hyperactivity disorder. Proc. Natl. Acad. Sci. U. S. A. 103, 19164–19169.

Koda, K., Ago, Y., Cong, Y., Kita, Y., Takuma, K., Matsuda, T., 2010. Effects of acute and chronic administration of atomoxetine and methylphenidate on extracellular levels of noradrenaline, dopamine and serotonin in the prefrontal cortex and striatum of mice. J. Neurochem. 114 (no-no).

Lapiz, M.D.S., Morilak, D.A., 2006. Noradrenergic modulation of cognitive function in rat medial prefrontal cortex as measured by attentional set shifting capability. Neuroscience 137, 1039–1049.

Larsen, R.S., Waters, J., 2018. Neuromodulatory correlates of pupil dilation. Front. Neural Circuits 12, 21.

Los, S.A., 1996. On the origin of mixing costs: exploring information processing in pure and mixed blocks of trials. Acta Psychol. 94, 145–188.

Los, S.A., Knol, D.L., Boers, R.M., 2001. The foreperiod effect revisited: conditioning as a basis for nonspecific preparation. Acta Psychol. 106, 121–145.

McGaughy, J., Ross, R.S., Eichenbaum, H., 2008. Noradrenergic, but not cholinergic, deafferentation of prefrontal cortex impairs attentional set-shifting. Neuroscience 153, 63–71.

Murphy, P.R., Vandekerckhove, J., Nieuwenhuis, S., 2014. Pupil-Linked Arousal Determines Variability in Perceptual Decision Making. pp. 10.

Navarra, R.L., Clark, B.D., Zitnik, G.A., Waterhouse, B.D., 2013. Methylphenidate and atomoxetine enhance sensory-evoked neuronal activity in the visual thalamus of male rats. Exp. Clin. Psychopharmacol 21, 363–374.

Navarra, R.L., Waterhouse, B.D., 2018. Considering noradrenergically mediated facilitation of sensory signal processing as a component of psychostimulant-induced performance enhancement. Brain Res. https://doi.org/10.1016/j.brainres.2018.06.027.

Newman, L.A., Darling, J., McGaughy, J., 2008. Atomoxetine reverses attentional deficits produced by noradrenergic deafferentation of medial prefrontal cortex. Psychopharmacology (Berlin) 200, 39–50.

Noorani, I., Carpenter, R.H.S., 2016. The LATER model of reaction time and decision. Neurosci. Biobehav. Rev. 64, 229–251.

Noudoost, B., Moore, T., 2011. The role of neuromodulators in selective attention. Trends Cognit. Sci. 15, 585–591.

Posner, M.I., 1980. Orienting of attention. Q. J. Exp. Psychol. 32, 3–25.

Robbins, T.W., Arnsten, A.F.T., 2009. The Neuropsychopharmacology of Fronto-Executive Function: Monoaminergic Modulation Executive Function: the Set of Processes that Help to Optimize Performance in Complex Conditions Requiring Several Components of Cognitive Function.

Seu, E., Lang, A., Rivera, R.J., Jentsch, J.D., 2009. Inhibition of the norepinephrine transporter improves behavioral flexibility in rats and monkeys. Psychopharmacology (Berlin) 202, 505–519.

Upadhyaya, H.P., Desaiah, D., Schuh, K.J., Bymaster, F.P., Kallman, M.J., Clarke, D.O., Durell, T.M., Trzepacz, P.T., Calligaro, D.O., Nisenbaum, E.S., Emmerson, P.J., Schuh, L.M., Bickel, W.K., Allen, A.J., 2013. A review of the abuse potential assessment of

atomoxetine: a nonstimulant medication for attention-deficit/hyperactivity disorder. Psychopharmacology (Berlin) 226, 189–200.
Varazzani, C., San-Galli, A., Gilardeau, S., Bouret, S., 2015. Noradrenaline and dopamine neurons in the reward/effort trade-off: a direct electrophysiological comparison in behaving monkeys. J. Neurosci. 35, 7866–7877.
Walker, R., Benson, V., 2013. Remote distractor effects and saccadic inhibition: spatial and temporal modulation. J. Vis. 13, 1–21.
Wardak, C., Ramanoël, S., Guipponi, O., Boulinguez, P., Ben Hamed, S., 2012. Proactive inhibitory control varies with task context. Eur. J. Neurosci. 36, 3568–3579.
Waterhouse, B.D., Navarra, R.L., 2018. The locus coeruleus-norepinephrine system and sensory signal processing: a historical review and current perspectives. Brain Res. 1–15.
Whelan, R., Conrod, P.J., Poline, J.B., Lourdusamy, A., Banaschewski, T., Barker, G.J., Bellgrove, M.A., Büchel, C., Byrne, M., Cummins, T.D.R., Fauth-Bühler, M., Flor, H., Gallinat, J., Heinz, A., Ittermann, B., Mann, K., Martinot, J.L., Lalor, E.C., Lathrop, M., Loth, E., Nees, F., Paus, T., Rietschel, M., Smolka, M.N., Spanagel, R., Stephens, D.N., Struve, M., Thyreau, B., Vollstaedt-Klein, S., Robbins, T.W., Schumann, G., Garavan, H., 2012. Adolescent impulsivity phenotypes characterized by distinct brain networks. Nat. Neurosci. 15, 920–925.
Witte, E.A., Marrocco, R.T., 1997. Alteration of brain noradrenergic activity in rhesus monkeys affect the alerting component of convert orienting. Psychopharmacology (Berlin) 132, 315–323.

Chapter V

Neuronal correlates of noradrenergic modulation of attention within the frontal eye field

I. Introduction

Several imaging and neuropsychological studies have found a link between the prefrontal cortex (PFC) impairment and the attention deficit hyperactivity decoders (ADHD). For example, ADHD patients has a reduced size of the PFC (Hill et al., 2003; Sowell et al., 2003) and metabolism (Yeo et al., 2000) and they could not perform tasks that involve PFC function as working memory, behavioral inhibition and reward reversal (Bedard et al., 2003; McLean et al., 2004). It has been proposed that ADHD symptoms arise from the dysfunction of noradrenergic modulation within the prefrontal cortex (Arnsten, 2006a,b; Shaw et al., 2007;Tripp and Wickens, 2009; Arnsten and Pliszka, 2011; Arnsten and Rubia, 2012; Cortese, 2012; Shaw et al., 2013). It has been shown recently that the treatment used for ADHD such as atomoxetine and methylphenidate increase the fronto-parietal network activation (Bush et al., 2013) and improves sustained attention respectively (Dockree et al., 2017, **ChapterIV**).

Up to now, two important models of the LC-NE system have been proposed. Aston-Jones et Cohen (2005) suggested that LC-NE system act as a balance between continuous exploitation of the available reward in the environment because it has high utility value and transient exploration of a new environment, in order to discover higher utility rewards. The direction of this balance shift is decided by the gain value that is evaluated thanks to the dynamic evaluation of cost and the benefit of the reward by orbito-frontal cortex (OFC) and anterior cingulate cortex (ACC)(Aston-Jones and Cohen, 2005a). The second model, suggests that LC-NE acts like a 'network reset signal' that generates network reorganization in order to shift the cognitive processes to the benefit of the relevant stimulus (Bouret and Sara, 2005a).

In the present work, we boosted NE transmission by systemic injection of (ATX) and we characterize the neuronal correlates of this manipulation within the frontal eye field (FEF), a prefrontal cortical region proposed to be the source of spatial attention and top-down control (Buschman et Miller 2007; Wardak et al., 2006; Ibos et al., 2013; Ekstrom et al., 2008) in

order to understand the contribution of LC-NE system both to normal and pathological attentional states and to disambiguate between these two models. Due to the experimental advert conditions, results are reported on only one monkey. Data from a second monkey will be collected in the coming months.

Overall we demonstrate that boosting NE transmission enhances behavioral performances during attention-related tasks and reduces noise correlations within FEF. We also demonstrate that boosting NE transmission decreases the rhythmic oscillations of noise correlations as well as the spike field coherence power. These findings are discussed in relation with the proposed models of LC-NE functions.

II. Method

Ethical statement

All procedures were in compliance with the guidelines of European Community on animal care (Directive 2010/63/UE of the European Parliament and the Council of 22 September 2010 on the protection of animals used for scientific purposes) and authorized by the French Committee on the Ethics of Experiments in Animals (C2EA) CELYNE registered at the national level as C2EA number 42 (protocole C2EA42-13-02-0401-01).

Surgical procedure

One male rhesus monkey (Macaca mulatta) weighing between 6-8 kg underwent a unique surgery during which his was implanted with two MRI compatible PEEK recording chambers placed over the left and the right FEF hemispheres respectively (figure 1A), as well as a head fixation post. Gas anesthesia was carried out using Vet-Flurane, 0.5 – 2% (Isofluranum 100%) following an induction with Zolétil 100 (Tiletamine at 50mg/ml, 15mg/kg and Zolazepam, at 50mg/ml, 15mg/kg). Post-surgery pain was controlled with a morphine pain-killer (Buprecare, buprenorphine at 0.3mg/ml, 0.01mg/kg), 3 injections at 6 hours interval (first injection at the beginning of the surgery) and a full antibiotic coverage was provided with Baytril 5% (a long action large spectrum antibiotic, Enrofloxacin 0.5mg/ml) at 2.5mg/kg, one injection during the surgery and thereafter one each day during 10 days. A 0.6mm isomorphic anatomical MRI scan was acquired post surgically on a 1.5T Siemens Sonata MRI scanner, while a high-contrast oil filled grid (mesh of holes at a resolution of 1mmx1mm) was placed in each recording chamber, in the same orientation as

the final recording grid. This allowed a precise localization of the arcuate sulcus and surrounding gray matter underneath each of the recording chambers. The second monkey involved in these experiments underwent training on the tasks, but couldn't get to the recording stage, due to health problems.

Behavioral task

During a given experimental session, the monkey was placed in front of a computer screen (1920x1200 pixels and a refresh rate of 60 Hz) with his head fixed. His water intake was controlled so that his initial daily intake was covered by his performance in the task, on a trial by trial basis. This quantity was complemented as follows. On good performance sessions, monkey received fruit and water complements. On bad performance sessions, water complements were provided at a distance from the end of the session. Each recording session consisted of random alternations of three different tasks (see below and figure 1B), so as to control for possible time in the session or task order effects. For all tasks, to initiate a trial, the monkey has to hold a bar in front of the animal chair, thus interrupting an infrared beam. (1) ***Fixation Task*** (figure 1B.1): A red fixation cross (0.7x0.7°), appeared in the center of the screen and the monkey was required to hold fixation during a variable interval randomly ranging between 7000 and 9500ms, within a fixation window of 1.5x1.5°, until the color change of the central cross. At this time, the monkey has to release the bar within 150-800 ms after color change. Success conditioned reward delivery. (2) ***Memory-guided saccade Task*** (figure 1B.2): A red fixation cross (0.7x0.7°) appeared in the center of the screen and the monkey was required to hold fixation for 500 msec, within a fixation window of 1.5x1.5°. A squared green cue (0.28x0.28°) was then flashed for 100ms at one of four possible locations ((10°,10°), (-10°,10°), (-10°,-10°) and (10°,-10°)). The monkey has to continue maintain fixation on the central fixation point for another 700–1900 ms until the fixation point disappeared. The monkey was then required to make a saccade towards the memorized location of the cue within 500-800ms from fixation point disappearance, and a spatial tolerance of 4°x4°. On success, a target, identical to the cue was presented at the cued location and the monkey was required to fixate it and detect a change in its color by a bar release within 150-800 ms from color change. Success in all of these successive requirements conditioned reward delivery. **(3) Attention task** (figure 1B.3): 100 % validity cued luminance change detection task with temporal distracters. To initiate a trial, the monkey has to hold a bar in front of the animal chair, thus interrupting an infrared beam. A blue fixation cross (0.7x0.7°) appeared in the center of the screen and the monkey was required to hold fixation

throughout the entire trial, within a fixation window of 2°x 2°. Failing to do, so abort the trial. Four gray square landmarks (0.5x0.5°), was presented simultaneously with the fixation cross and were placed at an equal distance from the fixation point, in the upper right, upper left, lower left and lower right quadrants of the screen, thus defining the corners of an imaginary square. Its specific eccentricity was adjusted from day to day between 10° to 15°, using a memory-guided saccade task, to ensure that the electrode contacts included neurons representing the cued spatial location. After a variable delay from fixation onset, ranging between 700 and 1900 ms, a green square was presented for 350 ms, indicating to the monkey in which of the four landmarks the rewarding target change in luminosity will take place. In the attention task the green square was small (0.2x0.2°) and it was presented close to the fixation cross in the same direction as the landmark to be attended (at 0.3° from the fixation point). After cue presentation, the monkey needed to orient his attention to the target landmark in order to monitor it for a change in luminosity while maintaining eye fixation onto the central cross. The change in target luminosity could occur anywhere between 500 to 2800 ms from cue onset. In order to receive his water or juice reward, the monkey was required to release the bar (thus restoring the infrared beam) in a time window of 200 to 700 ms following the change in target luminosity. In order to make sure that the monkey was correctly orienting their attention towards the cued landmark, unpredictable changes in the luminosity identical to the awaited target luminosity change could take place at the non-cued landmarks (distractors). On each trial, from none to three such unpredictable distractor luminosity changes could take place, no more than one per non-cued landmark position. The monkey has to ignore these distractors. Responding to such a distractor interrupted the trial and was counted as a "false alarm" trial. Failing to respond to the target ("miss") similarly aborted the ongoing trial.

Drug administration

Once the animal reached stable performance, Atomoxetine, a NE reuptake inhibitor (ATX, Tocris Bioscience, Ellisville, MO) and saline (control) administration sessions began. ATX or saline was administered intramuscularly 30 min prior to testing. The experiment was an alternation between a week of saline administration and a week with Two different doses of ATX: 0,3mg/kg and 1,3mg/kg. For a given week, the same dose of ATX was administered every day to the animal.

Neural recordings

On each session, bilateral simultaneous recordings in the two FEFs were carried out using three 24- contact Plexon U-probes. The contacts had an interspacing distance of 250 µm. Neural data was acquired with the Plexon Omniplex® neuronal data acquisition system. The data was amplified 400 times and digitized at 40,000 Hz. The MUA neuronal data was high-pass filtered at 300 Hz. The LFP neuronal data was filtered between 0.5 and 300 Hz. In the present paper, all analyses are performed on the multi-unit activity recorded on each of the 48 recording contacts. A threshold defining the multi-unit activity was applied independently for each recording contact and before the actual task-related recordings started. All further analyses of the data were performed in Matlab™ and using FieldTrip (Oostenveld et al., 2011), an open source Matlab™ toolbox.

Data Analysis

Data preprocessing. Overall, MUA recordings were collected from 48 recording channels on 14 independent recording sessions (3 for dose 1,3mg/kg, 4 for dose 0,3mg/kg, 7 saline). We excluded from subsequent analyses all channels with less than 5 spikes per seconds. For each session, we identified the task-related channels based on a statistical change (one-way ANOVA, $p<0.05$) in the MUA neuronal activity in the memory-guided saccade task, in response to either cue presentation ([0 400] ms after cue onset) against a pre-cue baseline ([-100 0] ms relative to cue onset), or to saccade execution go signal (i.e. fixation point off, [0 400] ms after go signal) against a pre-go signal baseline ([-100 0] ms relative to go signal), irrespective of the spatial configuration of the trial. In total, 372 channels were retained for further analyses out of 672 channels. In the following analyses we will focus only on investigating ATX effect regardless of the injected dose.

Distance between recording sites. For each electrode, pairs of MUA recordings were classified along four possible distance categories: D1, spacing of 250 µm; D2, spacing of 500 µm; D3, spacing of 750 µm and D4, spacing of 1mm. These distances are an indirect proxy to actual cortical distance, as the recordings were performed tangentially to cortical surface, i.e. more or less parallel to sulcal surface.

Behavioral performance. The percentage of correct trials were calculated and averaged over each session separately for each task.

Reaction Time (RT). RT were calculated for each trial and averaged for each session separately for each task. . Reported statistical analysis didn't vary whether mean or median RTs are considered.

Pre-cue response baseline. For each channel, the baseline activity is averaged over ([0 100]) ms before stimulus onset.

Max cue response amplitude. Response amplitude to the cue presentation corresponds to the maximum discharge of the cell to cue stimulus onset.

Latency to maximum peak response to the cue. For each channels the latency to maximum peak response to the cue onset is extracted.

Noise Correlations. For each channel, and each task, intervals of interest of 200ms were defined during the fixation epoch from 300 ms to 500 ms from eye fixation onset. Specifically, for each channel i, and each trial k, the average neuronal response $r_i(k)$ for this time interval was calculated and z-score normalized into $z_i(k)$, where $z_i(k)=r_i(k)-\mu_i/std_i$ and μ_i and std_i respectively correspond to the mean firing rate and standard deviation around this mean during the interval of interest of the channel of interest i. This z-score normalization allows capturing the changes in neuronal response variability independently of changes in mean firing rates. Noise correlations between pairs of MUA signals during the interval of interest were then defined as the Pearson correlation coefficient between the z-scored individual trial neuronal responses of each MUA signal over all trials. Only positive significant noise correlations are considered, unless stated otherwise. In any given recording session, noise correlations were calculated between MUA signals recorded from the same electrode, thus specifically targeting intra-cortical correlations. This procedure was applied independently for each task. Depending on the question being asked, noise correlations were either computed on activities aligned on fixation onset, or on activities aligned on cue onset.

Oscillations in noise correlations. To measure oscillatory patterns in the noise correlation time-series data, we computed, for each task, and each session (N=14), noise correlations over time (over successive 200ms intervals, sliding by 10ms, running from 300ms to 1500ms following cue offset for both tasks). A wavelet transform (Fieldtrip, Oostenveld et al., 2011) was then applied on each session's noise correlation time series. Statistical differences in the noise correlation power frequency spectra were assessed using a non-parametric Friedman test. When computing the noise correlations in time, we equalized the number of trials for all tasks and all conditions so as to prevent any bias that could be introduced by unequal numbers of trials. To control that oscillation in noise correlations in

time cannot be attributed to changes in spiking activity, a wavelet analysis was also run onto MUA time series data (data not shown).

Spike field Coherence (SFC). For each selected channel, SFC spectra were calculated between the spiking activity obtained in one channel and the LFP activity from the next adjacent channel in the time interval running from 300ms to 1500ms following cue offset for both tasks. We used a single Hanning taper and applied convolution transform to the Hanning-tapered trials. We equalized the number of trials for all tasks so as to prevent any bias that could be introduced by unequal numbers of trials. We used a 4 cycles length per frequency. SFC was measured separately for trials in which the cued location matched the preferred spatial location of the channel and trials in which the cued location did not match the preferred spatial location of the channel. Statistics were computed across channels x sessions, using a non-parametric Friedman test.

III. Results

Our main goal in this work is to investigate the neuronal correlates of noradrenergic modulation of attention within FEF. We boosted NE transmission by atomoxetine (ATX) injections. The whole study was an alternation between a week of saline systemic injection, serving as a control, and a week of ATX systemic injection. During each session and 30 min after ATX or saline injection, monkey was required to perform tasks with different levels of cognitive engagement and involving different types of cortical operations. The first task (***Fixation task***, figure 1B.1) was a central fixation task in which monkey was required to detect an unpredictable change in color of the fixation point, by producing a manual response within 150 to 800ms from color change. In the second task (***Memory guided saccade task***, figure 1B.2), monkey was required to hold the position of a spatial cue in memory for 700 to 1900ms and to perform a saccade towards that memorized spatial location on the presentation of a go signal. It required the production of a spatially oriented oculomotor response rather than a simple manual response. In the third task (**Attention task,** figure 1B.3), the monkey was required to ignore distractors, detect the luminosity change of the cued target and release the bar in a time window of 200 to 700 ms, while still fixating the central cross, to receive the reward. This latter task is more difficult than other tasks and requires a high level of cognitive engagement and allows managing the attention processing of the monkey.

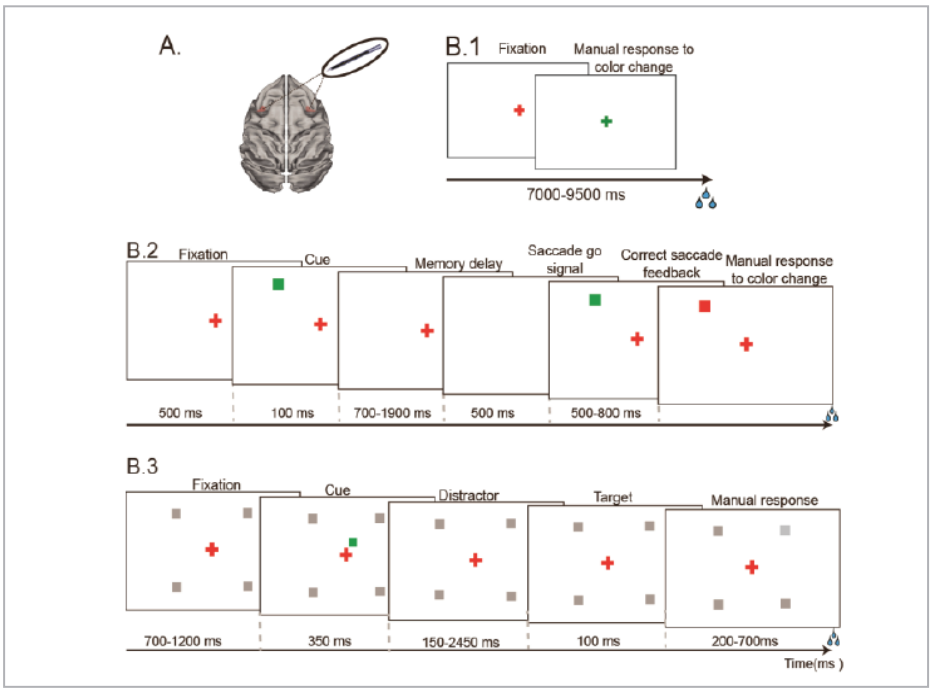

Figure1: Recordings sites. *On each session, 24-contact recording probes were placed in the left and right FEFs. (B.1)* ***Fixation task.*** *Monkey has to fixate a red central cross and was rewarded for producing a manual response 150 ms to 800 ms following fixation cross color change. (B.2)* ***Memory-guided saccade task.*** *Monkey has to fixate a red central cross. A visual cue was briefly flashed in one of four possible locations on the screen. Monkey was required to hold fixation until the fixation cross disappeared and then produces a saccade to the spatial location indicated by the cue within 300 ms from fixation point offset. On success, the cue re-appeared and the monkey has to fixate it. He was then rewarded for producing a manual response 150 ms to 800 ms following the color change of this new fixation stimulus. (B.3)* ***Attention task,*** *Monkey has to fixate a red central cross throughout the entire trial. A visual cue was briefly flashed in one of four possible locations on the screen near to the fixation cross. After cue presentation, the monkey needed to orient his attention to the target landmark in order to monitor it for a change in luminosity while maintaining eye fixation onto the central cross. In order to receive his water or juice reward, the monkey was required to release the bar (thus restoring the infrared*

Neuronal recordings were performed in the prefrontal cortex, specifically in the frontal eye field (FEF, figure 1A), a structure proposed to be the source of spatial attention top-down control (Buschman et Miller 2007; Wardak et al., 2006; Ibos et al., 2013; Ekstrom et al., 2008). In each session, multi-unit activity (MUA) and local field potential (LFP) were recorded bilaterally, while monkey performed these three tasks. In the following we will describe the effect of boosting NE transmission, independently of the injected dose of ATX, on behavioral performance, on the pre-cue baseline neuronal activity and the amplitude of response to the visual cue onset, on noise correlations and their associated rhythmic oscillations and finally on the coupling between LFP and MUA spiking activity, in specific frequency bands. Fixation task will be included only in the results of ATX effect on noise correlation calculated during fixation period.

1. Effects of Atomoxetine on behavioral performance: To assess the effect of boosting NE transmission on behavioral performances we computed **1) the percentage of correct trials (figure 2A):** Monkey had a higher overall performance on the memory guided saccade task as compared to the attention task, performance was higher under the saline condition than under the ATX conditions, and this difference was more marked for the memory guided saccade task than for the attention task (Figure 2A, 2way-ANOVA, Task x Injection type, task effect, $p<0.001$; injection type effect $p<0.05$, interaction $p> 0.7$). Post-hoc analyses indicate that the monkey has higher performances on the memory guided-saccade task than on the attention task both after saline injection (Wilcoxon rank sum test, $p<0.001$) and after boosting NE transmission (Wilcoxon rank sum test, $p<0.001$). No clear change in the number of correct trials due to ATX could be reported for either the memory saccade task (Wilcoxon rank sum test, $p>0.2$) nor the attention task (Wilcoxon rank sum test, $p>0.1$). **2) Reaction time (figure 2B):** boosting NE transmission decreased the reaction time of the monkey during attention task (figure 2B right, Wilcoxon rank sum test, $p<0.01$). In contrast, reaction times during memory guided saccade task was not affected by boosting NE transmission (figure 2B left, Wilcoxon rank sum test, $p>0.4$). These results indicate that boosting NE transmission improves the behavioral performance of the monkey only during the task that specifically requires a spatial attention orientation response as already reported in our behavioral ATX study (ChapterIV).

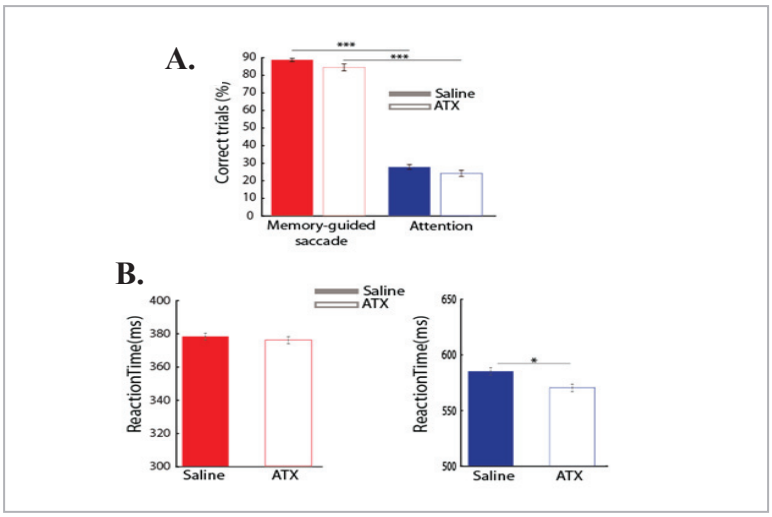

Figure2: Monkey performance. (A) *Average percentage of correct trials across saline sessions and ATX sessions separately for each task associated standard errors.* ***(B)*** *Average reaction time across saline session and ATX sessions separately as a function of trial duration associated standard errors (Right: Attention task. Left: Memory guided saccade task). Stars indicate statistical significance following a two-way ANOVA and rank sum post-hoc tests; *p<0.05; **p<0.01; ***p<0.001.*

2. Effects of Atomoxetine on pre-cue neuronal activity baseline, on neuronal response amplitude to visual cue and on latency to maximum peak response: Based on the improvement effect of the ATX on RT within attention task, we investigated how the ATX affect the pre-cue neuronal activity baseline and the amplitude response to the cue in both tasks. ***P*re-cue neuronal activity baseline**; for Attention task, we found that ATX has a major effect on the pre-cue baseline activity (Figure 3C.1, 2-way ANOVA, baseline response (for preferred and non preferred position) X injection type, ATX effect $p<0.001$, spatial selectivity effect $p>0.9$, interaction effect $p>0.9$). Post-hoc analyses indicate that ATX decreased the pre-cue baseline activity when the cue is in the preferred location of the channel (Wilcoxon tank sum test, $p<0.05$) as well as when the cue is located in the non-preferred location of the channel (Wilcoxon tank sum test, $p<0.05$). In contrast, for the memory guided saccade task, ATX do not have any effect on pre-cue baseline neuronal activity (Figure3 D.1, 2-way ANOVA, baseline response (for preferred and non preferred position) X injection type, ATX effect $p>0.3$, spatial selectivity effect $p>0.6$, interaction effect $p>0.9$).

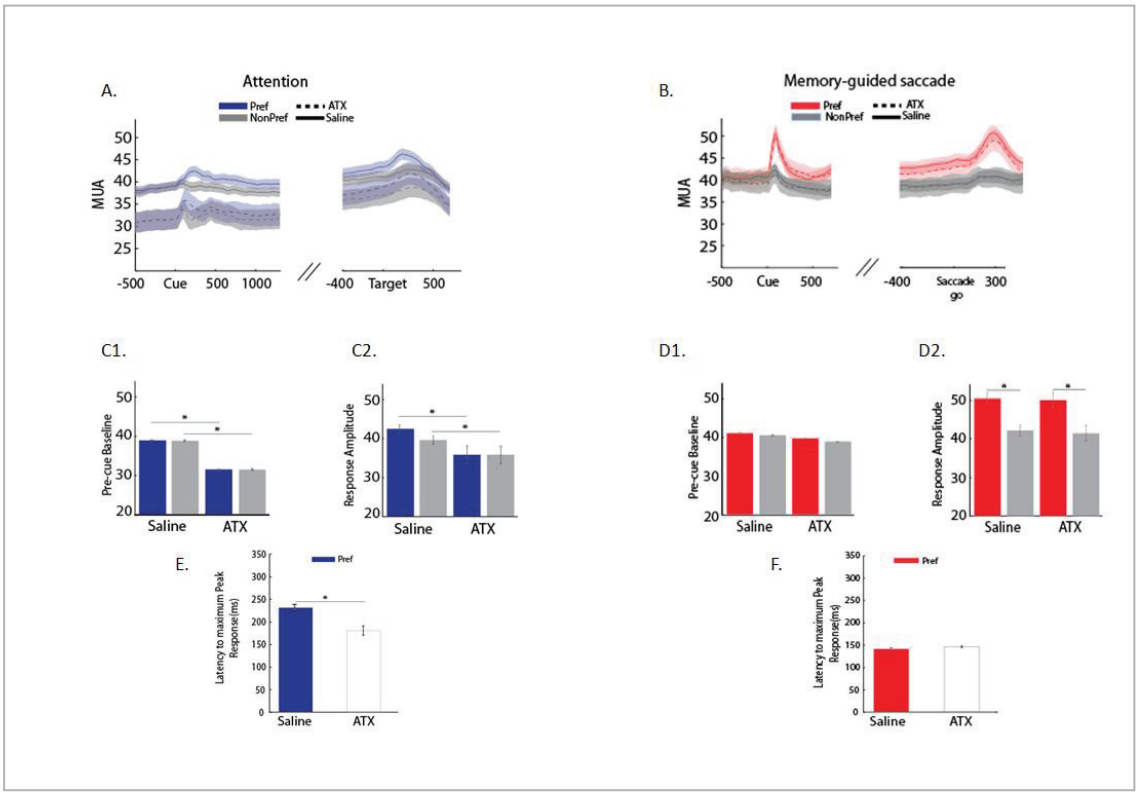

***Figure3**: **(A)** MUA in time for preferred and non preferred position aligned on cue and target onset for attention task (mean +/- s.e.) across saline and ATX sessions separately. **(B)** MUA in time for preferred and non preferred position aligned on cue and saccade go signal onset for memory guided saccade task (mean +/- s.e.) across saline and ATX sessions separately. **(C.1)** Average pre-cue*

baseline across channels for preferred and non preferred position for saline and ATX sessions separately for attention task associated standard errors. ***(C.2)*** *Average amplitude response to the cue across channels for preferred and non preferred position for saline and ATX sessions separately for attention task associated standard errors.* ***(D.1)*** *same as in (C.1) for memory-guided saccade task.* ***(D.2)*** *same as in* ***(E.)*** *Attention task. Average latency to maximum Peak response to the cue across channels, for preferred position, associated standard errors.* ***(F.)*** *memory guided saccade task. Average latency to maximum Peak response to the cue across channels, for preferred position, associated standard errors. Stars indicate statistical significance following a two-way ANOVA and rank sum post-hoc tests; *p<0.05; **p<0.01; ***p<0.001.*

For **the response amplitude to the cue onset**, results show that for attention task, ATX has an effect (figure3 (C.2), 2 way-ANOVA, amplitude response (for preferred and non preferred position) X injection type, ATX effect $p<0.001$, spatial selectivity effect $p>0.2$, interaction effect $p>0.9$). Post-hoc analyses indicate that ATX decreased significantly the amplitude response for both preferred (Wilcoxon tank sum test, $p<0.05$) and non-preferred position (Wilcoxon tank sum test, $p<0.05$). In contrast, in the memory guided saccade task, ATX doesn't affect the amplitude response to the cue and this both for the preferred and non-preferred locations, though a significant difference in amplitude response between the preferred and the non-preferred location can be observed (figure3 (D.2), 2 way-ANOVA, amplitude response (for preferred and non preferred position) X injection type, ATX effect $p>0.5$, spatial selectivity effect $p<0.01$, interaction effect $p>0.7$). Pos-hoc analyses indicate that the amplitude of response to the cue at the preferred location is higher than when the cue is at the non-preferred location both for saline (Wilcoxon tank sum test, $p<0.05$) and ATX (Wilcoxon tank sum test, $p=0.05$). Finally, we found that ATX decreased significantly the **latency to maximum peak response** for the attention task (Figure 3.E, ttest, $p<0.05$) but had no effect in the memory guided saccade task (Figure 3.F, ttest, $p>0.3$). This effect is consistent with previous results (Navarra et al., 2013).

To summarize, we have shown in this first part of our study that boosting NE transmission improves the reaction times specifically in the task that requires a high level of spatial attention orientation and not in the task that requires a spatial memory and oculomotor response production. Likewise, boosting NE transmission decreased the pre-cue baseline activity, the amplitude response and the latency to maximum peak response specifically for the spatial attention task. Overall this points towards a role of NE transmission on spatial attention orientation neuronal mechanisms.

3. Effects of Atomoxetine on interneuronal noise correlation: In order to characterize how ATX affect the inter-neuronal noise correlations we measured, for each session and each task, noise correlations between each pair of task-responsive channels (n=372, see Methods),

over equivalent fixation task epochs, running from 300 to 500 ms after eye fixation onset. As explained in the method of (***Chapter II***) this epoch was chosen because of the absence of any sensory event that could bias noise correlations effect across tasks as well as ATX effects for the present study.

Importantly, we found that noise correlations were significantly affected by ATX both within and across tasks (Figure 4A, 2way-ANOVA, Task X injection type, ATX effect $p<0.001$, task effect $p=0.001$, interaction $p=0$). First of all, the results show that after saline injections, noise correlations were higher in the fixation task than in the memory-guided saccade task (Wilcoxon rank sum test, $p<0.001$) and in the attention task (Wilcoxon rank sum test, $p<0.001$). They were also significantly higher in the memory guided saccade task than in the attention task (Wilcoxon rank sum test, $p<0.001$). Consistent with our previous work (Ben Hadj Hassen et al., (submitted)), we show again that in absence of any sensory or cognitive processing, noise correlations are strongly modulated by cognitive engagement and task demands. Furthermore, post-hoc analyses show that this relation between noise correlations and task engagement still exist even after ATX injection (Fixation higher than memory guided saccade, Wilcoxon rank sum test, $p<0.001$, Fixation higher than attention, Wilcoxon rank sum test, $p<0.001$ and memory guided saccade higher than attention, Wilcoxon rank sum test, $p<0.001$). In addition, results show that ATX strongly reduces noise correlations within each task (Fixation, Wilcoxon tank sum test, $p<0.01$, memory guided saccade, Wilcoxon rank sum test, $p<0.01$ and attention task, Wilcoxon rank sum test, $p<0.001$).

To summarize, these observations show that boosting NE transmission locally reduces shared neuronal variability, as is also observed under spatial attention orientation conditions (Cohen and Maunsell, 2009).

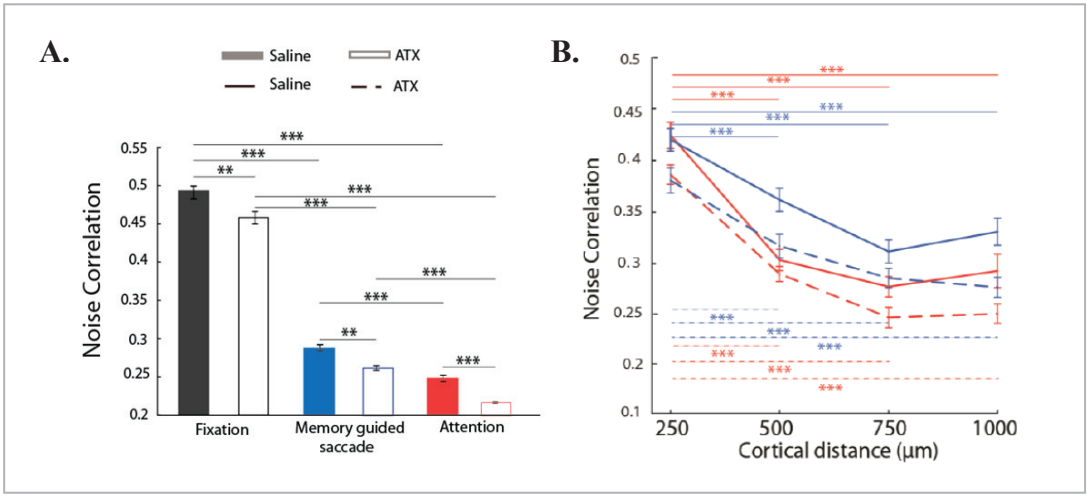

Figure 4: (A) Noise correlations as a function of task and injection type*. Average noise correlations across sessions for each of the three tasks separately for saline and ATX sessions (mean +/- s.e., noise correlations calculated on the neuronal activities from 300 to 500 after eye fixation onset. Black: fixation task; blue memory guided saccade task; red: attention task. Stars indicate statistical significance following a two-way ANOVA and rank sum post-hoc tests; *p<0.05; **p<0.01; ***p<0.001. across sessions for each of the three tasks (mean +/- s.e., noise correlations calculated on the neuronal activities* ***(B) Noise correlations as a function of cortical distance.*** *Average noise correlations (mean +/- s.e.) across sessions, for attention and memory-guided saccade task, from 300 ms to 500ms after eye fixation onset, as a function of distance between pairs of channels: 250µm; 500µm; 750µm; 1000µm. Stars indicate statistical significance following a two-way ANOVA and rank sum post-hoc tests; *p<0.05; **p<0.01; ***p<0.001.*

4. Effects of Atomoxetine on the relation between noise correlation and distance between pairs of neuron: Our recordings were performed as tangentially to FEF cortical surface as possible. The distance between the different recording probe contacts is thus a fair proxy to actual cortical tangential distance. Previous studies (Constantinidis et Goldman-Rakic 2002; Lee et al., 1998; Smith et Kohn 2008, Ben Hadj Hassen et al., 2019), have shown that noise correlations significantly decrease as the distance between the pair of signals across which noise correlations were computed increased. Our main goal here is to investigate if the ATX has an effect on the relation between noise correlations and distance as described above. While cortical distance effects onto noise correlations persist under ATX conditions, and ATX decreases noise correlations systematically across all distance, ATX effects varied as function of distance, in particular for the longest distances (3-way ANOVA, Injection x Task x Distance, ATX effect: $p<0.001$; task effect: $p=0.05$, Distance effect: $p<0.001$, interaction between injection and task: $p<0.01$, interaction between injection and distance, $p<0.05$ and interaction between task and distance, $p<0.05$). Post-hoc analyses indicate that this distance effect is statistically significant, for all tasks, beyond 500 µm (Wilcoxon rank sum test,

attention task: $p<0.001$ for 750 μm, $p<0.001$ for 1000 μm; Memory-guided saccade task: $p<0.001$ for 750 μm, $p<0.001$ for 1000 μm).

Overall, these observations demonstrate for the first time that boosting NE transmission descreases shared neuronal variability, in a distance dependent manner. These effects are similar to those observed under spatial attention orientation (Cohen and Maunsell, 2009)though of much higher overall amplitude.

5. Effects of Atomoxetine on rhythmic fluctuation of noise correlations and on spike field coherence. We have demonstrated in ***Chapter II*** that noise correlations in time express rhythmic fluctuations that take place in two distinct frequency ranges: a high alpha frequency range (10-16 Hz) and a beta frequency range (20-30Hz). Importantly, we have shown that alpha and beta oscillation phase in noise correlations were predictive of behavioral performance. According to our results in the present study, we found that ATX improved the behavioral performance by reducing the reaction time and the signal processing by reducing noise correlations between pairs of neurons. Thus, the important question is what is the exact effect of ATX on the rhythmic fluctuations of noise correlations? Does ATX reduces or increases the frequency of noise correlation oscillations? First of all, our observations (Figure 5(A), left and right) confirm the rhythmic oscillations of noise correlations in time described in ***Chapter II*** that take place in a high alpha frequency range (10-16 Hz) and a beta frequency range (20-30Hz) for both tasks. Second, we report in saline condition a significant lower power of noise correlations oscillations in attention task than in memory guided saccade task. These results are hold true both when the target is rexpected in the preferred position (Alpha preferred position, Wilcoxon rank sum test, $p<0.001$, beta preferred position, Wilcoxon rank sum test, $p<0.001$) or in non-preferred position (Alpha non-preferred position, Wilcoxon rank sum test, $p<0.001$, beta non-preferred position, Wilcoxon rank sum test, $p<0.001$) of each individual channel. Thus, we confirm the relation between rhythmic fluctuations of noise correlation in time and the level of task engagement; Rhythmic oscillations are higher when task engagement level is low.

Furthermore, ATX has a significant effect on the rhythmic fluctuations of noise correlations for alpha frequency (Memory guided saccade: ANOVA1, $p<0.001$, Attention task: ANOVA1, $p<0.001$). For the memory guided saccade task (Figure 5.A (left)), post-hoc analyses show that ATX decreased significantly the power of alpha and beta for both preferred (**Alpha**, Wilcoxon rank sum test, $p<0.001$, **Beta**, Wilcoxon rank sum test, $p<0.001$)

and non-preferred position (**Alpha**, Wilcoxon rank sum test, p<0.001, **Beta**, Wilcoxon rank sum test, p<0.001). Post-hoc analyses show similar results for the attention task (**Alpha**, Wilcoxon rank sum test, p<0.001, **Beta**, Wilcoxon rank sum test, p<0.001) and non-preferred position (**Alpha**, Wilcoxon rank sum test, p<0.001, **Beta**, Wilcoxon rank sum test, p<0.001).

To summarize, boosting NE transmission decreased the global level of the oscillations of noise correlation, these effects specifically targeting the alph and beta ranges, and being more pronounced for the preferred than for non-prefereed spatial processing. Importantly, and in contrast with the previous results presented in this chapter, these effects are not task specific, task specificity only affecting the overall degree of noise correlations.

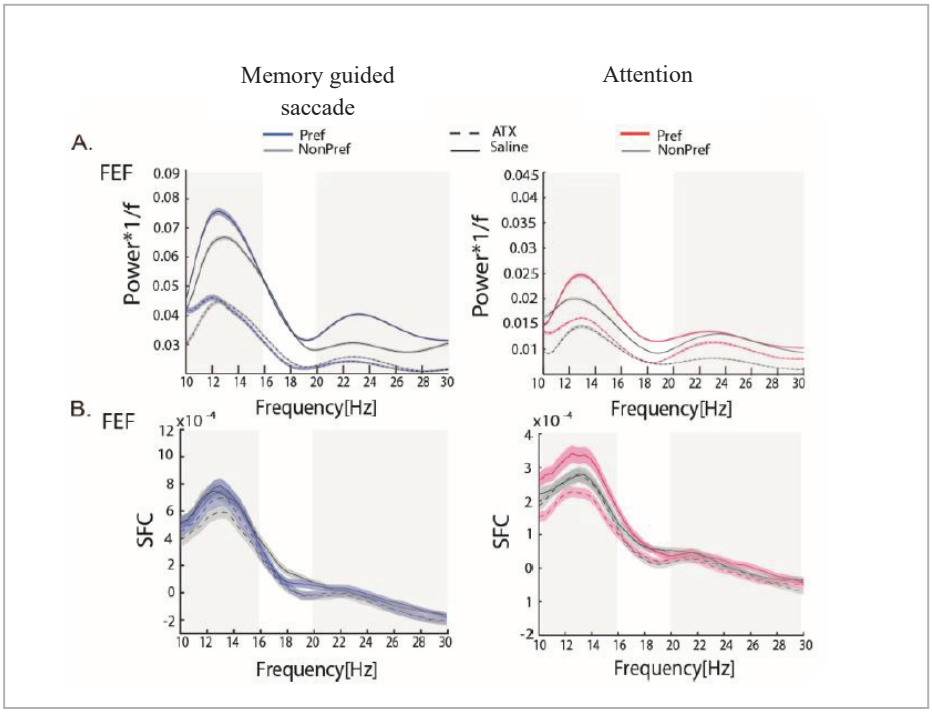

Figure 5: Rhythmic fluctuations in noise correlations and spike-field coherence*. (A) 1/f weighted power frequency spectra of noise correlation in time (average +/- s.e.m), for each task, calculated from 300ms to 1500ms following cue offset (Left; memory guided saccade, right; attention task).* ***(B)*** *Spike field coherence between LFP and spike data as a function of frequency, time intervals as in (A).*

We have shown in ***Chapter II*** that the difference of SFC modulation between tasks match the oscillatory power differences observed in the noise correlations (higher for task with low level engagement). Figure 5.B (left and right) shows that SFC modulation is higher for the memory guided saccade than for the attention task. Importantly, the SFC modulations difference matches with what we have described in our previous work (***Chapter II***) and with

what we described in the present work for the oscillatory power differences observed in the noise correlations, as a function of cognitive engagement and task demands. When investigating the specific effect of ATX we found that, for the attention task, ATX has a significant effect on SFC modulation (ANOVA1, $p<0.001$). Post-hoc analyses show that ATX decreased the SFC in alpha and beta frequency only for preferred position processing (Alpha, Wilcoxon rank sum test, $p<0.001$, beta, Wilcoxon rank sum test, $p<0.05$). Similar effects are found on for the memory guided saccade task (ANOVA1, $p<0.001$). However, and quite surprisingly, ATX decreased the SFC in alpha frequency only for non-preferred position (Alpha preferred, Wilcoxon rank sum test, $p>0.1$, Alpha non-preferred, Wilcoxon rank sum test, $p=0.01$) and in the beta frequency only for preferred position (Wilcoxon rank sum test, $p<0.05$).

Overall, we found that boosting NE transmission decreased the power of the oscillatory variations of noise correlations in the alpha and beta ranges and as well as on SFC modulation in same frequency ranges, indicating beyond selective effects of NE modulation onto baseline and stimulus related responses, NE also modulates the coupling between spikes and local field potentials, as well as the patterns of shared neuronal noise variability.

IV. Discussion

In this work, our main goal was to investigate the neuronal correlates of systemic noradrenergic modulation of attention within the frontal eye field (FEF). We boosted NE transmission by atomoxetine (ATX) i.m. injections, a selective NE reuptake inhibitor. After saline or ATX systemic injection, recordings were performed in the macaque FEFs, a cortical region proposed to be the source of spatial attention top-down control (Buschman and Miller, 2007; Ekstrom et al., 2008; Ibos et al., 2013; Wardak et al., 2006). To determine the neuronal processes underlying high NE transmission, we compared the effect of ATX injection and saline injections on behavioral performances, neuronal baseline and stimulus-related responses as well as on local and global neuronal processes by measuring noise correlations, their rhythmic oscillations and spike filed coherence modulation.

Overall, we demonstrate that boosting NE transmission improves the behavioral performances in the attention-related task, has an independent effect on baseline and stimulus-related response as well as on noise correlations within the FEF. Specifically we show for the first time that boosting NE transmission decreased noise correlations, its rhythmic oscillations

as well as SFC modulation. These findings are discussed below in relation with proposed models of LC-NE functions.

Effects of Atomoxetine on behavioral performance:

ATX is known to be used as a treatment for ADHD (Bymaster et al., 2002; S. V. Faraone et al., 2005; Michelson et al., 2001). Previous studies have shown that ATX enhanced behavioral performances and facilitated the early sensory signal processing in the visual thalamus (Navarra and Waterhouse, 2018, Reynaud et Frosel (***ChapterIV***)). Consistent with previous results, we found that ATX enhanced the behavioral performances by decreasing the reaction time and the latency to maximum peak response within FEF. Interestingly this effect takes place only in the attention task and not in the memory guided saccade task. While neuronal processes underlying saccade execution are localized in prefrontal cortex (Kastner et al., 2007), Coull et al (1995) have demonstrated that manipulation of noradrenergic transmission affects differently tasks sensitive to prefrontal cortex damage. In this context, our results support this ATX task specific effect. We found that ATX decreased the pre-stimulus baseline MUA activity and their amplitude of responses to the stimulus. This effect could be explained by the fact that within a novel environment, boosting NE transmission enhances scanning of environment and decreases attention to an individual stimulus (Arnsten et al., 1981; Berridge and Dunn, 1989). This will need to be further explored.

Overall we demonstrate that boosting NE transmission improved the behavioral response. In the attention task, the monkey has to ignore distractors and respond only to the luminosity change of the target. Previous studies have proposed that LC-NE enhancing role of cognitive function takes place within noisy environment containing irrelevant stimuli that could decrease subject performances (Carli et al., 1983; Oke and Adams, 1978; Roberts et al., 1975; Selden et al., 1990, 1991). In the other side, it's well documented that relevant stimuli elicit phasic activity of LC neurons (Aston-Jones & Bloom 1981b, Grant et al. 1988, Herve-Minvielle & Sara 1995, Rasmussen et al. 1986) and high NE transmission (Abercrombie et al. 1988, Brunet al. 1993). Furthermore, it has been demonstrated that fluctuations of phasic activity within monkey LC-NE system is linked with his performance on vigilance task(G Aston-Jones et al., 1997; G. Aston-Jones et al., 1997; Rajkowski et al., 1994b). Based on all these previous observations and our results, we conclude that ATX facilitates behavioral

response to stimulus, associated with utile reward, in the task-specific attention processes by filtering the irrelevant stimulus. This observation remind us the suggested role of phasic activity of LC-NE system, gain model proposed by Aston-Jones and Cohen (2005), in facilitating behavioral response to relevant event and ignoring the irrelevant one (Aston-Jones and Cohen, 2005a). Here we provide an evidence for LC-NE phasic activity role in optimizing the ongoing behavior during attention-related task.

To summarize, our results support the LC-NE activity role in adapting behavior to the current task by enhancing exploitation of the current environment when the utility of the reward is high.

Effects of Atomoxetine on local and global scale of FEF neuronal network:

Recently, Guedj et al., (2017) have shown , with an fMRI study, that boosting NE transmission during resting state induced a clear reorganization of brain activity between and within several resting state networks. Specifically, they highlight a decrease of the correlation between sensory-motor network and fronto-parietal network. In our previous work, ***ChapterII,*** results supported the co-existence, within FEF, of both **1) long-range global** noise correlation modulatory mechanisms identified through a very clear scaling of cortical distance, neuronal spatial selectivity and functional/layer specificity effects by general task demand and **2) short-range local** noise correlation modulatory mechanisms identified by the local change of noise correlation. Importantly, in the present work, we found that boosting NE transmission decreased inter-neuronal noise correlation within FEF during fixation task epoch characterized by absence of any sensory event. This effect on short-range local noise correlations modulatory mechanisms was robust across tasks with different engagement level. Furthermore, ATX decreased noise correlation across distance with respect of its link with task demand. These results suggest that boosting NE transmission has a local specific effect on both short-range local and long-range global correlation modulatory mechanisms within frontal cortex.

It has been demonstrated that LC-NE system modulates the oscillatory activity in several brain regions (Delagrange et al., 1993; Walling et al., 2011). We have demonstrated that noise correlations in time are found to express rhythmic oscillations in alpha (10-16Hz) and beta (20-30Hz) frequency ranges that are linked with behavioral performances ***ChapterII***. Based on results described above, one might hypothesis that LC-NE system will modulate these rhythmic fluctuations. Importantly, our results confirm the rhythmic oscillations of

noise correlations and support the proposed hypothesis; we found that under ATX noise correlation oscillations in alpha and beta frequency range are also present but with decreased power compared to saline condition for both tasks. In the same line, we found that ATX decreased the power of SFC within the identified specific frequency ranges.

To summarize, we demonstrated that boosting NE transmission decreased the inter-neuronal noise correlation within FEF, its rhythmic oscillations in alpha and beta frequency ranges and the SFC in the same frequency ranges. These observations support the role of LC-NE system proposed in 'reset signal' model of Bouret and Sara, (2005) in inducing network reorganization. Here we observed that boosting NE transmission induce a reorganization of the frontal eye field network of monkey. In our work, the network reorganization induce a decrease of noise correlations within frontal cortex, specifically within frontal eye field ;a cortical region proposed to be the source of spatial attention top-down control (Buschman and Miller, 2007; Ekstrom et al., 2008; Ibos et al., 2013; Wardak et al., 2006).

The existing literature doesn't provide enough information to decide between these two models. Based on our results we suggest, unlike what has been thought, that the two models act together in order to adapt the behavior performances to the ongoing task or environment. The next challenging step, to confirm our observations, is to investigate the neuronal correlates of boosting NE transmission on the correlation within fronto-parietal network, found to has a decreased correlation with LC-NE system under ATX (Guedj et al., 2017b).

Conclusion:

We thus demonstrate that ATX improve behavioral performences in task-specific manner by decreasing reaction time and the latency to the maximum response to the relevant stimulus. In addition, ATX decreases noise correlation within FEF, its rhythmic fluctuations in alpha and beta frequencies and SFC modulation. Further analyses will be needed to confirm our hypotheses concerning LC-NE system models.

V. References

Arnsten, A.F.T., D.S. Segal, S.E. Loughlin, et D.C.S. Roberts. 1981. « Evidence for an Interaction of Opioid and Noradrenergic Locus Coeruleus Systems in the Regulation of Environmental Stimulus-Directed Behavior ». Brain Research 222 (2): 351‑ 63.

Aston-Jones, G, J Rajkowski, et P Kubiak. 1997. « Conditioned Responses of Monkey Locus Coeruleus Neurons Anticipate Acquisition of Discriminative Behavior in a Vigilance Task ». Neuroscience 80 (3): 697‑ 715.

Aston-Jones, G., J. Rajkowski, et P. Kubiak. 1997. « Conditioned Responses of Monkey Locus Coeruleus Neurons Anticipate Acquisition of Discriminative Behavior in a Vigilance Task ». Neuroscience 80 (3): 697715.

Aston-Jones, Gary, et Jonathan D. Cohen. 2005. « Adaptive Gain and the Role of the Locus Coeruleus-Norepinephrine System in Optimal Performance ». The Journal of Comparative Neurology 493 (1): 99‑ 110.

Bedard, Anne-Claude, Abel Ickowicz, Gordon D. Logan, Sheilah Hogg-Johnson, Russell Schachar, et Rosemary Tannock. 2003. « Selective Inhibition in Children with Attention-Deficit Hyperactivity Disorder off and on Stimulant Medication ». Journal of Abnormal Child Psychology 31 (3): 315‑ 27.

Berridge, Cw, et Aj Dunn. 1989. « Restraint-Stress-Induced Changes in Exploratory Behavior Appear to Be Mediated by Norepinephrine-Stimulated Release of CRF ». The Journal of Neuroscience 9 (10): 3513‑ 21.

Bouret, Sebastien, et Susan J. Sara. 2005. « Network Reset: A Simplified Overarching Theory of Locus Coeruleus Noradrenaline Function ». Trends in Neurosciences 28 (11): 574‑ 82.

Buschman, Timothy J, et Earl K Miller. 2007. « Top-down versus Bottom-up Control of Attention in the Prefrontal and Posterior Parietal Cortices ». Science (New York, N.Y.) 315 (5820): 1860‑ 62.

Bush, George, Jennifer Holmes, Lisa M. Shin, Craig Surman, Nikos Makris, Eric Mick, Larry J. Seidman, et Joseph Biederman. 2013. « Atomoxetine Increases Fronto-Parietal Functional MRI Activation in Attention-Deficit/Hyperactivity Disorder: A Pilot Study ». Psychiatry Research 211 (1): 88‑ 91.

Bymaster, Frank P, Jason S Katner, David L Nelson, Susan K Hemrick-Luecke, Penny G Threlkeld, John H Heiligenstein, S Michelle Morin, Donald R Gehlert, et Kenneth W Perry. 2002. « Atomoxetine Increases Extracellular Levels of Norepinephrine and Dopamine in Prefrontal Cortex of Rat: A Potential Mechanism for Efficacy in Attention Deficit/Hyperactivity Disorder ». Neuropsychopharmacology 27 (5): 699‑ 711.

Carli, M., T.W. Robbins, J.L. Evenden, et B.J. Everitt. 1983. « Effects of Lesions to Ascending Noradrenergic Neurones on Performance of a 5-Choice Serial Reaction Task in Rats; Implications for Theories of Dorsal Noradrenergic Bundle Function Based on Selective Attention and Arousal ». Behavioural Brain Research 9 (3): 361‑ 80.

Cohen, Marlene R., et John H. R. Maunsell. 2009. « Attention Improves Performance Primarily by Reducing Interneuronal Correlations ». Nature Neuroscience 12 (12): 1594‑ 1600.

Constantinidis, Christos, et Patricia S. Goldman-Rakic. 2002. « Correlated Discharges among Putative Pyramidal Neurons and Interneurons in the Primate Prefrontal Cortex ». Journal of Neurophysiology 88 (6): 3487‑97.

Coull, J. T., H. C. Middleton, T. W. Robbins, et B. J. Sahakian. 1995. « Clonidine and Diazepam Have Differential Effects on Tests of Attention and Learning ». Psychopharmacology 120 (3): 322‑32.

Delagrange, P., M. H. Canu, A. Rougeul, P. Buser, et J. J. Bouyer. 1993. « Effects of Locus Coeruleus Lesions on Vigilance and Attentive Behaviour in Cat ». Behavioural Brain Research 53 (1‑2): 155‑65.

Ekstrom, Leeland B., Pieter R. Roelfsema, John T. Arsenault, Giorgio Bonmassar, et Wim Vanduffel. 2008. « Bottom-up Dependent Gating of Frontal Signals in Early Visual Cortex ». Science (New York, N.Y.) 321 (5887): 414‑17.

Faraone, Stephen V., Joseph Biederman, Thomas Spencer, David Michelson, Lenard Adler, Fred Reimherr, et Larry Seidman. 2005. « Atomoxetine and Stroop Task Performance in Adult Attention-Deficit/Hyperactivity Disorder ». Journal of Child and Adolescent Psychopharmacology 15 (4): 664‑70.

Guedj, Carole, Elisabetta Monfardini, Amélie J. Reynaud, Alessandro Farnè, Martine Meunier, et Fadila Hadj-Bouziane. 2017. « Boosting Norepinephrine Transmission Triggers Flexible Reconfiguration of Brain Networks at Rest ». Cerebral Cortex (New York, N.Y.: 1991) 27 (10): 4691‑4700.

Hill, Dina E., Ronald A. Yeo, Richard A. Campbell, Blaine Hart, Janet Vigil, et William Brooks. 2003. « Magnetic Resonance Imaging Correlates of Attention-Deficit/Hyperactivity Disorder in Children ». Neuropsychology 17 (3): 496‑506.

Ibos, Guilhem, Jean-René Duhamel, et Suliann Ben Hamed. 2013. « A Functional Hierarchy within the Parietofrontal Network in Stimulus Selection and Attention Control ». The Journal of Neuroscience: The Official Journal of the Society for Neuroscience 33 (19): 8359‑69.

Kastner, Sabine, Kevin DeSimone, Christina S. Konen, Sara M. Szczepanski, Kevin S. Weiner, et Keith A. Schneider. 2007. « Topographic Maps in Human Frontal Cortex Revealed in Memory-Guided Saccade and Spatial Working-Memory Tasks ». Journal of Neurophysiology 97 (5): 3494‑3507.

Lee, Daeyeol, Nicholas L. Port, Wolfgang Kruse, Apostolos P. Georgopoulos, et Neurology. 1998. Variability and correlated noise in the discharge of neurons in motor and parietal areas of the primate cortex. J Neurosci 18:1161–1170.

McLean, A., J. Dowson, B. Toone, S. Young, E. Bazanis, T. W. Robbins, et B. J. Sahakian. 2004. « Characteristic Neurocognitive Profile Associated with Adult Attention-Deficit/Hyperactivity Disorder ». Psychological Medicine 34 (4): 681‑92.

Michelson, D., D. Faries, J. Wernicke, D. Kelsey, K. Kendrick, F. R. Sallee, T. Spencer, et Atomoxetine ADHD Study Group. 2001. « Atomoxetine in the Treatment of Children and Adolescents with Attention-Deficit/Hyperactivity Disorder: A Randomized, Placebo-Controlled, Dose-Response Study ». Pediatrics 108 (5): E83.

Navarra, Rachel L., Brian D. Clark, Gerard A. Zitnik, et Barry D. Waterhouse. 2013. « Methylphenidate and Atomoxetine Enhance Sensory-Evoked Neuronal Activity in the Visual Thalamus of Male Rats ». Experimental and Clinical Psychopharmacology 21 (5): 363‑74.

Navarra, Rachel L., et Barry D. Waterhouse. 2018. « Considering Noradrenergically Mediated Facilitation of Sensory Signal Processing as a Component of Psychostimulant-Induced Performance Enhancement ». Brain Research, juin.

Oke, A. F., et R. N. Adams. 1978. « Selective Attention Dysfunctions in Adult Rats Neonatally Treated with 6-Hydoxydopamine ». Pharmacology, Biochemistry, and Behavior 9 (4): 429‑ 32.

Oostenveld, Robert, Pascal Fries, Eric Maris, et Jan-Mathijs Schoffelen. 2011. « FieldTrip: Open Source Software for Advanced Analysis of MEG, EEG, and Invasive Electrophysiological Data ». Intell. Neuroscience 2011 (janvier): 1:1–1:9.

Rajkowski, J., P. Kubiak, et G. Aston-Jones. 1994. « Locus Coeruleus Activity in Monkey: Phasic and Tonic Changes Are Associated with Altered Vigilance ». Brain Research Bulletin 35 (5‑ 6): 607‑ 16.

Roberts, D.C.S., A.P. Zis, et H.C. Fibiger. 1975. « Ascending Catecholamine Pathways and Amphetamine-Induced Locomotor Activity: Importance of Dopamine and Apparent Non-Involvement of Norepinephrine ». Brain Research 93 (3): 441‑ 54.

Selden, Nr, Tw Robbins, et Bj Everitt. 1990. « Enhanced Behavioral Conditioning to Context and Impaired Behavioral and Neuroendocrine Responses to Conditioned Stimuli Following Ceruleocortical Noradrenergic Lesions: Support for an Attentional Hypothesis of Central Noradrenergic Function ». The Journal of Neuroscience 10 (2): 531‑ 39.

Selden, N.R.W., B.J. Everitt, et T.W. Robbins. 1991. « Telencephalic but Not Diencephalic Noradrenaline Depletion Enhances Behavioural but Not Endocrine Measures of Fear Conditioning to Contextual Stimuli ». Behavioural Brain Research 43 (2): 139‑ 54.

Smith, Matthew A., et Adam Kohn. 2008. « Spatial and Temporal Scales of Neuronal Correlation in Primary Visual Cortex ». Journal of Neuroscience 28 (48): 12591‑ 603.

Sowell, Elizabeth R., Paul M. Thompson, Suzanne E. Welcome, Amy L. Henkenius, Arthur W. Toga, et Bradley S. Peterson. 2003. « Cortical Abnormalities in Children and Adolescents with Attention-Deficit Hyperactivity Disorder ». Lancet (London, England) 362 (9397): 1699‑ 1707.

Walling, Susan G., Robert A. M. Brown, J. Stephen Milway, Avery G. Earle, et Carolyn W. Harley. 2011. « Selective Tuning of Hippocampal Oscillations by Phasic Locus Coeruleus Activation in Awake Male Rats ». Hippocampus 21 (11): 1250‑ 62.

Wardak, Claire, Guilhem Ibos, Jean-René Duhamel, et Etienne Olivier. 2006. « Contribution of the Monkey Frontal Eye Field to Covert Visual Attention ». The Journal of Neuroscience: The Official Journal of the Society for Neuroscience 26 (16): 4228‑ 35.

Yeo, R. A., D. Hill, R. Campbell, J. Vigil, et W. M. Brooks. 2000. « Developmental Instability and Working Memory Ability in Children: A Magnetic Resonance Spectroscopy Investigation ». Developmental Neuropsychology 17 (2): 143‑ 59.

Chapter VI

General Discussion

The aim of my thesis project was to determine the neuronal correlates of cognitive engagement, task demands and noradrenergic modulation of attention onto the prefrontal cortex, specifically within the frontal eye field (FEF). My research work was based on the analyses of the variation of noise correlation as a function of several parameters in both normal and neuromodulated attentional states. These noise correlations express the amount of co-variability, in the trial-to-trial fluctuations of responses in pairs of neurons, to repeated presentations of identical stimuli, or under identical behavioral conditions. In ***chapter I***, I provide, based on previous studies, an operational definition of noise correlations and I describe how noise correlations vary as a function of neuronal distance, cortical layer, neuronal selectivity, cortical area and cognitive operations. Importantly, there is an important link between noise correlations and producing an optimal behavior, but this link is still unclear. My first hypothesis was the existence of important changes in noise correlations during adaptive cognitive control and this at multiple time-scales. Within ***chapter II***, my first research work during my thesis, I investigated how noise correlations are adjusted as a function of task engagement level within FEF. My aim through this first study was to determine how noise correlations vary within normal and dynamic attentional states. The next step was to determine the behavioral and neuronal correlates of boosting NE transmission. Before presenting this study in ***chapters IV and V,*** I have summarized in ***chapter III*** the physiological and behavioral data describing the LC-NE system as a major source of NE then I described the implication of NE in attention and the models proposed for LC-NE activity. In the last part of this ***chapter III,*** I confronted these models to NE neuronal modulation based on the existent literature. In ***chapter IV,*** I presented the second experimental study of my project, a collaborative work with Dr Fadila Hadj Bouziane, within which we aimed to determine the behavioral correlates of boosting NE transmission and particularly the role of NE in visuo-spatial attention. I participated in this study by training and recording data from two macaque monkeys and preprocessing the collected data. The major part of analyses was performed by Amelie Reynaud from the group of Dr Hadj Bouziane and Mathilda Froesel from our group. The last step was to determine the neuronal correlates of boosting NE transmission within FEF. My research work for this step is presented in ***Chapter V***. Due to experimental advert conditions, results are reported on only one monkey. Data from a second

monkey will be collected in the coming months. In the following, I will provide a discussion and perspectives based on my main contributions to the above described questions.

1. *How do noise correlations vary as a function of task demand?*

In this experimental first study (***chapter II***), MUA and LEP signals were recorded from the FEF, a cortical region which has been shown to be at the source of spatial attention top-down control (Buschman et Miller 2007; Wardak et al., 2006; Ibos et al., 2013; Ekstrom et al., 2008), while two monkeys performed three tasks with different engagement level. I analyzed (***Chapter II***), the variation of noise correlation as a function of several parameters. First of all, I have demonstrated for the first time that noise correlations decreases as the task engagement level increases. Furthermore, I found that these noise correlations are dynamically adjusted within the probability of occurrence of a behaviorally key task event associated with the reward response production (target presentation on the fixation and target detection tasks or saccade go signal on the memory guided saccade task). In other words, I have shown that, on each of the three tasks, at any given time in the fixation epoch prior to response production, the higher the probability of having to initiate a response, the lower the noise correlations. Overall, this supports the idea that noise correlations is a flexible physiological parameter that dynamically adjusts at multiple timescales to optimally meet ongoing behavioral demands, as has been demonstrated in multisensory integration (for example, Chandrasekaran 2017) and through learning and attention (Ni et al., 2018). Then I have investigated the mechanisms through which this could possibly take place. I found that noise correlations in time express rhythmic modulations in specific functional frequency ranges: the alpha (10- 16Hz), associated with attention, anticipation (Thut et al., 2006; Rihs et al., 2009), perception (Varela et al., 1981; Mathewson et al., 2009; Busch et VanRullen 2010), and working memory (Klimesch 1997), and beta (20-30Hz) frequency ranges, considered to reflect long-range processes and have been associated with cognitive control and flexibility (Engel et al., 2001; Okazaki et al., 2008; Iversen et al., 2009; Buschman et Miller 2007, 2009; Engel et Fries 2010) as well as with motor control (Joundi et al., 2012; Lalo et al., 2007; Courtemanche et al., 2003; for review see: Engel et Fries 2010). Looking for a functional link between spikes (on which noise correlations are calculated) and LFP, I measured the variation of spike field coherence across tasks as a function of layers. I found that lower alpha and beta in noise correlations, and accordingly in spike-field coherence, correspond to higher cognitive demands. Furthermore I found that spike-field coherence in beta range strongly decreases in

the more superficial cortical layers as compared to the deeper layers, as task cognitive demand increases. However, alpha spike-field coherence does not exhibit any layer specificity across task demands. Thus overall, alpha and beta rhythmicity account for strong fluctuations in behavioral performance, as well as for changes in spike-field coherence. Importantly, these observations coincide with recent evidence that cognition is rhythmic (Fiebelkorn et al., 2018; Fiebelkorn and Kastner, 2018) and that noise correlations play a key role in optimizing behavior to the ongoing time-varying cognitive demands (Ni et al., 2018).

The results described above and their contributions are summarized in the following figure.

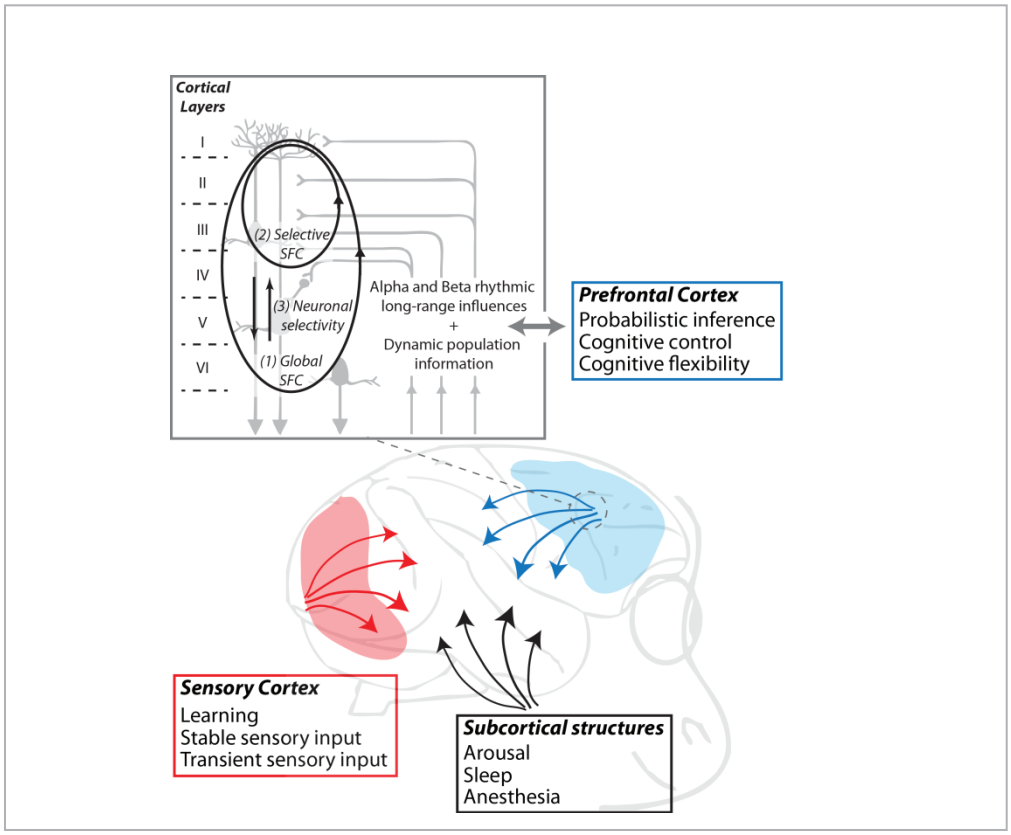

Figure1. *The dynamic adjustments in noise correlations correspond to a top-down control (blue) over local neuronal processes, mediated through long-range inter-areal influences. Beta rhythmicity is involved in a selective superficial SFC modulation (inset, (2)), and alpha rhythmicity is involved in a more global SFC modulation (inset, (1)). The rhythmic processes co-exist with selective changes in noise correlations as a function of neuronal selectivity (inset, (3)). These top-down dynamic adjustments in noise correlations are expected to add up onto state-related changes in noise correlations (black), possibly mediated through neuromodulatory mechanisms, and sensory bottom-up induced changes in noise correlations (red).*

2. *What are the behavioral correlates of boosting NE transmission?*

Optimal behavior depends on the precision of the visuo-spatial attention which enables us to selectively process visual information through prioritization of a spatial location while setting aside other locations. The underlying processes of spatial attention take place within the fronto-parietal cortex which is under the influence of norepinephrine (NE) (Noudoost and Moore 2011). It has been demonstrated that visuo-spatial attention has three sub-components (alerting, orientating and executive control; Posner 1980, Petersen and Posner 2012). In the absence of a direct evidence for an effect of NE onto this attentional sub-component, we investigated how boosting NE transmission affect the three specific attentional components and specifically we aim to 1) clarify the components that are under the influence of NE availability and 2) characterize the specific action of NE availability onto them. During the experiment, all animals performed two kinds of runs during the same session; **1) Pure runs**; monkeys were required to fixate a central cross to initiate the trial and then execute a saccade as fast as possible when a target appears randomly in the left or in the right side of the screen (10 degrees of eccentricity) and hold fixation during 300ms. **2) mixed runs**, derived from the attentional network task (Posner 1980). Monkeys were required to fixate a central cross to initiate the trial and execute a saccade towards **CUED** target. For 80 % of the trials, the peripheral cue was flashed for 100ms prior to the target onset on one side of the screen, accurately predicting the upcoming target location ('*valid* cue'). In the remaining 20% of the trials, the cue was either absent ('*no* cue'), or presented on the opposite side of target location ('*invalid* cue'), or two cues were simultaneously presented ('*neutral* cue'). Our results demonstrated that ATX does not have the same effect on the different attentional sub-processes tested in the present work, namely alerting, orienting and the distractor interference effect. Specifically, ATX improves the orienting process by decreasing the RTs in the trials where the cue accurately predicted the location of the target (valid trials in mixed runs), i.e. the most prevalent trials in our task. This result is in line with two previous studies that reported that clonidine, which decreases NE transmission, attenuated the orienting process in humans (Coull et al. 2001; Clark et al. 1989) in a predictive context and not in less predictive one (Witte and Marrocco 1997). However, we found that ATX increased the RTs in non cued trials in both types of runs. We suggested that the difference of ATX effect on pure versus mixed runs might be interpreted in terms of a trade-off in performance that depended on the context. Thus our results are in line with the idea that the LC-NE system facilitates the

mobilization of sensory and attentional resources to process information of the environment (Varazzani et al. 2015) and to provide behavioral flexibility, notably in the ability to shift attentional set (Lapiz and Morilak 2006; McGaughy et al. 2008; Newman et al. 2008; Seu et al. 2009; Cain et al. 2011; Bradshaw et al. 2016). NE-dependent improvement in performance has been reported in other tasks involving working memory (Gamo et al. 2010), cognitive control (Faraone et al. 2005), sustained attention (Berridge et al. 2012) or sensory discrimination (Gelbard-sagiv et al. 2018). Our results further suggest that, beyond a global adjustment of the behavior to the context, ATX fine-tunes the behavior at the level of the trial to maximize reward rate, leading to a trade-off in the infrequent trials (Aston-Jones and Cohen 2005; Bouret and Sara 2005; Corbetta et al. 2008; Fazlali et al. 2016). To summarize, up to now our observations demonstrated that boosting NE transmission has a specific effect onto the dynamic and flexible components of attention, namely spatial **orienting and executive control when the context is highly predictive**. Based on the existing literature, we wanted to go further in our analyses and clarify by which mechanisms ATX adapt the behavioral performance to the ongoing context. For example, Noorani and Carpenter (2016) have suggested, by using LATER model statistics, that the detection of a target involves both a perceptual process that can be modelled by an accumulation of information, and a decision-making step more related to top-down processes, that can be modelled by the application of a decision threshold (Noorani and Carpenter 2016). Using the same LATER model we found that under ATX and during **mixed runs** monkeys **1)** adapted better theirs behavior on the ongoing task, by a specific improvement of attentional orienting, thanks to **lower decisional threshold** to execute a saccade toward the target and **2) accumulated faster** the available sensory evidence during trials in which the target was preceded by a predictive spatial cue (validly cued trials). However, during **pure runs** we observed a slower accumulation rate in the ATX condition compared to the saline. This finding is in line with an increasing number of studies showing that NE influences **bottom-up processes**, even at very early-stages of sensory signal processing improving the signal-noise ratio in sensory cortex in response to incoming stimuli, to shape the behavior according to the environment (Navarra and Waterhouse 2018; Waterhouse and Navarra 2018).

To summarize, our have demonstrated that ATX has a specific effect onto the dynamic and flexible components of attention, namely spatial **orienting and executive control when the context is highly predictive.** In the same context, ATX induces a low decisional threshold and faster accumulation rate of the available sensory information.

Overall results bring new evidence to the role of NE on attentional processes. We demonstrated that ATX has a context-dependent effect onto attentional processes. Second we have shown that the mechanism, exerted at different levels, underlying its action on spatial attention is complex. All this is likely reflecting changes within sensory cortex leading to faster accumulation rate to incoming stimuli as well as the adjustment of the decisional threshold via an action of NE within prefrontal regions (Robbins and Arnsten 2009; Arnsten 2011; Arnsten and Pliszka 2011).

3. *What are the neuronal correlates of boosting NE transmission?*

In the third experimental study (***chapter V***), I recorded MUA and LFP signals within frontal eye field (FEF) while one monkey was doing three tasks with different engagement level (Fixation, Memory guided saccade and attention task). As the parameter that will be analyzed in this study are based on the results of my first study (***chapter II***), I had two aims. My first aim was to confirm results found in ***chapters II*** and ***IV*** and the second one was to determine the neuronal correlates of boosting NE transmission within FEF.

Starting by the behavioral results; consistent with previous study and our previous work ATX enhanced performances by decreasing reaction time. Furthermore we found that latency to maximum peak response within FEF decreases under ATX compared to saline condition. This supports the role of NE in facilitating the early sensory signal processing in the visual thalamus (Navarra and Waterhouse, 2018, Reynaud et Freosel (***ChapterIV***)). Importantly, this effect was specific to attention task and not to the task that requiring a spatial memory and oculomotor response production. The absence of ATX effect, for memory guided saccade, on both reaction time and latency to maximum peak response could arise from ATX task-specific effect as suggested by Coull et al (1995). They have demonstrated that manipulation of noradrenergic transmission affects differently tasks sensitive to prefrontal cortex damage. This will need to be further explored. Overall, we found the same effect of ATX on behavioral performances than our previous work ***chapter IV***.

In ***Chapter II,*** I demonstrated for the first time that noise correlations decreases when the task engagement level increases. Our observations in the present study replicate these findings on an independent data set. Furthermore, the results in this study support the results and the proposed hypothesis in our previous work, ***Chapter II.*** We suggested the existence, within FEF, of noise correlation modulatory mechanisms identified through a very clear scaling of cortical distance, neuronal spatial selectivity and functional/layer specificity effects

by general task demand. Importantly, we found that boosting NE transmission decreased inter-neuronal noise correlations within FEF during fixation task epoch characterized by absence of any sensory event. This effect on local noise correlations modulatory mechanisms was robust across tasks with different engagement level. Furthermore, ATX decreased noise correlations was not homogenous across cortical distances. These results suggest that boosting NE transmission has a local specific effect on both short-range local and long-range global correlation modulatory mechanisms within prefrontal cortex. Accordingly, we have demonstrated that the alpha (10-16Hz) and beta (20-30Hz) rhythmic oscillations of noise correlations in time are also decreased by NE neuromodulation. Thus, ur results bring new evidence to the role of NE on attentional processes on the **behavioral** and **neuronal** level.

Behavioral level. We demonstrate that boosting NE transmission improved behavioral response in attention task within which monkey has to ignore distracters. This finding is in line with the role of LC-NE system on cognitive function. Several studies have proposed that LC-NE enhancing role of cognitive function takes place within noisy environment containing irrelevant stimuli that could decrease subject performances (Carli et al., 1983; Oke and Adams, 1978; Roberts et al., 1975; Selden et al., 1990, 1991) and that phasic activity of LC neurons is elicited by relevant stimuli (Aston-Jones & Bloom 1981b, Grant et al. 1988, Herve-Minvielle & Sara 1995, Rasmussen et al. 1986) and high NE transmission (Abercrombie et al. 1988, Brunet al. 1993). We conclude that ATX facilitates behavioral response to stimulus, associated with utile reward, in task-specific attention processes by filtering the irrelevant stimulus. This support the suggested role of phasic activity of LC-NE system, gain model proposed by Aston-Jones and Cohen (2005), in facilitating behavioral response to relevant event and ignoring the irrelevant one (Aston-Jones and Cohen, 2005a). Here we provide evidence for LC-NE phasic activity role in optimizing the ongoing behavior during attention-related task.

Neuronal level. We demonstrated that boosting NE transmission decreased the inter-neuronal noise correlation within FEF, its rhythmic oscillations in alpha and beta frequency ranges and SFC in the same frequency ranges. These observations support the role of LC-NE system proposed in 'reset signal' model of Bouret and Sara, (2005) in inducing network reorganization. Here we observed that boosting NE transmission induce a reorganization of monkey frontal eye field local computation. In our hands, this network reorganization induces a decrease of noise correlations within frontal cortex, specifically within frontal eye field, a

cortical region proposed to be the source of spatial attention top-down control (Buschman and Miller, 2007; Ekstrom et al., 2008; Ibos et al., 2013; Wardak et al., 2006).

Based on the behavioral and neuronal effect of ATX that we reported, we suggest, unlike what has been thought, that the two LC-NE models act together in order to adapt the behavior performances to the ongoing task or environment. This will need to be further explored at the neuronal level.

Final conclusion and perspectives

My research work of thesis has demonstrated:

❖ Neuronal aspect:

- Noise correlations decreases as the engagement level and task demands increases both across tasks and within-trials.

- Rhythmic modulations of noise correlations in the alpha and beta frequency range that account both for overt behavioral performance and for layer specific modulations in spike-field coherence.

- Noise correlation has a strong functional role in cognitive flexibility.

❖ Neuronal aspect and pharmacological:

- ATX improved attentional orienting component of visuo-spatial attention, in predictive context, by a faster accumulation rate in the valid trials, rather than by a change in the decision threshold.

- ATX enhance behavioral performance in a task-specific manner.

- ATX enhance neuronal processes in a task-specific manner.

- ATX decreases noise correlations within FEF, its rhythmic fluctuations in alpha (10-16 Hz) and beta (20-30Hz) frequency ranges and the SFC modulation.

- It very likely that the proposed models of LC-NE system: ‘gain model’ and ‘network organization model’ act together and have both an important link with the underlying mechanism of attentional processing.

The next challenging step, to confirm our observations, is to investigate the effect of ATX on the correlation within the fronto-parietal network, found to has a decreased correlation with LC-NE system under ATX (Guedj et al., 2017b).

References

Arnsten, A.F., 2001. Modulation of prefrontal cortical-striatal circuits: relevance to therapeutic treatments for Tourette syndrome and attention-deficit hyperactivity disorder. Adv. Neurol. 85, 333–341.

Arnsten, A.F.T., Pliszka, S.R., 2011. Catecholamine influences on prefrontal cortical function: relevance to treatment of attention deficit/hyperactivity disorder and related disorders. Pharmacol. Biochem. Behav. 99, 211–216.

Aston-Jones, G., Bloom, F.E., 1981. Activity of norepinephrine-containing locus coeruleus neurons in behaving rats anticipates fluctuations in the sleep-waking cycle. J. Neurosci. Off. J. Soc. Neurosci. 1, 876–886.

Aston-Jones, G., Cohen, J.D., 2005. Adaptive gain and the role of the locus coeruleus-norepinephrine system in optimal performance. J. Comp. Neurol. 493, 99–110.

Berridge, C.W., Shumsky, J.S., Andrzejewski, M.E., McGaughy, J.A., Spencer, R.C., Devilbiss, D.M., Waterhouse, B.D., 2012. Differential sensitivity to psychostimulants across prefrontal cognitive tasks: differential involvement of noradrenergic α_1 - and α_2 -receptors. Biol. Psychiatry 71, 467–473.

Bouret, S., Sara, S.J., 2005. Network reset: a simplified overarching theory of locus coeruleus noradrenaline function. Trends Neurosci. 28, 574–582.

Busch, N.A., VanRullen, R., 2010. Spontaneous EEG oscillations reveal periodic sampling of visual attention. Proc. Natl. Acad. Sci. U. S. A. 107, 16048–16053.

Buschman, T.J., Miller, E.K., 2009. Serial, covert shifts of attention during visual search are reflected by the frontal eye fields and correlated with population oscillations. Neuron 63, 386–396.

Buschman, T.J., Miller, E.K., 2007. Top-down versus bottom-up control of attention in the prefrontal and posterior parietal cortices. Science 315, 1860–1862.

Cain, R.E., Wasserman, M.C., Waterhouse, B.D., McGaughy, J.A., 2011. Atomoxetine facilitates attentional set shifting in adolescent rats. Dev. Cogn. Neurosci. 1, 552–559.

Carli, M., Robbins, T.W., Evenden, J.L., Everitt, B.J., 1983. Effects of lesions to ascending noradrenergic neurones on performance of a 5-choice serial reaction task in rats; implications for theories of dorsal noradrenergic bundle function based on selective attention and arousal. Behav. Brain Res. 9, 361–380.

Chandrasekaran, C., 2017. Computational principles and models of multisensory integration. Curr. Opin. Neurobiol. 43, 25–34.

Corbetta, M., Patel, G., Shulman, G.L., 2008. The reorienting system of the human brain: from environment to theory of mind. Neuron 58, 306–324.

Coull, J.T., Middleton, H.C., Robbins, T.W., Sahakian, B.J., 1995. Clonidine and diazepam have differential effects on tests of attention and learning. Psychopharmacology (Berl.) 120, 322–332.

Coull, J.T., Nobre, A.C., Frith, C.D., 2001. The noradrenergic alpha2 agonist clonidine modulates behavioural and neuroanatomical correlates of human attentional orienting and alerting. Cereb. Cortex N. Y. N 1991 11, 73–84.

Courtemanche, R., Fujii, N., Graybiel, A.M., 2003. Synchronous, focally modulated beta-band oscillations characterize local field potential activity in the striatum of awake behaving monkeys. J. Neurosci. Off. J. Soc. Neurosci. 23, 11741–11752.

Ekstrom, L.B., Roelfsema, P.R., Arsenault, J.T., Bonmassar, G., Vanduffel, W., 2008. Bottom-up dependent gating of frontal signals in early visual cortex. Science 321, 414–417.

Engel, A.K., Fries, P., 2010. Beta-band oscillations--signalling the status quo? Curr. Opin. Neurobiol. 20, 156–165.

Engel, A.K., Fries, P., Singer, W., 2001. Dynamic predictions: oscillations and synchrony in top-down processing. Nat. Rev. Neurosci. 2, 704–716.

Faraone, S.V., 2005. Improving mental health care for children and adolescents: a role for prevention science. World Psychiatry Off. J. World Psychiatr. Assoc. WPA 4, 155–156.

Fiebelkorn, I.C., Kastner, S., 2018. A Rhythmic Theory of Attention. Trends Cogn. Sci.

Fiebelkorn, I.C., Pinsk, M.A., Kastner, S., 2018. A Dynamic Interplay within the Frontoparietal Network Underlies Rhythmic Spatial Attention. Neuron 99, 842-853.e8.

Gamo, N.J., Wang, M., Arnsten, A.F.T., 2010. Methylphenidate and atomoxetine enhance prefrontal function through α2-adrenergic and dopamine D1 receptors. J. Am. Acad. Child Adolesc. Psychiatry 49, 1011–1023.

Gelbard-Sagiv, H., Magidov, E., Sharon, H., Hendler, T., Nir, Y., 2018. Noradrenaline Modulates Visual Perception and Late Visually Evoked Activity. Curr. Biol. CB 28, 2239-2249.e6.

Grant, S.J., Redmond, D.E., 1984. Neuronal activity of the locus ceruleus in awake Macaca arctoides. Exp. Neurol. 84, 701–708.

Guedj, C., Monfardini, E., Reynaud, A.J., Farnè, A., Meunier, M., Hadj-Bouziane, F., 2017. Boosting Norepinephrine Transmission Triggers Flexible Reconfiguration of Brain Networks at Rest. Cereb. Cortex N. Y. N 1991 27, 4691–4700.

Ibos, G., Duhamel, J.-R., Ben Hamed, S., 2013. A functional hierarchy within the parietofrontal network in stimulus selection and attention control. J. Neurosci. Off. J. Soc. Neurosci. 33, 8359–8369.

Iversen, J.R., Repp, B.H., Patel, A.D., 2009. Top-down control of rhythm perception modulates early auditory responses. Ann. N. Y. Acad. Sci. 1169, 58–73.

Joundi, R.A., Jenkinson, N., Brittain, J.-S., Aziz, T.Z., Brown, P., 2012. Driving Oscillatory Activity in the Human Cortex Enhances Motor Performance. Curr. Biol. 22, 403–407.

Klimesch, W., 1997. EEG-alpha rhythms and memory processes. Int. J. Psychophysiol. Off. J. Int. Organ. Psychophysiol. 26, 319–340.

Lalo, E., Gilbertson, T., Doyle, L., Di Lazzaro, V., Cioni, B., Brown, P., 2007. Phasic increases in cortical beta activity are associated with alterations in sensory processing in the human. Exp. Brain Res. 177, 137–145.

Lapiz, M.D.S., Morilak, D.A., 2006. Noradrenergic modulation of cognitive function in rat medial prefrontal cortex as measured by attentional set shifting capability. Neuroscience 137, 1039–1049.

Mathewson, K.E., Gratton, G., Fabiani, M., Beck, D.M., Ro, T., 2009. To See or Not to See: Prestimulus α Phase Predicts Visual Awareness. J. Neurosci. 29, 2725–2732.

McGaughy, J., Ross, R.S., Eichenbaum, H., 2008. Noradrenergic, but not cholinergic, deafferentation of prefrontal cortex impairs attentional set-shifting. Neuroscience 153, 63–71.

Navarra, Rachel L, Waterhouse, B.D., 2018. Considering noradrenergically mediated facilitation of sensory signal processing as a component of psychostimulant-induced performance enhancement. Brain Res.

Navarra, Rachel L., Waterhouse, B.D., 2018. Considering noradrenergically mediated facilitation of sensory signal processing as a component of psychostimulant-induced performance enhancement. Brain Res.

Newman, L.A., Darling, J., McGaughy, J., 2008. Atomoxetine reverses attentional deficits produced by noradrenergic deafferentation of medial prefrontal cortex. Psychopharmacology (Berl.) 200, 39–50.

Ni, A.M., Ruff, D.A., Alberts, J.J., Symmonds, J., Cohen, M.R., 2018. Learning and attention reveal a general relationship between population activity and behavior. Science 359, 463–465.

Noorani, I., Carpenter, R.H.S., 2016. The LATER model of reaction time and decision. Neurosci. Biobehav. Rev. 64, 229–251.

Noudoost, B., Moore, T., 2011. CONTROL OF VISUAL CORTICAL SIGNALS BY PREFRONTAL DOPAMINE. Nature 474, 372–375.

Okazaki, M., Kaneko, Y., Yumoto, M., Arima, K., 2008. Perceptual change in response to a bistable picture increases neuromagnetic beta-band activities. Neurosci. Res. 61, 319–328.

Oke, A.F., Adams, R.N., 1978. Selective attention dysfunctions in adult rats neonatally treated with 6-hydoxydopamine. Pharmacol. Biochem. Behav. 9, 429–432.

Petersen, S.E., Posner, M.I., 2012. The attention system of the human brain: 20 years after. Annu. Rev. Neurosci. 35, 73–89.

Posner, M.I., 1980. Orienting of attention. Q. J. Exp. Psychol. 32, 3–25.

Rihs, T.A., Michel, C.M., Thut, G., 2009. A bias for posterior alpha-band power suppression versus enhancement during shifting versus maintenance of spatial attention. NeuroImage 44, 190–199.

Robbins, T.W., Arnsten, A.F.T., 2009. The Neuropsychopharmacology of Fronto-Executive Function: Monoaminergic Modulation Executive function: the set of processes that help to optimize performance in complex conditions requiring several components of cognitive function.

Roberts, D.C.S., Zis, A.P., Fibiger, H.C., 1975. Ascending catecholamine pathways and amphetamine-induced locomotor activity: Importance of dopamine and apparent non-involvement of norepinephrine. Brain Res. 93, 441–454.

Selden, N., Robbins, T., Everitt, B., 1990. Enhanced behavioral conditioning to context and impaired behavioral and neuroendocrine responses to conditioned stimuli following ceruleocortical noradrenergic lesions: support for an attentional hypothesis of central noradrenergic function. J. Neurosci. 10, 531–539.

Selden, N.R.W., Everitt, B.J., Robbins, T.W., 1991. Telencephalic but not diencephalic noradrenaline depletion enhances behavioural but not endocrine measures of fear conditioning to contextual stimuli. Behav. Brain Res. 43, 139–154.

Seu, E., Jentsch, J.D., 2009. Effect of acute and repeated treatment with desipramine or methylphenidate on serial reversal learning in rats. Neuropharmacology 57, 665–672.

Thut, G., 2006. -Band Electroencephalographic Activity over Occipital Cortex Indexes Visuospatial Attention Bias and Predicts Visual Target Detection. J. Neurosci. 26, 9494–9502.

Varela, F.J., Toro, A., John, E.R., Schwartz, E.L., 1981. Perceptual framing and cortical alpha rhythm. Neuropsychologia 19, 675–686.

Wardak, C., Ibos, G., Duhamel, J.-R., Olivier, E., 2006. Contribution of the monkey frontal eye field to covert visual attention. J. Neurosci. Off. J. Soc. Neurosci. 26, 4228–4235.

Waterhouse, B.D., Navarra, R.L., 2018. The locus coeruleus-norepinephrine system and sensory signal processing : A historical review and current perspectives. Brain Res. 1–15.

Witte, E.A., Marrocco, R.T., 1997. Alteration of brain noradrenergic activity in rhesus monkeys affects the alerting component of covert orienting. Psychopharmacology (Berl.) 132, 315–323.