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***INVOLVEMENT OF THE LATERAL PREFRONTAL CORTEX IN AUDITORY ATTENTION  
MECHANISMS***

For the degree of **Master 1 Biologie Intégrative : Physiologie et Neurosciences**

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## **ABSTRACT**

Previous studies have shown, with different paradigms, the involvement of the lateral prefrontal cortex in both top-down (TD) attentional preparation and bottom-up (BU) attention processes. The main purpose of the present work is to study the role of the IPFC in the balance between TD and BU auditory attention. To assess TD auditory anticipation, we adapted the Posner paradigm detection task using central visual cues and monaural auditory targets. BU attentional capture was triggered by a binaural distracting sound (phone ring, bell ring...). We recorded EEG in 7 patients with lesion of the IPFC and 7 matched controls. We computed the event-related-potentials (ERPs) elicited by the visual cues (visual evoked responses, CNV), distracting sounds (auditory evoked responses, P3a, RON) and target sounds (auditor evoked potentials, P3b) in each group. Behaviorally, the patients showed a longer reaction times. Electrophysiologically, the patients presented alterations in the TD mechanisms of attention (less effective cue processing, diminished attentional preparation and reduced target processing) and BU mechanisms of attention (less effective distractor processing, increased attentional capture and later reorientation to the relevant task) suggesting a prolonged focus on task-irrelevant stimuli.

**Key Words : lateral prefrontal cortex, ERP, distractibility, attentional preparation, auditory**

## **RESUME**

De précédentes études ont montré, à travers différents protocoles, l'implication du cortex préfrontal latéral dans les mécanismes top-down (TD) de préparation attentionnelle et bottom-up (BU) attentionnelle. Cette étude se focalise sur le rôle du IPFC dans la balance entre l'attention auditive TD et BU. Dans le but de déclencher l'anticipation auditive TD, nous avons adapté le paradigme de détection de Poser en utilisant des indices visuels centraux et des cibles auditives monaurales. La capture attentionnelle BU a été déclenchée par des sons distracteurs binauraux (sonnerie de téléphone...). Nous avons enregistré l'EEG de 7 patients avec des lésions du IPFC et 7 contrôles appariés. Nous avons rassemblé les potentiels évoqués suscités par l'indice visuel (réponses visuelles évoquées, CNV), les sons distracteurs (réponses auditives évoquées, P3a, RON) et les sons cibles (réponses auditives évoquées, P3b) pour chaque groupe. Au niveau comportemental les patients ont montré une augmentation du temps de réaction. Au niveau électrophysiologique, les patients ont présenté à la fois des mécanismes TD (diminution de traitements de la cue et de la préparation attentionnelle) et BU (diminution de traitements de distracteurs, grande capture attentionnelle et diminution du réengagement dans la tâche en cours) altérés.

**Mots Clés : cortex préfrontal latéral, PE, distractibilité, préparation attentionnelle, audition**

## INTRODUCTION

The lateral prefrontal cortex (IPFC) is the cortex of the anterior pole of the mammalian brain. The IPFC has been shown to be involved in attentional selection or orientation (Corbetta & Shulman, 2002). It has been found, in human and monkey electrophysiological studies, functional magnetic resonance imaging (fMRI) and single-cell studies, that the IPFC regulates inhibition and excitation in distributed neural networks, for example, visual (Rainer et al., 1998 ; Barcelo et al., 2000) and auditory (Voisin et al., 2006) (for review see Knight et al, 1999).

Attention is the cognitive function that enables to optimize, voluntary or not, the processing of specific information.

Two types of attention processes have been identified: voluntary attention (endogenous), i.e top-down (TD) attention, and involuntary (exogenous), i.e bottom-up (BU) attention (James, 1890). The first enables a good performance by voluntary selecting the relevant information in the environment. It has been characterized by increased cortical responses to task-relevant sounds and reduced responses to task-irrelevant stimuli (Bidet-Caulet et al, 2007 & 2010). The second enables the evaluation of those potentially important events that are not relevant to the current task (e.g. fire alarm). One's attention can be involuntarily captured by unexpected stimuli resulting in a diversion from the on-going task.

Anticipatory attention is one of the mechanisms of voluntary attention. This mechanism has been studied mostly with variants of the Posner paradigm. In behavioral studies, a valid indication of an upcoming target (informative) enables faster responses compared to uninformative cues, reflecting a deployment of anticipatory attention process. This anticipatory attention would result in increased processing of expected stimuli, reflected by increased amplitude of the N1 component (Hillyard et al., 1998), and in facilitated stimulus detection (Posner, 1980). Anticipatory attention is reflected by a sustained frontal negativity, known as the Contingent Negativity Variation (CNV). This slow wave occurs between the presentation of a warning stimulus and an imperative stimulus (Brunia and Van Boxtel, 2001). It has been previously shown that patients with IPFC lesion present a decrease in amplitude of the CNV (Rosahl & Knight, 1995).

On the other hand, unexpected salient stimuli automatically generate BU attentional capture. Several brain responses are relevant to this mechanism. After the P50 and N1 sensory responses, the involuntary orienting response is observed in response to an unexpected stimuli as a frontal positivity named novelty P3 or P3a, followed by a late frontal negativity (Reorienting Negativity, RON). This

RON was interpreted as reflecting the reallocation of attention back to the original task (Escera et al., 2000).

Interestingly, responses to distracting sounds were found to be larger in patients with IPFC damage (Chao and Knight, 1998), suggesting an impairment in the ability to inhibit task-irrelevant distractors in these patients.

The balance between the TD and BU attentional processes is crucial to being task-efficient while staying aware of our surrounding environment without being fully distracted. If the TD mechanisms dominate, one may not react to vitally important events occurring outside the focus of attention. If the BU mechanisms dominate, one's behavior appears fragmented and distracted, making goal-directed actions less effective. The IPFC seems to be involved in both BU and TD mechanisms of auditory attention. However, the role of the IPFC in the dynamic interaction between TD and BU attention processes remains unknown.

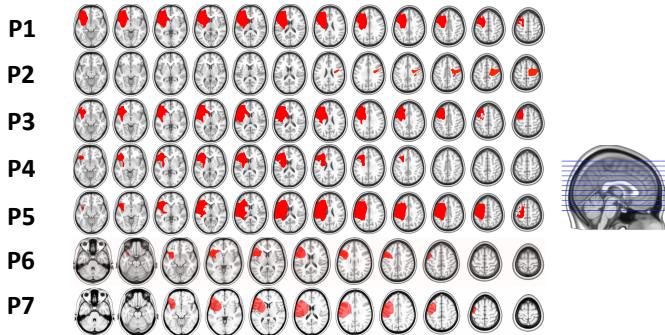
The main purpose of this work is to study the role of the IPFC in the balance between TD and BU auditory attention. We adapted the Posner paradigm detection task using central visual cues and monaural auditory targets. To assess TD anticipation, visual cues could be either informative (arrow indicating the side of the upcoming target) or uninformative (double arrow pointing to both sides). BU attentional capture was triggered by a binaural distracting sound (phone ring, bell ring...) played in 25% of the trials between the cue and the target. We recorded EEG in 7 patients with lesion of the IPFC and 7 matched controls. We computed the event-related-potentials (ERPs) elicited by the visual cues (visual evoked responses, CNV), distracting sounds (auditory evoked responses, P3a, RON) and target sounds (auditor evoked potentials, P3b) in each group. To examine the functional significance of the IPFC in distractibility and preparatory attention, we compared ERPs in IPFC and Control groups, as a first analysis step. This would give us a better understanding of the dynamics involved in the generation and modulation of the balance between TD and BU auditory attention.

## MATERIALS AND METHODS

### Subjects

7 patients (2 males, age=60.14+/-3.9 years, education level=16.5+/-0.9 years, 1 left handed) and 7 matched controls, in age, level of education and dominant hand, (2 males, age=58+/-3.4 years, education level=16.9+/-0.7 years, 1 left handed) participated in this study. The patients were selected based on the location and size of the brain lesion in the IPFC (see Fig. 1). Lesions were reconstructed

following one of two procedures according to the available anatomical data for each patient (CT or MRI). Either the lesions were manually drawn using CTs and MRIcro software (<http://www.mricro.com>) on slices of a T1-weighted single subject template MRI scan from the Montreal Neurological Institute (MNI) ([www.bic.mni.mcgill.ca/cgi/icbm\\_view](http://www.bic.mni.mcgill.ca/cgi/icbm_view)), distributed with MRIcro. Or, the lesions were drawn on the MRI files (T1 and T2) first converted from DICOM to NFT, then normalized to the MNI152 space in SPM8 (<http://www.fil.ion.ucl.ac.uk/spm/software/spm8/>). Reconstruction of lesion on horizontal slices, determination of lesion volume and putative cytoarchitectonic areas damaged were computed using MRIcro. The lesions were at least 11 year-old and located unilaterally mostly in the IPFC (centered in the Brodmann's areas 9 and 46). One patient had a right IPFC lesion. All the lesions were due to a stroke. All subjects had normal or corrected-to-normal vision and were free of medical complications, psychiatric disorders, substance abuse, psychoactive drug treatment, or other neurological diseases. Comprehension, hearing and motor abilities were intact in all patients. All aspects of the research were explained to the subject who signed statements of consent approved by the Human Subjects Review Committees of the Martinez Veterans Administration Research Service and the Committee for the Protection of Human Subjects for University of California, Berkeley.



**Figure 1 - MRI scans of patients presenting unilateral damage centered in the IPFC** The red areas on the horizontal sections indicate the location of the lesion.

## Stimuli

A visual cue of 200ms duration was presented centrally. This cue came in two forms, either as an informative cue (a one sided arrow pointing left L or right R) or an uninformative cue (a two sided arrow). The target sound was a monaural harmonic sound of 50ms duration. The delay between cue onset and target onset was randomly chosen between 1150-1350 ms. 30 different distracting sounds (DIS) of 300ms duration were presented binaurally (bell ring, phone ring...). The DIS could be played at any time between 945 and 350ms before target onset. Three categories of DIS were considered based on the latency before target onset, from 945 to 750ms (DIS1), from 745 to 550ms (DIS2), and from 545 to 350ms (DIS3).

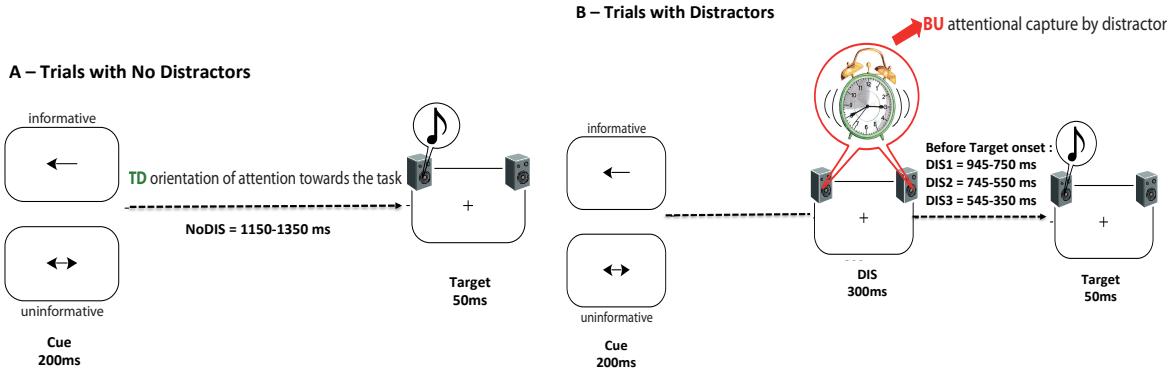
Concerning the cue, the trials were equally divided: L 33.33% / R 33.33% / N 33.33%. Concerning the distractors, only 25% of the trials included them. As for the target sound, its side corresponded in 100% of the trials to the side indicated by the cue. With a neutral cue, the target sound was presented equally between the left and right ear. The detailed percentages of each type of trials are presented in the Table 1. The stimuli were presented using the Presentation software (Neurobehavioral Systems, Albany, CA, USA).

cue	distractor	target	% of trials	
INF L	no	L	25.00	66.66
	yes	L	8.33	
INF R	no	R	25.00	
	yes	R	8.33	
UNINF	no	L	12.50	33.33
	yes	L	4.17	
	no	R	12.50	
	yes	R	4.17	

**Table 1 - Proportion of each type of trial (%).** Relationship between cue, distractor and target events are presented in this table.

### Task

Subjects were asked to keep their eyes fixated on a cross in the center of the monitor screen and to avoid blinking as well as any eye movement. In each condition, the subjects pressed the left button on the mouse as fast as possible and as soon as they heard the target sound even though it could induce more errors. They were asked to orient their attention, in the presence of an informative cue, to the side indicated, whereas this orientation was not possible with uninformative cues. The subjects were informed that in some trials a distracting sound could be played between the cue and the target sound. In that case, they had to try to ignore it.



**Figure 2 - Schematic representation of the protocol used in the experiment.** The paradigm introduced central visual cues and monaural auditory targets, to which subjects were instructed to react as fast as possible. The TD modulation (Fig 2-A) was triggered with the use of informative or uninformative cues. To assess the BU modulation (Fig 2-B), binaural distracting sounds were played between the cue and the target, in 25% of the trials. Three categories of distractors were used with different latencies relative to the target onset.

## Procedure

Before starting the experiment, both patients and controls were screened for cognitive dysfunction with the Mini-Mental State Examination (MMSE).

Subjects sat in an armchair in a sound attenuated and electrically shielded room at 1,5m from the screen. The subjects were equipped with earphones. Before each EEG recording, we tested the hearing threshold using the Bekesy tracking method with the target sound. In the experiment, the target and distractor sounds were then presented 15dB and 60dB respectively above the hearing threshold in each ear. Moreover, we ran a practice block to test the comprehension of the attention task in itself and so that the subject could familiarize himself with the sounds.

During the experiment, fifteen blocks were presented to each subject. Each block lasted approximately 5 minutes making it 90 minutes per recording (pause included). All blocks contained, in a random order, the different previously exposed trials. In case of excessive artifacts on the EEG or target anticipation, one or more additional blocks were recorded. Hits, False Alarms (FA) and Reaction Time (RT) were collected using Presentation (Neurobehavioral Systems).

## EEG Recordings and Processing

The EEG were recorded from 64 electrodes using an ActiveTwo system (BioSemi, DC amplifier, 24-bit resolution, biopotential measurement system with Active Electrodes). Vertical and horizontal eye movements were recorded from four additional electrodes placed at both external canthi, and below

and above the left eye. Data was amplified (-3dB at ~819Hz low-pass, DC coupled), digitalized (1024Hz), and stored for offline analysis.

## **Data Processing and Analysis**

The EEG processing and the ERP analysis was done using ELAN software (Aguera et al. 2011, <http://elan.lyon.inserm.fr/>), a software bundle for electrophysiology data analysis developed at the Brain Dynamics & Cognition team of the Lyon Neuroscience Research Center.

### ***EEG Processing***

The EEG signal was 0.5-40Hz band-pass filtered and referenced offline to the average of the ear lobes. Eye movement related activity (blinks and saccades) were removed from all electrodes using an inverse Independent Component Analysis (ICA). ICA is a technique that provides a spatial filter that captures these blink artifacts in a limited number of independent components (1 or 2). In 2 participants, the flat or excessively noisy signals at 1 or 2 electrodes were replaced by their values interpolated from the remaining adjacent electrodes using spherical spline interpolation (Perrin et al., 1989). To further clean the data from residual muscle or other artifacts, an automatic then manual rejection of the artifact trials was done.

Concerning the 1PFC patient with a right-sided lesion, we switched the distribution of the electrodes from the left to the right hemisphere so that all ipsilesional (or contralesional) electrodes could be averaged across participants. For example, FC1 refers to the averaged ERP data from the FC1 electrode from left lesions combined with data from the FC2 electrode from right lesions.

### ***ERP Processing and Analysis***

ERPs were separately averaged for each event of the trial: cue-ERPs, target-ERPs and distractor-ERPs. Cue-ERPs were averaged locked to the cue-onset and corrected with a -100 to 0 ms baseline before all trial onset. Target-ERPs were averaged locked to the target-onset. When analyzing the target processing, in NoDIS conditions, the baseline used was -100 to 0ms before target onset. To observe the impact of each kind of distractor (DIS1, DIS2, DIS3) on target processing, the baseline used was -100 to 0ms before all trial cue onset. Distractor-ERPs were averaged locked to distractor onset and corrected with a -100 to 0 ms baseline before all distractor onset. Scalp ERP maps were generated using a two-dimensional spherical spline interpolation (Perrin et al. 1989).

## **Statistical Analysis**

When possible non parametric tests were used in this experiment due to the small number of subjects.

### ***Behavioral Data***

The RT (ms) and FA (%) were averaged for each condition individually and as a whole. The difference in the total number of FAs between the two groups was assessed using a non-parametric Mann & Whitney test. Concerning the RTs, we performed a repeated measure ANOVA with cue (informative or uninformative), distractors (NoDis, DIS1, DIS2, DIS3) as within-subject factors and group (Control or PFC patients) as a between-subject factor. If an effect was put forth, Newman-Keuls post-hoc tests were realized to assess the differences. These tests were conducted on the software Statistica using a p<0.05 to determine the significance. To give an idea of the variability within the population, the error bars will represent the standard error of the mean (SEM).

### ***ERP Data***

A preliminary analysis was realized by comparing both groups (IPFC, Control) without distinguishing the conditions (according to the type of cue or distractor). We compared specific ERP components at specific latencies, using non-parametric Mann & Whitney analysis.

Four groups of electrodes were formed based on the location of the differences between the ERP components of both IPFC and Control (see Fig.3): a frontal group (Fz, FCz, FC1, FC2, F1, F2); a central group (Cz, FCz, FC1, FC2, C1, C2); a centro-parietal group (CPz, CP1, CP2, Pz, P1, P2) and parieto-occipital group (POz, Pz, PO3, PO4, P1, P2, P3, P4).

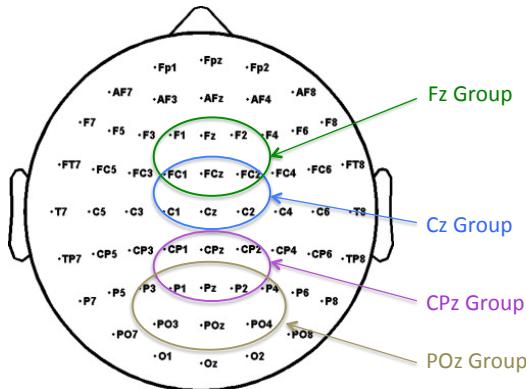
After cue onset, two electrophysiological components were analyzed on the Cz group in successive 100ms time-windows: 1) a fronto-central negativity from 300-400ms 2) the CNV from 950-1150ms.

After DIS onset, four electrophysiological components were analyzed on the Fz group : 1) the auditory N1 from 90 to 130ms with a 40ms time-window 2) the auditory P50 from 15 to 55ms, with a 40ms time-window 3) the P3a from 300 to 350ms with a 50ms time-window 4) the late frontal negativity (RON) from 350 to 450ms with a 50ms time-window. On the POz group, the P3b was analyzed from 300-400ms in two successive 50ms time-windows.

After target onset, the P2/P3b response was analyzed on the Cz and CPz groups from 200-300ms, in two successive 50ms time-windows. The N1 response was analyzed on the Cz group from 90 to 130ms with a 40ms time-window.

We further assessed the effect of the distractor position on the latency of the N1 response to target on the FCz electrode. The latency of the N1 in each condition and each subject was defined as the latency of the minimum in the 70-170ms time-window. We used a repeated-measure ANOVA with group (IPFC, Control) as a between-subject factor and distractor (NoDIS, DIS1, DIS2, DIS3) as a within-subject factor. If an effect was put forth, Newman-Keuls post-hoc tests were realized to assess the

differences. These tests were conducted on the software Statistica. On the graphs, the error bars represent the SEM.



**Figure 3 - Scalp Distribution of the 64 electrodes of the BioSemi head-cap** Four groups of electrodes were formed and centered on the locations of the components differing between the IPFC and Control group: a frontal group (Fz, FCz, FC1, FC2, F1, F2) (in green); a central group (Cz, FCz, FC1, FC2, C1, C2) (in blue); a centro-parietal group (CPz, CP1, CP2, Pz, P1, P2) (in purple) and parieto-occipital group (POz, Pz, PO3, PO4, P1, P2, P3, P4) (in brown).

## RESULTS

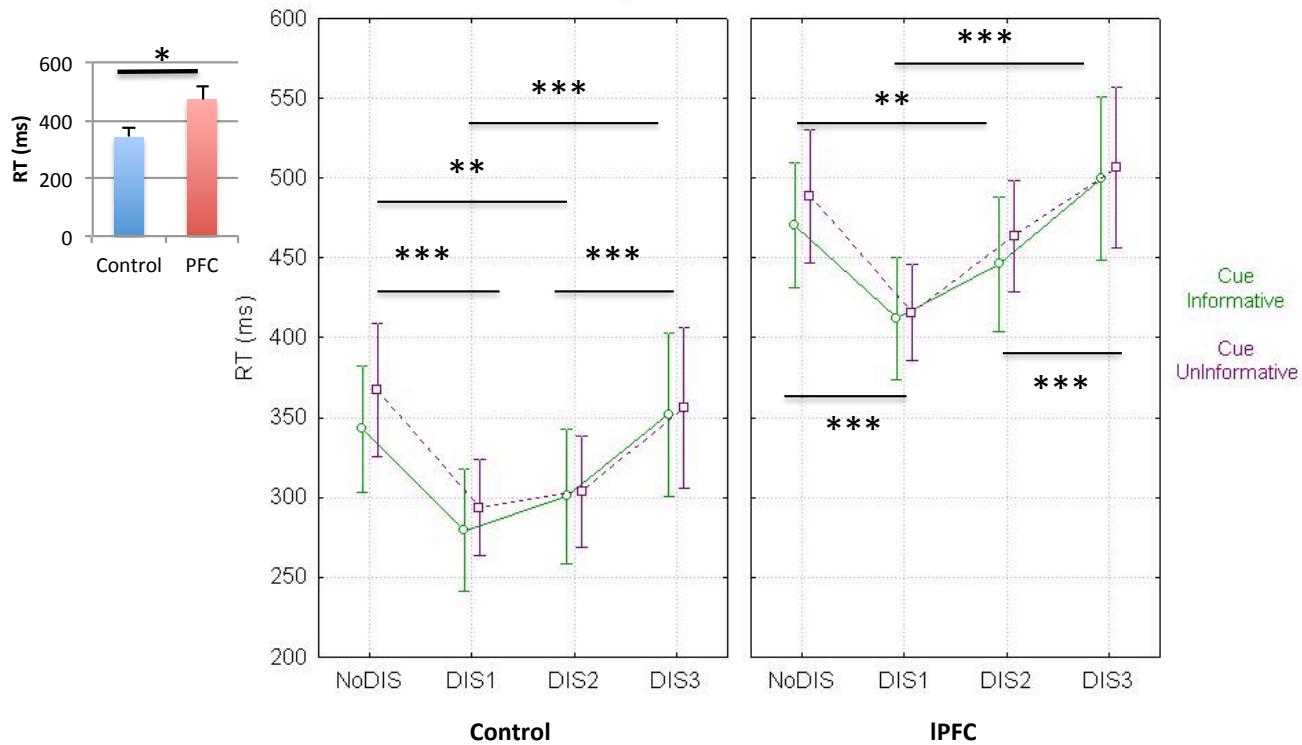
### Behavioral Data

IPFC patients and their match controls presented similar MMSE scores (Mann-Whitney test  $P=0.47$ ).

The two groups totalized a similar number of FAs (Control:  $1.7 \pm 0.8\%$ , IPFC  $2.6 \pm 0.7\%$ ).

To compare both group RTs, we searched for an interaction between the cue (informative or uninformative), the distractors (NoDis, DIS1, DIS2, DIS3) and the group (Control or IPFC).

We performed a repeated-measure ANOVA, with cue, DIS and group as factors. A significant cue effect ( $p=0.028$ ) indicated faster RT in the informative conditions than in the uninformative conditions. A significant DIS effect was also observed in this task ( $p=0.000009$ ). Post-hoc analysis showed a significant RT-reduction in the presence of DIS in position 1 or 2, compared to the conditions without DIS or with the DIS in third position (noDIS vs DIS1:  $p=0.00024$ ; noDIS vs DIS2:  $p=0.011$ ; DIS1vsDIS3:  $p=0.00018$ ; DIS2vsDIS3:  $p=0.0039$ ) (see Fig4). Moreover, the IPFC group was found significantly slower than the control group (mean RT, Control  $341.8 \pm 33.66$  ms, IPFC  $471.39 \pm 44.08$  ms,  $p=0.018$ ). No significant interaction was found.



**Figure 4 - Mean reaction time (RT, ms) for the two groups (Control and IPFC) according to the type of cue and the position of the distractors.** Control (blue) and IPFC (red) groups in informative (green) or uninformative (purple) cue conditions were faster in the DIS1 and DIS2 conditions. Control and IPFC seemed to have a shorter RT in the informative condition whether the distractor was present or not. The IPFC group showed a slower RT in general compared to the Control group. No significant interaction between these factors has been found. The error bars represent the SEM ; Stars indicate significant differences assessed by post-hoc tests. \* p<0.05, \*\*p<0.01, \*\*\*p<0.001

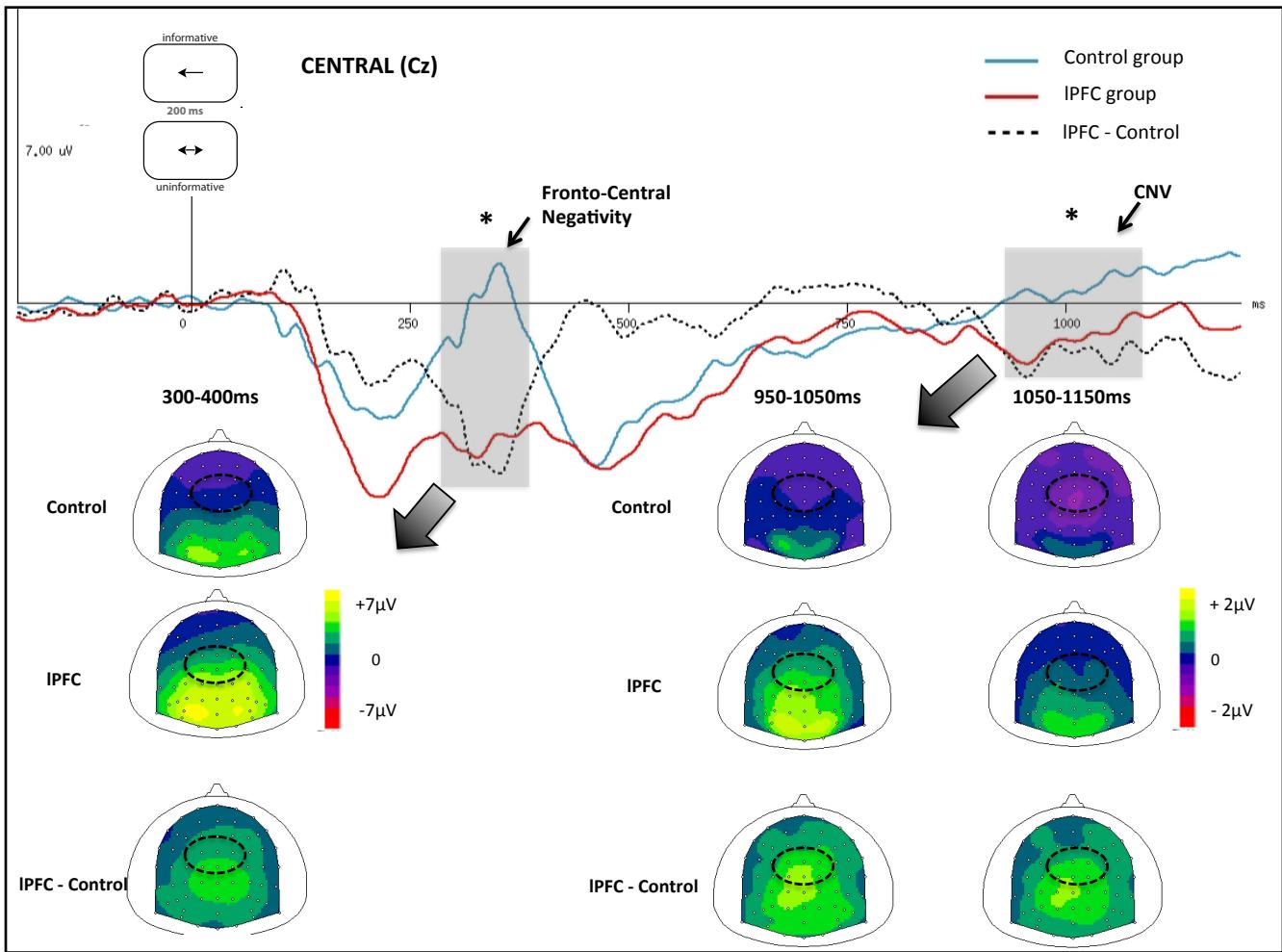
### Electrophysiological Data

We chose to only present the comparison between the IPFC and Control group, independently of the type of cue and of the distractor position.

#### *Cue-RPs in trials without distractor (NoDIS)*

Two main components, both concentrated in central electrodes, were found to be different in Control and IPFC after cue presentation (see Fig5). Between 300-400ms from the cue onset, it was shown that the Control group presented a fronto-central negativity absent in the IPFC group ( $p=0.025$ ).

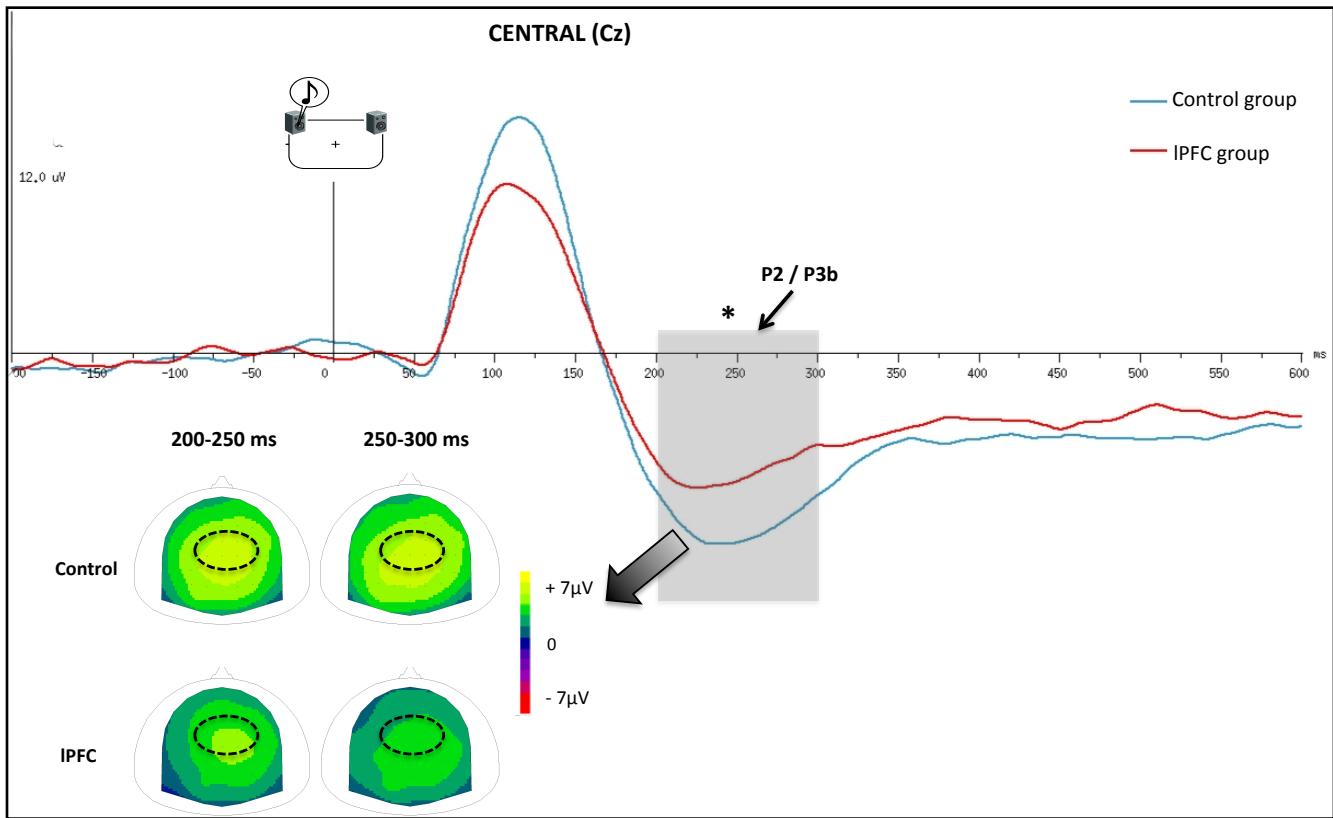
A sustained negativity, CNV, was put forth between 950-1150ms from the cue onset. This component was diminished in the IPFC group and seemed to increase with time in the Control group (950-1050ms,  $p=0.013$  ; 1050-1150,  $p = 0.018$ ).



**Figure 5 - ERP to the visual cue in IPFC and Control groups in trials without distractor.** Mean ERPs to the cue at the central electrode group in Control or IPFC group are depicted in blue and red, respectively. The difference between cue ERPs of both groups is represented by a dashed curve. Two central components were significantly different between the Control and IPFC group: a frontal-central negativity (300-400ms) and the CNV (950-1150ms). Large Top View topographies were added to illustrate each of these components. The dashed-circle represents the group of electrodes used for the analysis. Stars indicate significant differences assessed by a Mann-Whitney test. \*  $p < 0.05$

#### *Target-RPs in trials without distractor (NoDIS)*

No significant effect was observed on the N1 response to target at fronto-central electrodes. A significant difference was observed between IPFC patients and Controls at central electrodes between 200-300ms after target onset (see Fig7). The Control group presents a larger P2/P3b complex than IPFC patients (200-250ms,  $p=0.048$ ; 250-300ms,  $p=0.035$ ). No significant effect was observed on the P3b response to target at parietal electrodes.

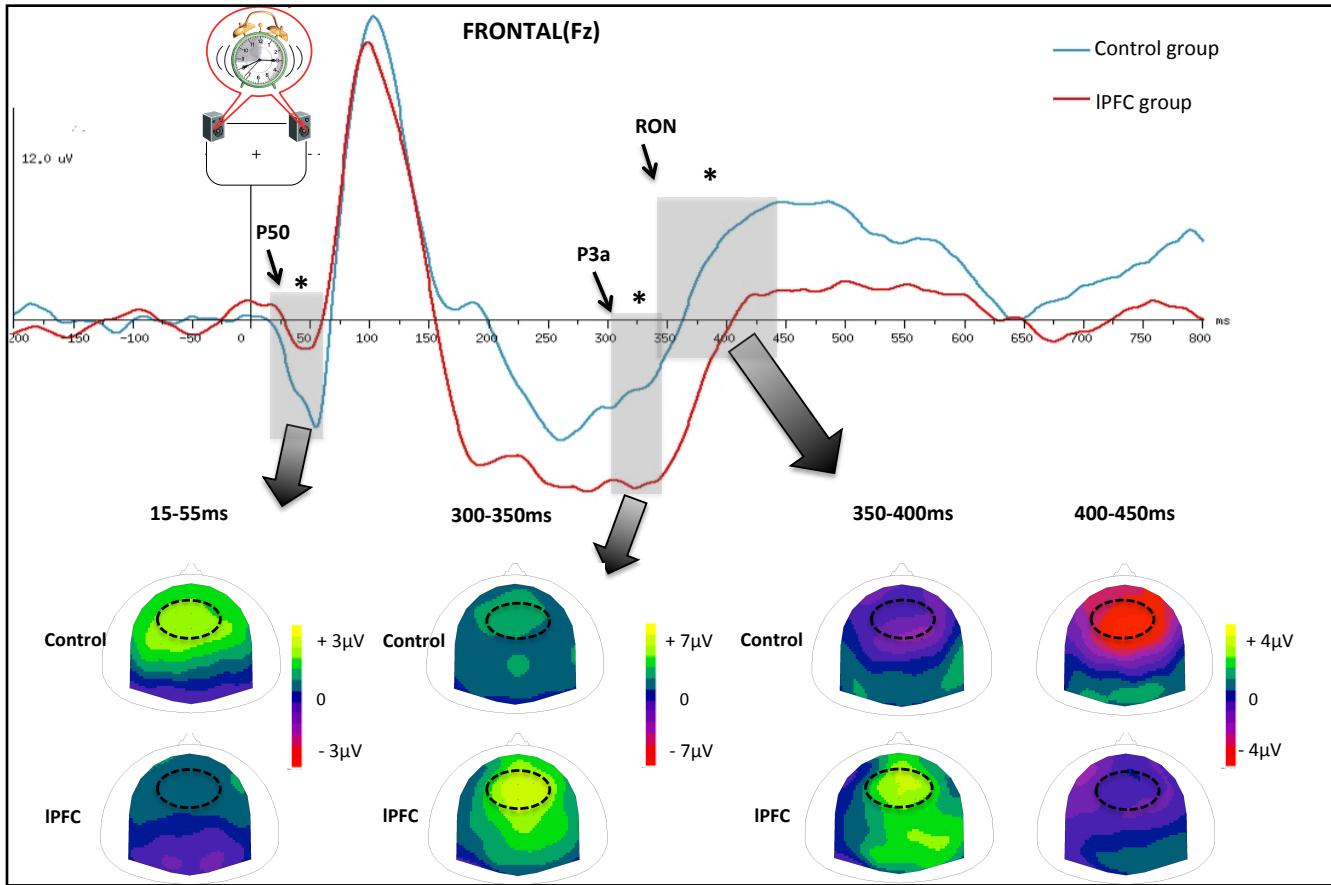


**Figure 6 - ERP to the auditory target in IPFC and Control groups in trials without distractor.** Mean ERPs to the target at the frontal electrode group in Control or IPFC group are depicted in blue and red, respectively. The P2/P3b (200-300ms) complex was revealed significantly different larger in Control group. Large Top View topographies were added to illustrate this complex. The dashed-circle represents the group of electrodes used for the analysis. Stars indicate significant differences assessed by a Mann-Whitney test. \* p<0.05

#### Distractor-RPs (DIS)

After averaging all the distractor trials, four main components were identified in response to distractors, concentrated in the frontal electrodes (see Fig7). Using a 40ms-window, between 15-55ms from the DIS onset, it was shown that the Control group presented a more pronounced positivity wave, P50, than the IPFC group ( $p=0.048$ ). Following this component, the negative response N1 was analyzed between 90-130ms from the DIS onset with a 40ms time-window. No significant N1 effect was observed between the IPFC and Control groups. Another frontal positivity, P3a, was put forth, with a 50ms-window, between 300-350ms from the DIS onset. This component was significantly larger in the IPFC group ( $p=0.048$ ). Using a 50ms-window, between 350-450ms from the DIS onset, an important frontal negativity, RON, was shown to be reduced in the IPFC group (350-400ms,  $p=0.013$ ; 400-450,

$p=0.048$ ). No significant effect was observed at parietal electrodes between 300 and 400ms after DIS onset.



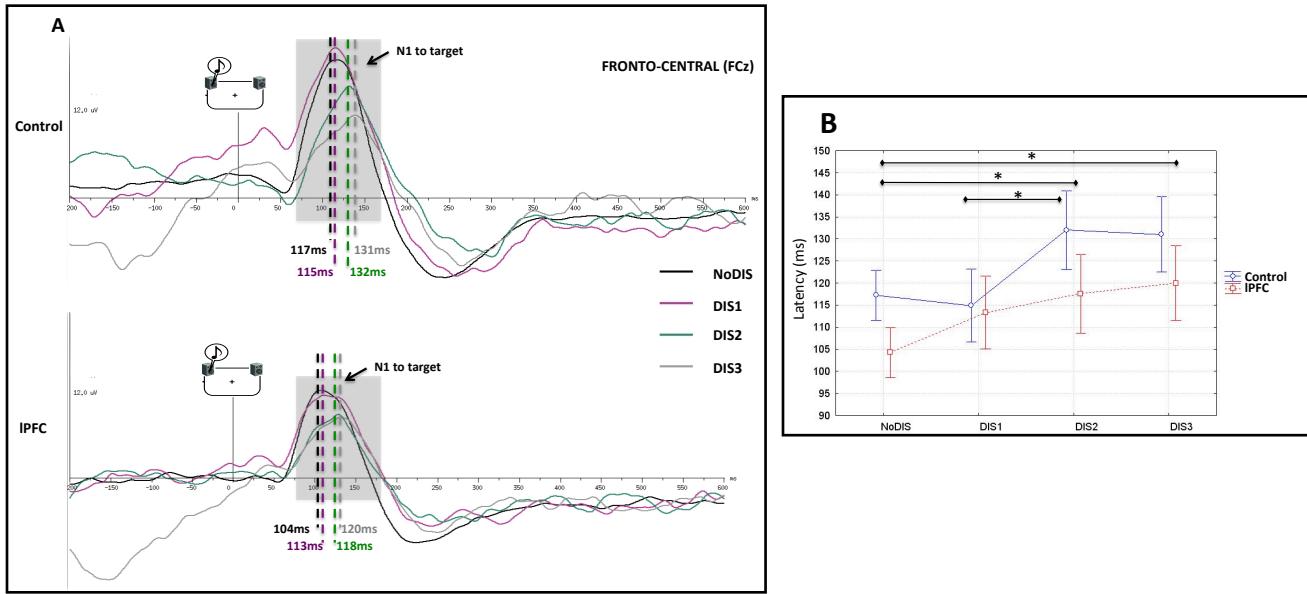
**Figure 7 - ERP to auditory distractor in IPFC and Control groups.** Mean ERPs to the distractor at the frontal electrode group in Control or IPFC group are depicted in blue and red, respectively. Three frontal components were significantly different between the Control and IPFC groups: the P50 (15-55ms), the P3a (300-350ms), the RON (350-450ms). Large Top View topographies were added to illustrate each of these components. The dashed-circle represents the group of electrodes used for the analysis. Stars indicate significant differences assessed by a Mann-Whitney test. \*  $p<0.05$

#### *Target-RPs in trials with distractors*

We observed the classic N1 response to an auditory sound, concentrated on frontal-central electrodes (FCz), between 70-170ms, whether distractors were present or not (see Fig8-A).

To better understand the impact of distracting sounds on target processing, we examined the latency of the target N1 according to the distractor position (noDIS, DIS1, DIS2, DIS3) in each group (IPFC, Control) (see Fig8-B). A significant main effect of the distractors was found ( $p=0.01$ ) with a repeated-measure ANOVA. Post-hoc analysis showed that the N1 latencies in DIS2 (mean, Control = 132 +/-

2.6ms, IPFC = 117.6 +/- 12.3ms) and DIS3 (mean, Control = 131 +/- 6.4ms, IPFC = 120 +/- 10.2ms) conditions were larger than in the NoDis conditions (mean, Control = 117.3 +/- 3.5ms, IPFC = 104.3 +/- 7.3ms) ( $p=0.02$  and  $p=0.03$  respectively). The N1 latency was significantly larger in DIS2 than in DIS1 (mean Control = 114.9 ms 5.6 X, IPFC = 113.3 +/- 10.2ms) condition ( $p=0.04$ ). No significant effect was observed between the NoDis and DIS1 conditions ( $p=0.52$ ), and between the DIS1 and DIS3 conditions ( $p=0.07$ ).



**Figure 8 - Impact of distractors on the target N1 latency.** Mean ERPs to the target at the FCz electrode according to the position of the distractor (NoDIS, DIS1, DIS2, DIS3) are depicted in black, purple, green and grey, respectively. In both IPFC and Control groups, the target N1 latency was found to be different according to the position of the distractor (A). The latency (ms) of each group (Control or IPFC group) are depicted in blue and red, respectively. The interaction between the groups and the position of the distractors (NoDIS, DIS1, DIS2, DIS3) was analyzed (B). It suggested that in both groups the latency increased in the DIS2 and DIS3 conditions in comparison to the NoDIS and DIS1 conditions. The error bars represent the SEM ; Stars indicate significant differences assessed by post-hoc tests. \*  $p<0.05$ , \*\* $p<0.01$ , \*\*\* $p<0.001$

## DISCUSSION

In this study, the main objective was to test the involvement of the IPFC in the balance between TD and BU attention mechanisms when they are triggered at the same time. On one hand, the visual cues induced TD mechanisms. When no task-irrelevant sound was played, we found alterations, after IPFC damage, of the visual cue processing (N2), of the anticipatory attention mechanisms (CNV) and of auditory target processing (P2, P3b). On the other hand, BU attentional capture was assessed in the

presence of irrelevant sounds. We found differences, after IPFC damage, in the orienting brain responses (P3a) and in the reorienting of attention towards the initial task (RON).

Both groups displayed few FAs and similar RT patterns depending on the position of the distractor. Informative cues lead to a faster RT in both groups compared to uninformative cues, as documented in previous studies (Posner, 1980 ; Hillyard et al., 1998). This result seems to show an enhanced anticipatory attention with informative cues. In general, we found that patients with IPFC damage were slower in comparison to the Control group, in accordance with previous studies (Chao & Knight, 1998). In addition, we found that both groups responded faster to the target when early distractors (DIS1, DIS2) were played compared to without distractor or with late distractor (DIS3). It would seem that the distractors induced 2 types of responses. On one hand, distractors would induce a sustained arousal increase resulting in faster RT to the target. On the other hand, each distractor generates a short attentional capture. The effect of attentional capture is observed behaviorally only with late distractors, where subjects seem not to have enough time to reengage in the ongoing-task, and thus leading to a delayed processing of target sound.

#### *Lateral prefrontal lesion effects on TD/voluntary auditory attention*

We first observed a fronto-central negativity ERP component onsetting at about 300ms from the cue presentation, highly reduced in IPFC patients. It was found at the same latency in young (unpublished data) and old controls, but is smaller in IPFC patients (present study), as documented by Knight (1997). This response probably corresponds to the fronto-central N2 described in several previous studies (for review see Folstein and Van Petten, 2008) and thought to index an alerting system facilitating behavioral detection (Suwazono et al, 2000). This result may reflects impairments in more general processing deficits after a IPFC damage, in accordance with the slower responses to the target of the IPFC group. Between 950-1150ms from cue onset, we put forth the deployment of a slow central negativity, i.e CNV. In accordance with Rosahl & Knight (1995), a reduction of the CNV in patients with IPFC lesions was observed in comparison to the control group. This component reflects the preparation of a signaled movement and the simultaneous anticipatory attention for the imperative stimulus. Previous studies have shown the correlation between a faster RT and a larger amplitude of this ‘expectancy wave’ (Brunia & Van Boxtel, 2001). Thus, a reduced CNV suggests impairments in the attentional preparation mechanisms after IPFC damage which could result in the observed longer RT.

We then observed the ERP to the auditory target, where a positive centrally distributed component was reduced after IPFC damage between 200 and 300ms. Based on previous studies (Knight et al, 1980 ; Soltani and Knight, 2000), this component seems to reflect the P2/P3b complex. The P2, centrally located, reflects sensory auditory processing (Knight et al, 1980). The P3b, with a more parietal distribution, is elicited by relevant infrequent stimuli in task situations and reflects target processing (Knight & Scabini, 1998). This complex is found to be reduced in the IPFC group, underlining less effective target processing.

To summarize, TD anticipatory attention mechanisms seem to be altered in IPFC patients. Indeed, a less effective cue processing leads to a diminished attentional preparation, resulting in reduced target processing.

#### *Lateral prefrontal lesion effects on BU attentional capture*

We first observed a positive frontally distributed ERP component onsetting at about 40ms from the distractor presentation. This waveform seems diminished after IPFC damage. The P50 response reflects early sensory processing as described by Hillyard (1998). These results suggest a less effective processing of the distractor after IPFC damage.

Between 300 and 350ms from the distractor onset, we put forth a positive wave, i.e Novelty P3 or P3a. Previous studies have shown the importance of this response in the orienting of attention towards the unexpected stimulus. The bigger the amplitude of the novelty P3 the higher the distractibility (Escera, 2000). In agreement with Knight et al (1984), an increased amplitude of the P3a in patients with IPFC lesions was observed in comparison to the Control group. This effect suggests an enhanced processing and automatic detection of the task-irrelevant sound after IPFC damage.

Following the involuntary orienting of attention (P3a), we found a sustained frontal negative response (RON), as discovered by Schroger & Wolff (1998) between 350 to 450ms. This ERP waveform is reduced in patients with IPFC damage compared to controls. This component may reflect the activation of the IPFC cortex controlling the direction of attention, to redirect the focus of attention to relevant aspects of stimulation after a momentary distraction (Escera et al, 2001). It seems to indicate that patients have a harder time to reengage in the ongoing task.

We then observed the impact of the distractors on the auditory target N1 latency. IPFC and Control groups presented shorter N1 latencies when no or early irrelevant sounds were played, as oppose to an increased N1 latency with late distractors. This suggests that target processing is delayed with late distractor probably due to ongoing attentional capture. Indeed, it seems to be dependent on the latency

between distractor and target onset. Thus, the latency between the early distractor and the target enabled the distractor processing to end before the target onset. In contrary, the late distractors processing is not finished before the target onset, inducing a delayed target processing.

To summarize, as seen in previous studies (Lovstad et al., 2011), the BU attentional capture mechanism seems to be altered in IPFC patients. Indeed, a less effective task-irrelevant sound processing leads to an increased distractibility (important attentional capture and prolonged focus to task-irrelevant stimuli) resulting in a delayed target processing.

Previous studies have shown, mostly in separate experiments, the involvement of the IPFC in BU and TD mechanisms. This present study has been able to assess both auditory attention mechanisms at the same time. Comparing patients with IPFC damage and matched controls, we found that both mechanisms are impaired after IPFC damage. It seemed that the more TD engagement was present the less effective BU attentional capture would be. To better understand the role of the IPFC in this interaction between TD anticipatory attention and BU attentional capture mechanisms, we would need to separate 1) The cues (informative-uninformative) to better assess the TD attention, 2) The position of the distractors (DIS1, DIS2, DIS3) to better understand the impact of attentional preparation on the attentional capture 3) The side of the electrodes in relation to the side of lesion (ipsi or controlateral).

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## **ANNEXE**

The Helen Wills Neurosciences Institute at UC Berkeley is a collaborative research community that questions how the brain functions, by using many disciplines (cognitive science, genetics, cell biology, biophysics, mathematics..). The goal is to understand how the brain generates behavior and cognition as well as better understand, diagnose and treat neurological disorders.

The Knight laboratory is a cognitive neuroscience research laboratory within the Institute. The director of the lab is Robert T. Knight, MD. The lab focusses on two different domains : 1) The contribution of prefrontal cortex to human behavior, by using electrophysiological, fMRI and behavioral techniques to study controls and neurological patients with frontal lobe damage. 2) The electrophysiology of network activity supporting goal-directed behavior in humans, by recording the electrocorticogram directly from the cortical surface in neurosurgical patients with implanted electrodes. This information is used to develop brain-machine interfaces for motor and language prosthetic devices.

During my internship, I studied under the supervision of Aurélie Bidet Caulet (CR) and in collaboration with two undergraduates. She works full time in “Le Centre de Recherche en Neurosciences de Lyon” where she studies the brain mechanisms of auditory attention in humans using different levels of electrophysiology recordings.