

# Impaired Facilitatory Mechanisms of Auditory Attention After Damage of the Lateral Prefrontal Cortex

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**There is growing evidence that auditory selective attention operates via distinct facilitatory and inhibitory mechanisms enabling selective enhancement and suppression of sound processing, respectively. The lateral prefrontal cortex (LPFC) plays a crucial role in the top-down control of selective attention. However, whether the LPFC controls facilitatory, inhibitory, or both attentional mechanisms is unclear. Facilitatory and inhibitory mechanisms were assessed, in patients with LPFC damage, by comparing event-related potentials (ERPs) to attended and ignored sounds with ERPs to these same sounds when attention was equally distributed to all sounds. In control subjects, we observed 2 late frontally distributed ERP components: a transient facilitatory component occurring from 150 to 250 ms after sound onset; and an inhibitory component onsetting at 250 ms. Only the facilitatory component was affected in patients with LPFC damage: this component was absent when attending to sounds delivered in the ear contralateral to the lesion, with the most prominent decreases observed over the damaged brain regions. These findings have 2 important implications: (i) they provide evidence for functionally distinct facilitatory and inhibitory mechanisms supporting late auditory selective attention; (ii) they show that the LPFC is involved in the control of the facilitatory mechanisms of auditory attention.**

**Keywords:** attention, brain event-related potentials, EEG, frontal, lesion

## Introduction

Top-down signals from the prefrontal cortex (PFC) are crucial for cognitive control enabling selective attention to environmental inputs. Functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) studies have found the PFC to be activated during visual and auditory tasks requiring top-down attention (reviewed in Kastner and Ungerleider 2000; Naghavi and Nyberg 2005). Moreover, patients with lesion of the lateral PFC (LPFC) have been shown to present impairments in top-down selective attention to both visual (Barcelo et al. 2000; Gehring and Knight 2002; Yago et al. 2004; Sinnett et al. 2009; Miller et al. 2011) and auditory (Knight et al. 1981; Woods and Knight 1986) stimuli. Finally, combined electroencephalographic measures (EEG) and transcranial magnetic stimulation (TMS) have demonstrated the causal role of lateral prefrontal top-down signals in modulating the neural processing of relevant visual stimuli (Miller et al. 2011; Zanto et al. 2011). Taken together, these findings suggest that the lateral prefrontal cortex plays a crucial role in the top-down control of selective attention.

Top-down modulation of sound processing by auditory selective attention has been characterized by increased cortical responses to task-relevant sounds and reduced responses to task-irrelevant stimuli (Bidet-Caulet et al. 2007; Chait et al. 2010). However, the effects of auditory selective attention have mostly been investigated by comparing the brain responses to the same stimuli when attended or ignored (unattended) (see Giard et al. 2000 for a review). This comparison cannot assess whether enhanced versus reduced sound processing by attention results from a unitary gain control mechanism which regulates activity either up or down along one continuum; or from the net activity of distinct top-down facilitation and inhibition processes. Nevertheless, there is growing evidence that selective attention operates via distinct facilitatory and inhibitory mechanisms enabling enhancement and suppression of sound processing, respectively. Using a neutral task in the auditory or visual modality, a number of EEG or magnetoencephalography (MEG) studies have dissociated 2 effects of auditory selective attention expressed as 2 different frontal activities: an inhibitory response to unattended sounds, of positive polarity, starting later in latency than a facilitatory response to attended sounds, of negative polarity (Alho et al. 1987, 1994; Donald 1987; Michie et al. 1990, 1993; Alain et al. 1993; Alain and Woods 1994; Schröger and Eimer 1997; Melara et al. 2002; Bidet-Caulet et al. 2007; Degerman et al. 2008).

Recent evidence in the visual modality suggests that enhancement and suppression are controlled by functionally distinct mechanisms; for example, they are differentially affected by aging (Gazzaley et al. 2005, 2008) and cognitive load manipulations (Rissman et al. 2009; Gil-Gomez de Liano et al. 2010). Furthermore, in a previous EEG study of auditory selective attention, we manipulated the cognitive load to test whether facilitatory and inhibitory mechanisms can operate independently (Bidet-Caulet et al. 2010). We measured the facilitatory and inhibitory effects by comparing the electrophysiological responses to the same sounds when they were attended or ignored, respectively, to the responses to these sounds in a control/neutral task in which attention was equally distributed towards all sounds. We found 2 late frontally distributed ERP components with distinct timing and scalp topographies that were differentially affected by cognitive load, providing evidence for independent facilitatory and inhibitory mechanisms supporting auditory selective attention.

In the present study, we recorded EEG in patients with LPFC lesion using a similar paradigm to assess whether the LPFC controls either or both facilitatory and inhibitory mechanisms of auditory selective attention. This permitted testing for

independence of these mechanisms: if only one of them is impaired in the patients with LPFC damage, this would provide compelling evidence for separate facilitatory and inhibitory mechanisms enabling auditory selective attention.

## Materials and Methods

### Subjects

Nine LPFC patients were selected on the basis of a unilateral focal lesion to their dorsolateral PFC (3 right and 6 left). Lesions were due to ischemic (8 patients) or hemorrhagic (1 patient) stroke. Maximal lesion overlap comprised Brodmann's areas 9 and 46, with variable amount of damage in Brodmann's areas 44, 45, 47, 4, 6, and 8, as well as some part of the insula but auditory cortices were always preserved (Fig. 1). Six patients had upper-motor-neuron weakness in the limbs contralateral to their lesions and responded with their ipsilesional hand. Testing took place at least 1 year after injury. The patients were free of medical complications, psychiatric disorders, substance abuse, psychoactive drug treatment, or other neurological diseases.

Nine healthy subjects (controls), free of neurological or psychiatric disease, were chosen to individually match the 9 LPFC patients in age, gender, handedness, and education level (Table 1). LPFC patients and their matched controls did not significantly differ in age (Mann–Whitney test  $P=0.894$ ) and education level (Mann–Whitney test  $P=0.893$ ).

All subjects gave written consent prior to being tested and were paid for their participation. This research was 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.

### Lesion Reconstruction

Lesions were reconstructed following one of 2 procedures according to the available anatomical data for each patient (computed tomography [CT] or MRI). Either, the lesions were manually drawn using CTs and MRIcro software (<http://www.mricro.com>) on slices of a  $T_1$ -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 ( $T_1$  and  $T_2$ ) first converted from DICOM to NifTI, then normalized to the MNI152 space in SPM8 (<http://www.fil.ion.ucl.ac.uk/spm/software/spm8/>). Reconstruction of lesion on horizontal slices (and on a lateral perspective), determination of lesion volume and putative cytoarchitectonic areas damaged were computed using MRIcro. The tissue loss was  $105.5 \pm 53.5 \text{ cm}^3$  on average across patients.

### Stimuli and Tasks

Subjects were randomly presented with successive monaural standard (50-ms duration) and duration deviant (150-ms duration) band-pass noises (5-semitone wide, 5 ms rise/fall times) in each ear, and binaural pure tone in both ears (carrier frequency 988 Hz, 50-ms duration). The standard and deviant sounds were low-pitch noises (554–740 Hz) in one ear, and high-pitch noises (1319–1760 Hz) in the other ear. The loudness of these noises was matched in a previous subjective matching procedure in 11 subjects. The sound pitches presented in each ear

were balanced across blocks. In each block (~1 min), 110 sounds were played: 40 standards and 10 deviants in each ear (36.5% and 9.0% probability in each ear, respectively), and 10 binaural pure tones (9.0% probability). A deviant was always preceded by at least one standard in the same ear. The interstimulus interval (ISI) between 2 successive sound onsets varied between 400 and 600 ms. Subjects had to perform 3 different detection tasks in separate runs. In the selective attention tasks, subjects paid attention to the left or right ear (in different runs) and pressed the button of a joystick when they heard a duration deviant in the attended ear (attention to left ear or attention to right ear task, respectively). In the neutral task, subjects distributed attention equally to both ears and pressed a button when they heard a binaural sound. Thus, in the 2 selective attention tasks, half of the standard sounds were considered as attended (in the attended ear) and half were considered as ignored (in the unattended ear). In the neutral task, all standard sounds (in both right and left ears) were considered as “neutral” standard sounds.

### Procedure

Before starting the experiment, all the subjects (patients and controls) were screened for cognitive dysfunction using the mini-mental state examination (MMSE) procedure.

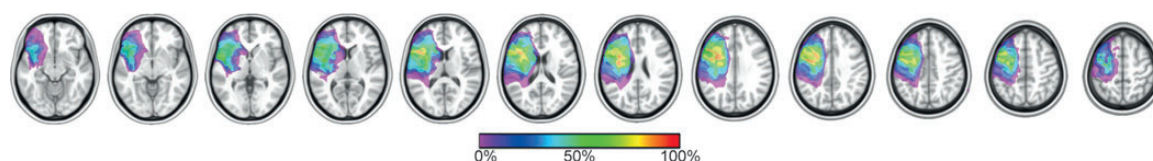
Participants were seated in a sound-attenuated EEG recording room. Sounds were delivered using Presentation software (Neurobehavioral Systems, Albany, CA, USA), through earphones. First, the hearing threshold was measured for each standard sound, in each participant using a modified Bekesy procedure (so as to present the sounds, during the experiment, 50 dB above the mean hearing threshold for each subject). Second, participants were familiarized with the sounds, and were trained on the 3 different attention tasks. EEG was then recorded while subjects performed 12 blocks of the attention tasks (4 in each attention task), resulting in a total of 160 attended and 160 ignored standard sounds presented in each ear, and 160 neutral standards presented binaurally. The order of the 12 attention blocks was balanced across participants using a Latin-square design. During the experiment, subjects were instructed to perform as accurately and as quickly as possible. They were also asked to keep their eyes fixated on a centrally presented cross and to minimize any eye movements and blinks while performing the tasks.

### Behavioral data

In the attention tasks, a button press within the interval of 200–1000 ms after target onset was considered a correct response, and a press at any other time was counted as a false alarm. Behavioral accuracy was then assessed using a  $d'$  measure of sensitivity, which takes into account the false alarm rate to correct for response bias. Mean reaction times and  $d'$  were computed for each attention task, separately.

### EEG Recording

EEG data were recorded from 64 electrodes using the ActiveTwo system (BioSemi, the Netherlands). Vertical and horizontal eye movements were recorded from electrodes placed at both external canthi and below the left eye. Data were amplified (−3 dB at ~204 Hz low-pass, DC coupled), digitized (1024 Hz), and stored for offline analysis. Data were referenced offline to the average potential of 2 earlobe electrodes.



**Figure 1.** Patient MRIs. Horizontal MRI slices of the MNI showing the group-averaged reconstruction of the extent of the damage in patients with LPFC lesion. Patients with right hemisphere lesions were transcribed to the left hemisphere for display purposes. The color bar indicates the percent of patients with a lesion in a specific region. The greatest lesion overlap across the patients occurs in Brodmann's areas 9 and 46.

**Table 1**

Group demographics

	LPFC patients	Controls
Age (years $\pm$ SEM)	58.3 $\pm$ 3.1	57.2 $\pm$ 3.8
Gender	5F, 4M	5F, 4M
Handedness	8R, 1L	8R, 1L
Education level (years $\pm$ SEM)	15.6 $\pm$ 1	15.7 $\pm$ 0.7
MMSE score	26.1 $\pm$ 0.9	29.6 $\pm$ 0.3

Note: Age, gender breakdown, dominant hand breakdown, education level, mini-mental state examination (MMSE) score for each tested group. (SEM, standard error of the mean; F, Female; M, Male; R, right-handed; L, left-handed).

### EEG Data Analysis

Trials corresponding to the responses to standard sounds delivered after a target, before or after a button press were excluded. Prior to ERP analysis, eye-related activities were detected using independent component analysis (ICA) and were selectively removed during/via the inverse ICA transformation. Only 1 or 2 ICs were removed in each participant. Trials contaminated with excessive muscular activity were excluded from further analysis. In 6 participants, the flat or excessively noisy signals at 1 or 2 electrodes were replaced by their values interpolated from the remaining electrodes using spherical spline interpolation (Perrin et al. 1989). Averaging time-locked to standard sounds onset, was computed for each attention condition (attended, ignored, and neutral) and each ear of presentation, in each group of participants, separately. Across subjects, a mean value of  $129 \pm 2.2$  trials was averaged for each condition, in each participant. With this procedure, the average frequency content of the sounds was the same for all obtained ERPs, only the attention orientation and the ear of presentation varied. ERPs were corrected according to a  $-100$  to  $0$  ms baseline before the standard onset, and were digitally filtered (low-pass  $30$  Hz). Since the shortest ISI was  $400$  ms, only the  $-100$  to  $400$  ms time-window was retained for further analysis. ERP scalp topographies were computed using spherical spline interpolation (Perrin et al. 1987, 1989).

In patients with right LPFC lesion, left and right hemisphere electrodes were switched so that the responses to all ipsilesional (or contralesional) electrodes could be averaged across participants. For example, FC1i refers to the averaged ERP data from the FC1 electrode for left lesions combined with data from the FC2 electrode for right lesions.

EEG data analysis was performed using ELAN software (Aguera et al. 2011, <http://elan.lyon.inserm.fr/>).

### Statistical Analysis

Performance and electrophysiological data are presented for stimuli delivered in the ipsilesional or contralesional ear according to the side of the lesion. Responses to left or right ear stimuli in controls were compared against ipsilesional or contralesional responses in patients, respectively. Power considerations due to the size of the groups precluded definitive conclusions about hemispheric laterality.

To assess differences between matched groups, age, education level, and MMSE score were submitted to nonparametric nonpaired Mann–Whitney tests.

To assess the effect of the task on performances, reaction times (RT) and accuracy ( $d'$ ) were submitted to repeated-measure ANOVAs (rmANOVAs) with TASK (3 levels: Attention to left/ipsilesional ear, Attention to right/contralesional ear, Neutral) as within-subject factor, and GROUP (2 levels: patient vs. control) as between-subject factor. To further assess the effect of selective attention on performances, the differences in RT and  $d'$  between each attention task and the neutral task (Attention to left/ipsilesional ear—Neutral, Attention to right/contralesional ear—Neutral) were computed and submitted to rmANOVA with ATTENTION EFFECT (2 levels: Attention to left/ipsilesional ear—Neutral, Attention to right/contralesional ear—Neutral) as within-subject factor, and GROUP (2 levels: patient vs. control) as between-subject factor.

To assess statistical differences between conditions in ERP values, average amplitudes in the time-windows of interest were submitted to

rmANOVAs with ATTENTION (3 levels: Attended, Neutral, and Ignored) and EAR of sound delivery (2 levels: left/ipsilesional vs. right/contralesional) as within-subject factors, and GROUP (patient vs. control) as between-subject factor. These analyses were performed on successive 50-ms time-windows from  $150$  to  $400$  ms post stimulus. This choice was based on previous studies (Giard et al. 2000; Bidet-Caulet et al. 2010) and visual inspection of the data.

To improve the signal-to-noise ratio of the responses for statistical analysis, we clustered electrodes over regions of interest. The clusters were fronto-central (F3, F1, Fz, F2, F4, FC3, FC1, FCz, FC2, FC4, C3, C1, Cz, C2, and C4), left/ipsilesional frontal (FC1 and FC3), and right/contralesional frontal (FC2 and FC4).

For all statistical effects involving more than one degree of freedom in the numerator of the  $F$  value, the Greenhouse–Geisser correction was applied to correct for possible violations of the sphericity assumption. We report the uncorrected degree of freedom and the corrected probabilities.

Significant main effects obtained with rmANOVAs were further explored using post hoc permutation tests based on randomization (Edgington 1995). Each randomization consisted in (1) the random permutation of the 9 or 18 pairs (corresponding to the 9 or 18 subjects) of values, (2) the sum of squared sums of values in each of the 2 obtained samples, and (3) the computation of the difference between these 2 statistic values. We did 10 000 such randomization to obtain an estimate of the distribution of this difference under the null hypothesis. We then compared the actual difference between the values in the 2 conditions of interest to this distribution. For ERP analysis, to correct for multiple post hoc tests, only effects with  $P < 0.01$  were considered significant.

Significant 3-way interaction effects obtained with rmANOVAs were further explored by computing post hoc rmANOVAs for each group separately and then for each ear of presentation.

To estimate the facilitatory and inhibitory effects of attention, we computed the difference between the averaged ERPs to attended and neutral sounds, or between the averaged ERPs to ignored and neutral sounds, respectively.

In planned comparisons, we tested for potential group differences, irrespective of the ear of sound delivery. We compared using permutation tests (see above) the facilitatory effect in each group (patient vs. control) in the  $150$ – $200$  and  $200$ – $250$  ms time-windows, and the inhibitory effect in the  $250$ – $300$ ,  $300$ – $350$ , and  $350$ – $400$  ms time-windows.

To assess interhemispheric differences in the patient group, irrespective of the ear of sound delivery, we used permutation tests (see above) to compare the facilitatory effect in each hemisphere (ipsilesional vs. contralesional) in the  $150$ – $200$  and  $200$ – $250$  ms time-windows, and the inhibitory effect in the  $250$ – $300$ ,  $300$ – $350$ , and  $350$ – $400$  ms time-windows.

rmANOVAs were performed using SPSS software (IBM, Armonk, NY, USA), permutation tests were performed with custom matlab programs (Mathworks, Natick, MA, USA).

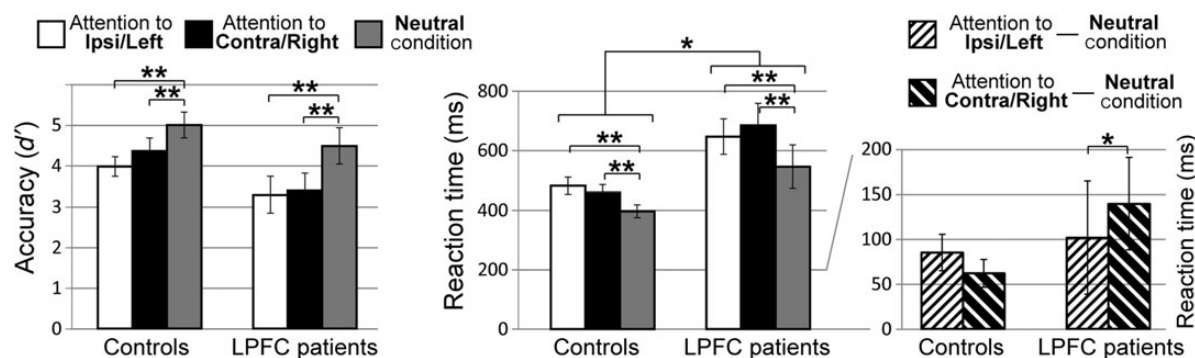
## Results

### Behavioral data

LPFC patients presented a lower MMSE score (nonparametric Mann–Whitney test  $P = 0.003$ ) than their matched control subjects (Table 1).

In ANOVAs, a significant main effect of GROUP was found on participant reaction times ( $F_{1,16} = 249.3$ ,  $P = 0.017$ ) but not on  $d'$  ( $F_{1,16} = 2.4$ ,  $P = 0.137$ ), indicating that the LPFC patients were slower than the controls, but did not significantly differ in accuracy (Fig. 2). We also observed a significant main effect of TASK on both reaction times ( $F_{2,32} = 9.6$ ,  $P = 0.004$ ) and  $d'$  ( $F_{2,32} = 13.6$ ,  $P < 0.001$ ) measures. Post hoc permutation tests showed that all participants were faster and more accurate ( $P < 0.005$ ) in the neutral task than in the selective attention tasks (Attention to left/ipsilesional ear, Attention to right/





**Figure 2.** Behavioral results. Accuracy ( $d'$ , left panel) and reaction time (middle panel) in each of the 3 attention tasks in each group. Right panel: Difference in reaction time between the attention task and the neutral task in each group. The significant differences are indicated (\* $P < 0.05$ , \*\* $P < 0.01$ ). Error bars represent 1 SEM.

contralesional ear). The TASK by GROUP interaction did not reach significance.

A significant ATTENTION EFFECT by GROUP interaction ( $F_{1,16} = 5.6$ ,  $P = 0.031$ ) was found when subtracting the RT in the neutral task from the RT in each attention task (Attention to left/ipsilesional ear—Neutral, Attention to right/contralesional ear—Neutral), indicating a larger cost in RT when attention was directed to the contralesional ear compared with the ipsilesional ear in LPFC patients.

### Scalp EEG: Main Attention Effect

The standard sounds elicited ERPs with a similar morphology in both groups of subjects (Fig. 3A). The major waves were a negative peak (N100) with a latency at 100 ms, followed by a less prominent positive wave (P200) peaking between 200 and 225 ms. The main attention effect was reflected in the difference between the averaged ERPs to attended and ignored sounds (Fig. 3A). Both patients and controls showed the “classical” pattern of a frontal negativity to attended standard sounds compared with ignored sounds starting at 150 ms, as indicated by a significant main effect of ATTENTION on all 50-ms time-windows between 150 and 400 ms post stimulus onset ( $F_{2,32} > 9.3$ ,  $P < 0.004$ ) on the large fronto-central group of electrodes (see Materials and Methods).

The attention effect was not found modulated by the GROUP factor except in the 200–250 ms time-window (see the following). No other main effect or interaction effect was found significant.

### Scalp EEG: Timing of Facilitatory and Inhibitory Effects of Attention

ERPs to neutral sounds, which were between ERPs to attended and ignored sounds in amplitude (Fig. 3A), enabled dissociation of the facilitatory and inhibitory attention effects, as indexed by the difference between the averaged ERPs to attended and neutral sounds, and between the averaged ERPs to ignored and neutral sounds, respectively (Fig. 3A).

Post hoc analysis of the main ATTENTION effect (Fig. 3B, see Supplementary Fig. 1 for individual values and Supplementary Fig. 2 for group topographies) revealed, in both patients and controls, a frontal response of negative polarity to attended sounds compared with neutral sounds significant between 150 and 200 ms ( $P = 0.002$ ) and between 200 and 250 ms ( $P < 0.001$ ), but not later on ( $P > 0.054$ ). Conversely, a frontal response of positive polarity to ignored sounds

compared with neutral sounds was significant between 250 and 300 ms ( $P < 0.001$ ), between 300 and 350 ms ( $P = 0.003$ ), and between 350 and 400 ms ( $P < 0.001$ ), but not earlier between 150 and 250 ms ( $P > 0.033$ ).

In both patients and controls, facilitatory and inhibitory effects present different timing: a facilitatory transient effect starts at 150 ms and lasts 100 ms, whereas an inhibitory effect begins at 250 ms and remains until at least 400 ms.

### Scalp EEG: Influence of Frontal Damage and of the Stimulated Ear on Attention Effects. (Fig. 4)

A significant ATTENTION by EAR by GROUP interaction was found between 200 and 250 ms ( $F_{2,32} = 4.5$ ,  $P = 0.020$ ), but not for the other time-windows.

Post hoc rmANOVAs of this 3-way interaction, for each group separately, revealed a significant main effect of ATTENTION in both LPFC patients ( $F_{2,16} = 6.3$ ,  $P = 0.020$ ) and their matched controls ( $F_{2,16} = 16.8$ ,  $P < 0.001$ ), and a significant ATTENTION by EAR interaction effect in LPFC patients only (patients:  $F_{2,16} = 4.8$ ,  $P = 0.024$ ; controls:  $F_{2,16} = 0.7$ ,  $P = 0.495$ ).

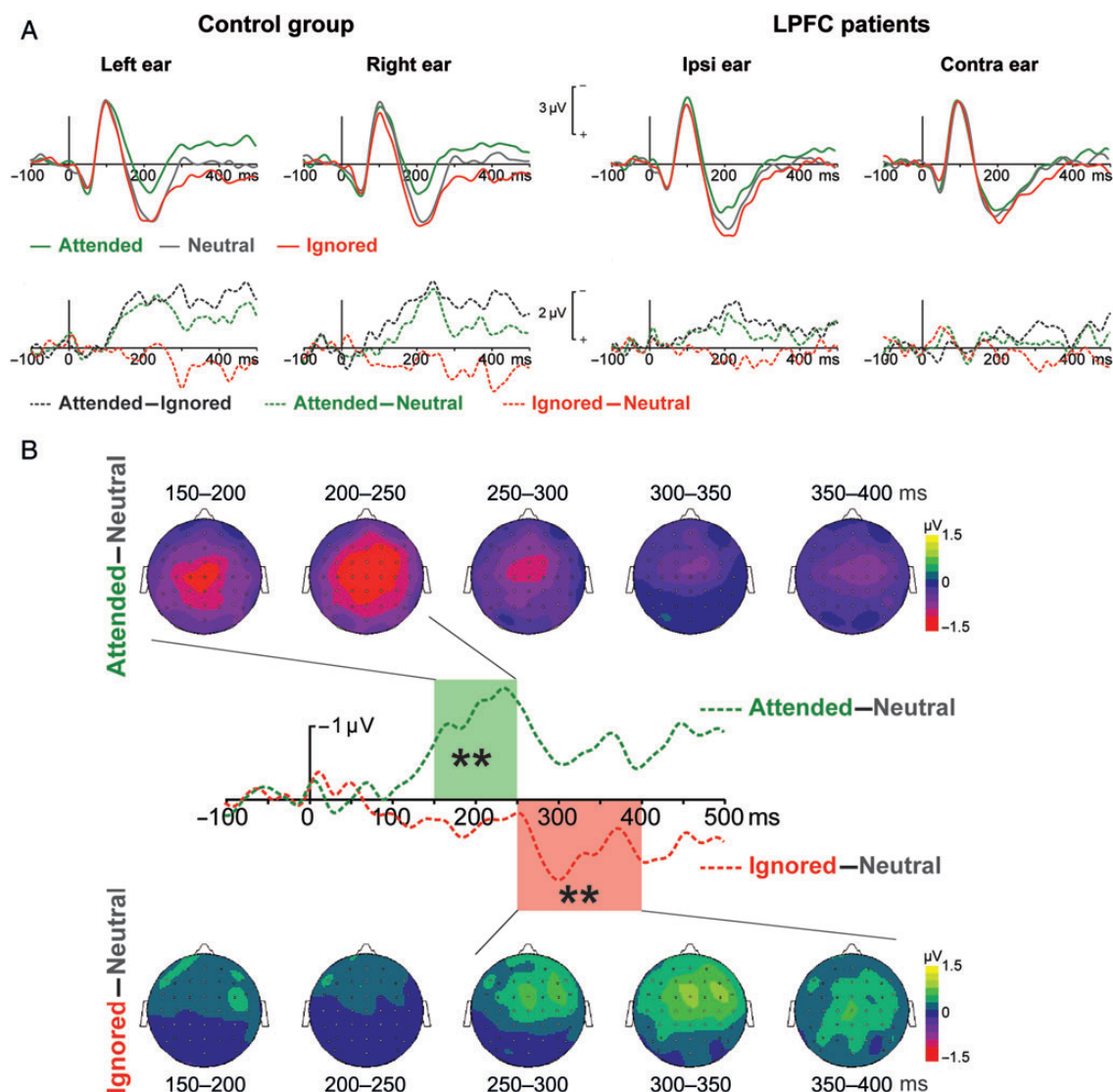
Post hoc rmANOVAs of the ATTENTION by EAR interaction in LPFC patients revealed a significant effect of ATTENTION for sounds presented to the ipsilesional ear ( $F_{2,16} = 8.5$ ,  $P = 0.003$ ), but not to the contralesional ear ( $F_{2,16} = 1.5$ ,  $P = 0.255$ ). Post hoc analysis showed that the significant ATTENTION effects for the ipsilesional ear were related to a significant difference between ERP amplitudes to attended and neutral sounds ( $P < 0.050$ ) rather than to a difference between ERP amplitudes to ignored and neutral sounds ( $P = 0.078$ ) (Fig. 4, see Supplementary Fig. 3 for individual values).

The facilitatory effect was globally reduced in LPFC patients compared with controls between 200 and 250 ms ( $P < 0.050$ , PFC:  $-0.7 \pm 0.4$   $\mu$ V, controls:  $-2.0 \pm 0.5$   $\mu$ V). No significant difference was found between PFC patients and controls for the inhibitory effect between 250 and 400 ms ( $P > 0.436$ ).

In sum, these results show that the facilitatory effect is reduced (and absent when the sounds are presented in the ear contralateral to the lesion), whereas the inhibitory effect was not significantly affected in LPFC patients.

### Scalp EEG: Topography of Attention Effects in LPFC Patients

In LPFC patients, a significant HEMISPHERE effect was found on the facilitatory effect between 150 and 200 ms ( $P = 0.027$ , ipsilesional hemisphere:  $-0.5 \pm 0.6$   $\mu$ V, contralesional



**Figure 3.** ERP results. (A) Top row: Mean ERPs at the fronto-central electrode group to attended, neutral, and ignored standard sounds are depicted in green, gray, and red, respectively, as a function of the stimulated ear (Left/Right or Ipsi/Contra), in each group separately ( $n = 9$ ). Bottom row: The differences between ERPs to attended and neutral, and to ignored and neutral standards are represented by green and red dashed lines, respectively, as a function of the stimulated ear (Left/Right or Ipsi/Contra), in each group separately ( $n = 9$ ). (B) Top panel: Scalp topographies (top views) of the mean difference between ERPs to attended and neutral sounds in successive 50-ms time-windows. Middle panel: The differences between ERPs to attended and neutral, and to ignored and neutral sounds, are represented by green and red dashed lines, respectively. Green and red shaded areas correspond to the time-windows with a significant difference between ERPs to attended and neutral, and to ignored and neutral sounds, respectively ( $**P < 0.01$ ). Bottom panel: Scalp topographies (top views) of the mean difference between ERPs to ignored and neutral sounds in successive 50-ms time-windows. Data are presented for the average of patients and control subjects pooled together ( $n = 18$ ).

hemisphere:  $-0.9 \pm 0.7 \mu\text{V}$ ), and between 200 and 250 ms ( $P = 0.012$ , ipsilesional hemisphere:  $-0.4 \pm 1.1 \mu\text{V}$ , contralesional hemisphere:  $-1.2 \pm 0.9 \mu\text{V}$ ), as reflected by a reduced facilitatory effect at ipsilesional frontal electrodes. No significant effect of HEMISPHERE was observed on the inhibitory effect between 250 and 400 ms ( $P > 0.290$ ).

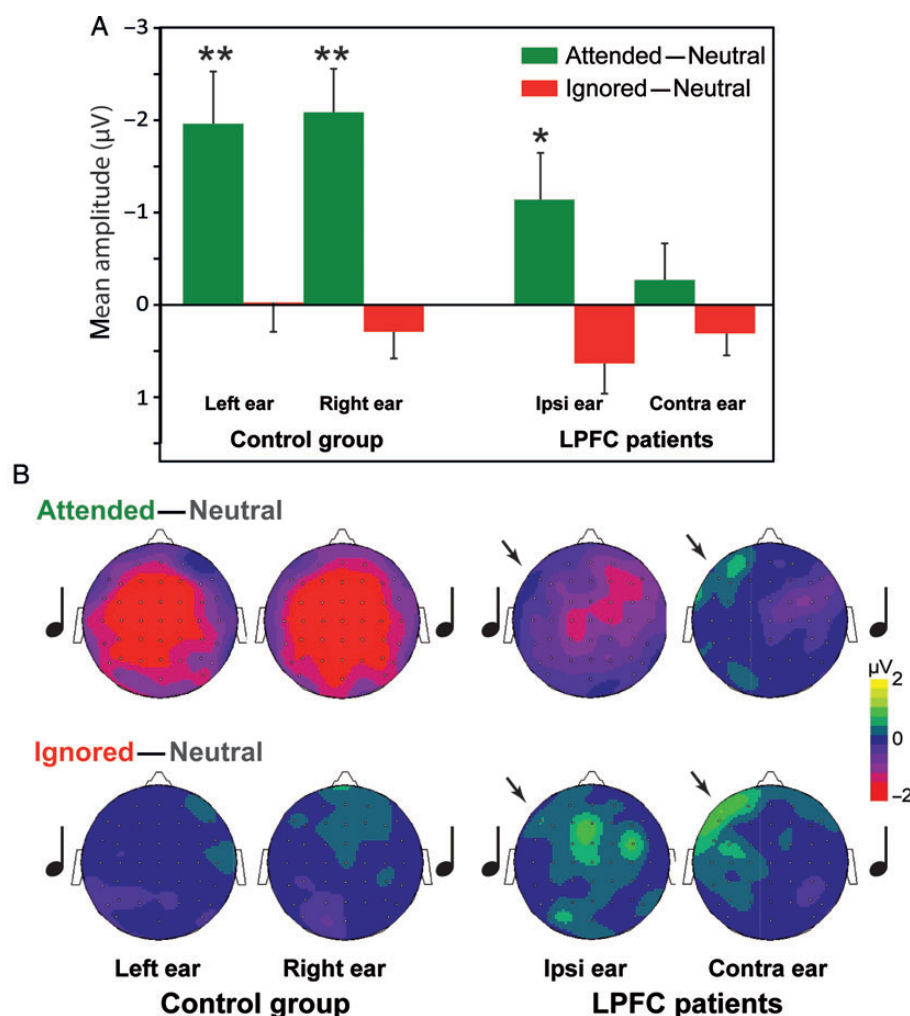
These results indicate that the facilitatory effect is further reduced in LPFC patients at electrodes located over the frontal damaged areas, whereas the main frontal topography of the inhibitory effect was not significantly affected by the lesion.

## Discussion

Unilateral LPFC lesions result in a decrease in reaction times to auditory targets delivered in the ear contralateral to damage.

This behavioral deficit was accompanied by a reduced frontal negative polarity ERP component indexing the facilitatory effects of attention, with the most prominent decrease evident for sounds delivered in the contralesional ear, over the damaged frontal regions. However, the positive polarity ERP component related to the inhibitory attention effects was not found to be reduced in comparison to controls and was activated in the same latency range as controls. These results provide new insight into the specific role of the LPFC in selective attention.

We first observed a frontally distributed ERP component of negative polarity onset at  $\sim 150$  ms that differentiated the responses to attended and ignored standard sounds in both patient and control participants. This component corresponds to the Nd or PN ("Processing Negativity") attentional wave described in several previous studies (reviewed in Giard et al.



**Figure 4.** Effect of frontal damage and of the stimulated ear on the attention effects. (A) Mean amplitude differences (fronto-central electrodes, 200–250 ms time-window) between the ERPs to attended and neutral sounds (green), and to ignored and neutral sounds (red), as a function of the stimulated ear (Left/Right or Ipsi/Contra), in each group separately ( $n = 9$ ). The significant differences are indicated (\* $P < 0.05$ , \*\* $P < 0.01$ ). Error bars represent 1 SEM. (B) Corresponding scalp topographies (top views) of the attention effects (200–250 ms).

2000). This ERP response is felt to index late selective attention mechanisms involved in controlling and maintaining the representation of stimuli according to their behavioral relevance (Näätänen 1982, 1992; Giard et al. 2000).

To dissociate facilitatory and inhibitory components of attention, we employed a novel paradigm with a neutral condition wherein the participants had to detect binaural pure tones. This neutral task has been used to dissect the facilitatory and inhibitory mechanisms of auditory selective attention (Bidet-Caulet et al. 2007, 2010). While the perfect neutral condition is elusive, the current choice is an improvement over a passive task (what is the subject actually doing?) or a secondary visual task (intermodal attention is then involved). In this neutral condition, participants' auditory attention was equally distributed towards all monaural standard sounds. The neutral condition did not require selective attention, but only necessitated broad auditory attention towards all sounds in order to detect the salient binaural pure tones, which may contribute to enhanced performances in this task.

Using this neutral condition, we found that, in both patients and controls, the Nd response could be dissociated into 2 distinct components: (i) a transient negative ERP component in

response to attended standards, from 150 to 250 ms after sound onset; and (ii) a positive ERP component in response to ignored standards, onsetting at 250 ms. These findings are consistent with several previous scalp EEG studies showing a positive response or "rejection positivity" to unattended sounds compared with a neutral condition, occurring substantially later in latency than the negative response to attended sounds (Alho et al. 1987, 1994; Donald 1987; Berman et al. 1989; Michie et al. 1990, 1993; Schröger and Eimer 1997; Melara et al. 2002; Degerman et al. 2008). Similar to young healthy adults (Bidet-Caulet et al. 2010), both patients and their age-matched controls show facilitatory mechanisms starting earlier than inhibitory mechanisms during late auditory selection. These facilitatory and inhibitory attentional mechanisms are involved in late attentional selection processes by enhancing or reducing, respectively, high-level processing (e.g., categorization, memorization) of the stimuli according to their behavioral saliency.

The impact of LPFC lesion on auditory selective attention has been investigated in previous works. Using a similar but more difficult task, a reduced Nd was found in patients with LPFC damage (Knight et al. 1981; Woods and Knight 1986),



suggesting a role of this structure in the control of auditory selective attention. However, these works only compared ERPs with attended and ignored sounds and could not assess if this Nd reduction resulted from an alteration of the facilitatory or inhibitory mechanisms of attention. In the present study, using the neutral condition, we show that the Nd decrease observed after 150 ms is due to a reduction in facilitatory, rather than in inhibitory, mechanisms of auditory attention. The specificity of this reduction is further supported by its dependence upon the ear of sound delivery: the facilitatory component is further reduced in patients with LPFC damage when they are attending to the ear contralateral to the lesion. This result is consistent with previous findings in the visual modality showing that the LPFC exerts facilitatory modulation of relevant stimulus processing in visual areas at early sensory as well as later processing stages via an intrahemispheric feedback (Barcelo et al. 2000; Yago et al. 2004).

Given the spatial smoothing inherent to scalp EEG, the precise brain origin of the facilitatory component is difficult to localize. In response to sounds, ERPs with a frontal distribution could originate from the frontal cortices or from the superior temporal gyri (auditory areas). A reduced frontal facilitatory component could thus reflect either a decreased facilitatory input from the frontal cortices, or a reduced activity in the auditory cortices. Both frontal and temporal activities would be further affected when the lesioned hemisphere is targeted by contralesional stimulation. However, a unilateral frontal lesion is more likely to result in a larger reduction of frontal activations over the lesioned hemisphere, whereas it would induce a bilateral scalp decrease of activations from the auditory cortices (Knight et al. 1980). The fact that the facilitatory component is further reduced over the region of the damage suggests that the LPFC is probably responsible for the generation of this frontal negative component. Thus, the facilitatory component of the Nd is more likely to index an attentional facilitatory control signal originating in the LPFC than enhanced sound processing within the auditory cortices.

Inhibitory mechanisms were not reliably affected by the LPFC lesion. This result could be explained in 2 ways: (i) either the LPFC is not involved in the inhibitory mechanisms and another brain region controls these mechanisms, (ii) or the inhibitory mechanisms are late enough so that the LPFC damage can be compensated by the non-lesioned LPFC. LPFC damage has been shown to lead to increased distractibility (Malmo 1942; Bartus and Levere 1977; Woods and Knight 1986; Chao and Knight 1995, 1998) suggesting that the LPFC also exerts inhibitory modulation of irrelevant information processing. In particular, middle latency potentials (within the first 60 ms after sound onset) to task-irrelevant sounds generated in the primary auditory cortex were found to be enhanced in patients with LPFC damage (Chao and Knight 1998) supporting a key role of lateral PFC in early sensory inhibition. These previous results may seem contradictory to the present findings. However, they suggest that the LPFC participates in the early filtering and rejection of irrelevant stimuli (in the first 100 ms of processing), whereas the present study addresses late selective attention mechanisms (after 150 ms). One hypothesis reconciling these results would be that the LPFC could play a role in inhibitory attentional mechanisms at early sensory stages only rather than at later steps of the selection process.

Despite some inconsistent results, there is growing evidence that the lateral frontal cortex, in particular in the right

hemisphere, plays a crucial role in inhibition of motor responses (e.g., Jonides et al. 1998; Konishi et al. 1999; Nielson et al. 2002; Aron et al. 2003), cognitive sets (e.g., Konishi et al. 1999), or memories (Anderson et al. 2004). The fact that the attentional inhibitory component was found unaffected by LPFC lesion in the present work could be due to the size of the patient cohort, or to the functional distinction between attentional inhibitory mechanisms (reduction of stimulus processing) and inhibitory mechanisms targeting other brain processes such as motor processing, memorization, or task set maintenance.

The absence of any left–right asymmetry in the scalp distribution of the inhibitory effect in these unilaterally lesioned patients further suggests that the LPFC does not contain the principal generators of the late inhibitory attentional component. This is in agreement with fMRI connectivity findings in the visual modality suggesting that inhibitory attentional mechanisms were enabled by the medial PFC and the posterior cingulate cortex whereas facilitatory mechanisms were supported by the right medial frontal gyrus and the bilateral inferior frontal gyri (Chadick and Gazzaley 2011), lesioned in most of the LPFC patients presented here. In the same line, electrical stimulation of the anterior cingulate cortex has been shown to reduce auditory evoked activity in superior temporal auditory cortices in monkeys (Muller-Preuss et al. 1980; Muller-Preuss and Ploog 1981). These evidences suggest a crucial role of inhibitory attentional control by the medial frontal cortex, rather than by the lateral frontal cortex. Taken together, these findings rather argue for the first hypothesis, that is, the LPFC would not be involved in inhibitory attentional mechanisms during late auditory selection.

The differential impact of LPFC lesion on the facilitatory and inhibitory components of auditory attention suggests selective enhancement and suppression of the neural activity observed in auditory cortical regions according to sound relevance (Bidet-Caulet et al. 2007) would be controlled by distinct facilitatory and inhibitory attentional mechanisms. This result is consistent with recent findings showing that enhancement and suppression are differentially affected by aging (Gazzaley et al. 2005, 2008) and cognitive load manipulations (Rissman et al. 2009; Bidet-Caulet et al. 2010; Gil-Gomez de Liano et al. 2010), as well as coupled with distinct networks (Chadick and Gazzaley 2011). The present results provide evidence that, facilitatory signals enabling enhancement of task-relevant sound processing in auditory cortices originate in the LPFC.

## Conclusion

PFC lesions reduced the facilitatory ERP component of auditory attention, with the most prominent decreases evident when the sounds were delivered to the ear contralesional to lesioned PFC and over the damaged brain regions. Conversely, neither the amplitude nor the topography of the inhibitory component was reliably affected by PFC damage and the inhibitory ERP occurred at the same latencies as in the control group. These results suggest that the frontally distributed negative ERP component in response to attended sounds indexes a facilitatory attentional mechanism, controlled by the lateral prefrontal cortex, enabling late auditory selection. These findings provide further evidence for functionally independent facilitatory and inhibitory mechanisms supporting late auditory selective attention.

## Supplementary Material

Supplementary material can be found at: <http://www.cercor.oxfordjournals.org/>

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## Notes

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