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Lateral prefrontal cortex lesion impairs regulation of internally and externally directed attention

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ABSTRACT

Our capacity to flexibly shift between internally and externally directed attention is crucial for successful performance of activities in our daily lives. Neuroimaging studies have implicated the lateral prefrontal cortex (LPFC) in both internally directed processes, including autobiographical memory retrieval and future planning, and externally directed processes, including cognitive control and selective attention. However, the causal involvement of the LPFC in regulating internally directed attention states is unknown. The current study recorded scalp EEG from patients with LPFC lesions and healthy controls as they performed an attention task that instructed them to direct their attention either to the external environment or their internal milieu. We compared frontocentral midline theta and posterior alpha between externally and internally directed attention states. While healthy controls showed increased theta power during externally directed attention and increased alpha power during internally directed attention, LPFC patients revealed no differences between the two attention states in either electrophysiological measure in the analyzed time windows. These findings provide evidence that damage to the LPFC leads to dysregulation of both types of attention, establishing the important role of LPFC in supporting sustained periods of internally and externally directed attention.

Introduction

At any given moment during our waking hours, humans attend to either the external environment or internal milieu. The capacity to flexibly allocate neural resources between internally and externally directed attention states is essential for optimal cognitive performance (Buckner et al., 2008; Allen, 2013). Neuroimaging studies suggest the frontoparietal control network, which includes the lateral prefrontal cortex (LPFC), plays an important role in facilitating both attention states. In particular, the LPFC is recruited for numerous processes involving internally directed attention, which occupies as much as half of our waking state, including autobiographical memory retrieval (Addis et al., 2007), future planning (Spreng et al., 2010), and creative problem solving (Ellamil et al., 2012). The coordination of externally directed attention also draws upon the LPFC, including cognitive control (Miller and Cohen, 2001; Cole and Schneider, 2007) and selective attention (Desimone and Ducan, 1995; Corbetta and Shulman, 2002; Buschman and Miller, 2007). Human lesion studies have confirmed that the LPFC is necessary for externally directed attention (Barcelo et al., 2000; Voytek et al., 2010). Although the LPFC has been implicated in both attention states, its causal involvement in regulating internally directed attention has not been addressed. Here, we establish the critical role of LPFC in coordinating both internally and externally directed attention using a combination of electrophysiological and lesion approaches.

The LPFC's involvement in regulating attention states draws support from both theoretical and empirical work. A theoretical framework of internally directed attention has proposed the importance of the LPFC, in cooperation with the Default Network, in producing an internal train of

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thought (Smallwood et al., 2012). More broadly, Dixon and colleagues highlight the role of intentionality and propose that the LPFC is recruited when either internally or externally directed attention is intentionally engaged (Dixon et al., 2014). Consistent with these theoretical suggestions, neuroimaging evidence reveals enhanced functional coupling between the LPFC and Default Network during an autobiographical planning task involving internally directed attention, and with the Dorsal Attention Network during a Tower of Hanoi task involving externally directed attention. These findings indicate that LPFC can flexibly couple with the relevant neural network to support goal-directed cognition (Spreng et al., 2010). In line with this finding, Vincent and colleagues reported that the frontoparietal control network, which includes the LPFC, is anatomically positioned between the Default Network implicated in internally directed attention and Dorsal Attention Network implicated in externally directed visuospatial attention. Its unique position allows it to flexibly integrate information from both networks and adjudicate between competing stimuli from the internal vs. external environments (Vincent et al., 2008). Together, both theoretical and empirical suggestions converge on the role of the LPFC in regulating various attentional states.

Electrophysiological studies have identified theta and alpha power as key markers of externally and internally directed attention, which may serve as mechanisms by which these attention states are regulated. Successful performance in various externally directed tasks involving high level cognitive processes often engages theta power. For example, frontocentral midline theta power has been associated with cognitive control (Cavanagh et al., 2009; Cavanagh and Frank, 2014), including working memory (Missonnier et al., 2006; Sauseng et al., 2010), conflict detection (Hanslmayr et al., 2008; Töllner et al., 2017), and target detection (Pennekamp et al., 1994; Cavanagh et al., 2012). In contrast, studies have focused on posterior alpha as an index of both internal and external attention. While externally directed processes involving selective attention have been associated with alpha decreases (Pfurtscheller, 1992; Pfurtscheller et al., 1996), internal attention has been primarily linked to alpha increases. For instance, O'Connell and colleagues reported increased alpha power over parietal sites during internally directed attention as indexed by missed targets in an externally directed steady state visual evoked potential (SSVEP) task (O'Connell et al., 2009). Further, simultaneous EEG and fMRI recordings of resting state – a prevalent form of internally directed attention in an experimental context in which no task constraints are placed on the subject and no stimuli are presented – reveal positive correlations between posterior alpha power and activation of the Default Network (Mantini et al., 2007; Jann et al., 2009). Of relevance to our experimental task, these findings converge on enhanced frontocentral midline theta as an electrophysiological signature of externally directed attention and posterior alpha increase as a signature of internally directed attention.

The present study used a combined electrophysiological and neuropsychological approach to determine whether LPFC is causally involved in facilitating internally and externally directed attention. We recorded EEG in patients with LPFC lesion and healthy controls as they performed an attention task that required them to direct their attention either to the external environment or internal milieu. We compared frontocentral midline theta and posterior alpha between externally and internally directed attention states. Given the novelty of the experimental paradigm, our first objective was to validate the task by examining these electrophysiological measures of the two attention states in healthy controls. We hypothesized increased frontocentral midline theta power in the externally directed attention state and increased posterior alpha power in the internally directed attention state. The main objective was to assess whether LPFC is a critical brain region for regulating sustained periods of internally vs. externally directed attention. In contrast to healthy controls, our hypothesis was that patients with lesion in the LPFC would be impaired in attentional regulation as indexed by reduced differences in electrophysiological measures between the two attention states.

Methods

Subjects

Nine patients with lesions in the lateral prefrontal cortex, and thirteen age and gender matched healthy controls participated in the experiment. Patients were recruited from and tested at two sites. Seven patients with LPFC lesions were tested at the University of California, Berkeley, and two were tested at Oslo University Hospital/University of Oslo. Exclusion criteria included a history of psychiatric disease, substance abuse requiring treatment, premorbid head injury, comorbid neurological disease, IQ < 85, or sensory impairment. Table S1 summarizes subjects' demographic information and patient characteristics.

The LPFC group consisted of nine patients with a unilateral focal lesion in the dorsolateral PFC (2 right, 7 left). Their lesions were due to low-grade astrocytoma resection ($n = 2$ at Oslo), and ischemic or hemorrhagic stroke ($n = 7$ at Berkeley). Both patients with low-grade astrocytoma showed no evidence of recurrence in an MRI taken within a month of testing. Maximal lesion overlap was observed in Brodmann Areas 9 and 46. Fig. 1a shows the lesion overlap for LPFC patients. Individual lesion reconstructions for all patients are shown in Figure S1.

Healthy controls were recruited to match the patients by gender and age within 5 years. The two groups did not significantly differ in gender ($\chi(1) = .01$, $p = .94$), age ($t\ (20) = .01$, $p = .99$), or education ($t\ (20) = .21$, $p = .84$). All subjects provided written informed consent, and were paid for their participation. This study was approved by the Institutional Review Boards at the University of California, Berkeley and Oslo University Hospital, and the Norwegian Regional Committee for Medical Research Ethics, Region South.

Lesion reconstruction

Lesion reconstructions were based on structural MRIs obtained after study inclusion. Lesions were outlined by manually drawing on Fluid Attenuated Inversion Recovery (FLAIR), T1 and T2 weighted images of each participant's brain using MRIcron (www.mccauslandcenter.sc.edu/mricro/mricron/) and Adobe Photoshop CC 2015 (http://www.adobe.com/). T1, T2 and FLAIR images were first co-registered to a T1 MNI Template (normalized from 152 T1 scans), using Statistical Parametric Mapping software's (SPM8: www.fil.ion.ucl.ac.uk/spm/) New Unified Segmentation routine. The manual delineation of the lesions was performed on axial mosaics of the normalized T1 scans. When available, high-resolution FLAIR and T2-weighted images were also used as aids to determine lesion borders. The resulting lesion masks were converted to three-dimensional MNI space using the Statistical Parametric Mapping software's (SPM8: www.fil.ion.ucl.ac.uk/spm/) Mosaic to Volume routine. Lesions were reconstructed under the supervision of a neurologist (RTK). We calculated lesion sizes using the MRIcron descriptive statistics function after a lesion had been manually delineated.

Task paradigm and stimuli

Subjects were presented with a series of standard tones (800Hz) and target tones (1000Hz) presented in a random order with probabilities of 0.8 and 0.2, respectively. All auditory stimuli were pure tones presented through stereo speakers. The duration of each tone was 200ms, and the inter-trial interval was randomly jittered between 800 and 1200ms. Subjects were asked to keep their eyes fixated on the cross in the center of the screen throughout the task. Fig. 1b illustrates the experimental paradigm.

In the externally directed attention (EDA) condition, subjects were instructed to focus on the tones and press a button to target tones as quickly and accurately as possible. Mean reaction time and accuracy measures were computed. Accuracy measures included hit rate, false alarm rate, as well as d prime: $d' = Z\text{ (hit rate)} - Z\text{ (false alarm rate)}$. In the internally directed attention (IDA) condition, they were instructed to