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Preserved metacognitive ability despite unilateral or bilateral anterior prefrontal resection

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ABSTRACT

Brodmann area 10 (BA10) is thought to be at the summit of the prefrontal cortex's hierarchical organization. It is widely accepted that metacognitive abilities depend on the structural and functional properties of BA10. Our objective was to assess whether metacognition can be maintained after low-grade glioma surgery with BA10 resection. Three groups of participants were recruited: (i) patients having undergone resection of the right prefrontal cortex, including BA10 (n = 9); (ii) patients having undergone resection of the right prefrontal cortex but not BA10 (n = 10); and (iii) healthy controls (n = 38). Importantly, we also included a patient (referred to as "PR") with resection of BA10 in the two hemispheres. The patients with resection of right BA10 had metacognitive performances that were indistinguishable from those of brain-damaged control patients and healthy controls. Crucially, PR's metacognitive ability was not only maintained but was even in the upper quartile of normal performances. Our findings demonstrate that the brain can redistribute and remap metacognition in response to injury. We thus provide experimental evidence against the conventional hypothesis whereby cognitive functions are directly and lastingly linked to particular cortical structures. The latter hypothesis seems to be particularly false for the highest levels of human cognition and for BA10.

1. Introduction

The prefrontal cortex is the most anterior part of the brain, and is located in front of the premotor areas. Its astonishing phylogenetic expansion during hominid evolution (Passingham, 2002; Preuss, 2009; Semendeferi, Lu, Schenker, & Damasio, 2002; Teffer & Semendeferi, 2012) has enabled human beings to develop high-order cognitive and social skills – some of which are unique in the animal kingdom. The most anterior part of the prefrontal cortex (Brodmann area 10, BA10) has undergone a number of specific changes, such as an increase in its relative size when compared with the apes but also relative to the rest of the brain (Holloway, 2002; Semendeferi, Armstrong, Schleicher, Zilles, & Van Hoesen, 2001). Moreover, specific cytoarchitectonic changes have also been observed in BA10; this area has a particularly complex dendritic system and an elevated number of reciprocal connections with other supramodal prefrontal areas and with high-order association areas outside the prefrontal cortex (Jacobs et al., 2001; Ongur, Ferry, & Price, 2003; Ramnani & Owen, 2004; Schoenemann, Sheehan, & Glotzer, 2005; Semendeferi et al., 2002; Vincent, Kahn, Snyder, Raichle, & Buckner, 2008). Unsurprisingly, a broad range of studies have suggested that BA10 has a critical role in various aspects of human cognition, including contextual cognitive control (i.e. monitoring), information coordination, decision-making, self-awareness, mentalization and metacognition, in particular (Badre, 2008; Badre & D'Esposito, 2009; Christoff & Gabrieli, 2000; Gilbert et al., 2006; Koechlin & Hyafil, 2007; Koechlin, Ody, & Kouneiher, 2003; Ridderinkhof, van den Wildenberg, Segalowitz, & Carter, 2004).

Metacognition (i.e. "knowing about knowing") refers to the set of psychological processes involved in monitoring and organising our self-directed cognition (Flavell, 1979; Metcalfe & Shimamura, 1994). This complex ability constitutes one of the foundations of self-awareness (Nelson, 1996) and is pivotal in the development of monitoring and cognitive control (Fernandez-Duque, Baird, & Posner, 2000). Metacognition allows the reorganization of ongoing mental operations and thus changes in cognitive strategies and action plans (Flavell, 1979; Nelson & Narens, 1990; Nelson & Narens, 1994). Existing models suggest that metacognition arises from the dynamic interactions between lower and upper cognitive levels (Shea et al., 2014; Shimamura, 2008). This type of dynamic hierarchical organization could give rise to self-reflectiveness and self-analysis.

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It is accepted that metacognitive abilities depend critically on the structural and functional properties of the anterior prefrontal cortex in general and BA10 in particular (most notably in the right hemisphere). For instance, Fleming et al.'s morphometric study (2010) (Fleming, Weil, Nagy, Dolan, & Rees, 2010) found a positive correlation between the grey matter volume in the anterior prefrontal cortex (particularly in the right BA10) and perceptual metacognitive performances in healthy controls (HCs). Furthermore, functional magnetic resonance imaging (fMRI) studies have revealed a correlation between metacognitive performance and anterior prefrontal cortex activity (Fleming, Huijgen, & Dolan, 2012; Molenberghs, Trautwein, Bockler, Singer, & Kanske, 2016; Yokoyama et al., 2010). Lastly, earlier neuropsychological studies have shown that damage to left or right anterior prefrontal cortex affects subjective reports of visual experiences by increasing the threshold for access to consciousness of rapidly presented digits (Del Cul, Dehaene, Reyes, Bravo, & Slachevsky, 2009) or by decreasing metacognitive accuracy (Fleming, Ryu, Golfinos, & Blackmon, 2014). Taken as a whole, the literature data suggest that the anterior prefrontal cortex has a role in metacognitive ability.

Although a number of researchers have specifically focused on the anterior prefrontal cortex, others have examined metacognition in a network paradigm by using connectivity-based fMRI. For example, Baird, Smallwood, Gorgolewski, and Margulies (2013) showed that metacognitive ability for perceptual decisions was associated with an increase in functional connectivity between lateral regions of the anterior prefrontal cortex, the right dorsal anterior cingulate cortex, the bilateral putamen, the right caudate and the thalamus, whereas metamemory accuracy was associated with an increase in functional connectivity between the medial prefrontal cortex, the right central precuneus and the inferior parietal lobule. These findings indicated that (i) metacognition engages a broad network, (ii) the metacognitive network is modulated by the nature of the metacognition task, and (iii) more specialized subnetworks might underpin domain-specific components (Fleming et al., 2014; McCurdy et al., 2013).

It has previously been shown that in patients with a diffuse low-grade glioma (DLGG), brain regions with a supposedly crucial role in high-order cognitive functions can be surgically removed without inducing permanent or major cognitive disturbances. For example, this was the case for Broca's area with regard to language (Plaza, Gatignol, Leroy, & Duffau, 2009), for the medial prefrontal cortex with regard to both empathy (Herbet et al., 2015) and mentalizing (Herbet, Lafargue, Bonnetblanc, Moritz-Gasser, & Duffau, 2013; Herbet et al., 2014), and for the inferior parietal lobe with regard to awareness of intending to act (Lafargue & Duffau, 2008). This high degree of plasticity is usually explained by the lesion's slow growth, which enables progressive, functional reorganization (Bonnetblanc, Desmurget, & Duffau, 2006; Duffau, 2005; Keidel, Welbourne, & Lambon Ralph, 2010) in a much more efficient manner than an acute lesion would (Desmurget, Bonnetblanc, & Duffau, 2007). Several functional reorganization patterns have been described in the context of DLGG patients - especially for the recruitment of perilesional adjacent areas and homotopic areas (Krainik et al., 2004; Thiel et al., 2001). Investigating the brain's ability to compensate for the removal of cortical areas offers a unique opportunity to study functional plasticity and the latter's limits. For example, recent studies have demonstrated that plasticity is rather high in cortical regions (except for primary unimodal areas and a small set of neural hubs) and rather low in connective tracts (Herbet, Maheu, Costi, Lafargue, & Duffau, 2016; Ius, Angelini, Thiebaut de Schotten, Mandonnet, & Duffau, 2011). Therefore, investigating plasticity potential of cortical areas can also help to determine the critical structures in a given network (i.e. those refractory to plasticity).

In this context, the primary objective of the present study was to examine whether perceptual metacognition can be maintained after the resection of BA10. In particular, we wanted to determine whether a human can have normal metacognitive performances after the unilateral or even bilateral resection of BA10. Hence, we assessed the ability of patients with resection of the anterior prefrontal cortex (including BA10) to accurately evaluate their own perceptual decisions. To this end, we used a well-validated experimental task that is known to functionally engage the anterior prefrontal cortex (especially in the right hemisphere) (Fleming et al., 2010). In contrast to an earlier neuropsychological study (Fleming et al., 2014), only patients having undergone surgery for DLGG were recruited – thus avoiding the inherent limitations of assessing lesioned patients with a variety of aetiologies. Our starting hypothesis was straightforward: if the surgical removal of the anterior prefrontal cortex cannot be compensated for by the remaining neural circuits, we should observe profound alterations in metacognitive accuracy. Furthermore, we hypothesized that these impairments should be more pronounced for bilateral resections (which rule out the possibility of homotopic functional reorganization) than for unilateral resections.

2. Materials and methods

2.1. Participants

In addition to the patient having undergone bilateral resection of BA10 (see below), 57 participants were included in the study. We studied three groups of participants: an "anterior prefrontal cortex" (aPF) group comprising 9 patients with unilateral resection of BA10 (4 females and 5 males; mean ± standard deviation (SD) age: 35 ± 6.98); a "brain damage" control (BDC) group comprising 10 patients with a prefrontal resection but not resection of BA10 (5 females and 5 males; mean ± SD age: 37.8 ± 8.51); and an HC group comprising 38 healthy adults free of known neurological or psychiatric disorders and matched with the patient groups in terms of sociodemographic characteristics (18 females and 20 males; mean ± SD age: 30.97 ± 10.15). All patients were recruited from the Department of Neurosurgery at Montpellier University Hospital (Montpellier, France). The main exclusion criteria were as follows: high-grade glioma, preoperative radiotherapy (since it can impair cognition), and a history of other neurological or psychiatric illnesses. All patients were operated on by the same neurosurgeon (HD) and were always evaluated during the post-acute recovery phase (i.e. at least three months after surgery). The participants' sociodemographic and clinical characteristics are summarized in Table 1, and neuropsychological data are summarized in Supplementary Material, Table 1. Individual neuropsychological measurements for each test are expressed as z-scores and were normalized for age and educational level. A Z value below -1.64 ($p < .05$) is considered to reflect performance outside the normal range. An overview of the anatomical data for the aPFC and BDC groups is given in Fig. 1. It should be noted that the resection cavity in the BDC group could (in some cases) overlap with that in the aPF group. All patients gave their informed consent prior to inclusion and the study was performed in compliance with the tenets of the Declaration of Helsinki.

One of the study participants (patient PR, a 43-year-old, right-handed, married man with two children) is probably the only person in the world to have undergone very extensive bilateral prefrontal resection. His neuropsychological assessments (conducted three months after the last of several operations) did not reveal any long-term cognitive disorders (Supplementary Material, Tables 2 and 3) other than impaired verbal memory retrieval. He left school at the age of 16 and works as butcher in a supermarket. Following a generalized seizure in 2004, MRI showed that a DLGG had invaded PR's left frontal cortex; he therefore underwent partial resection of the left prefrontal cortex. In 2008 (i.e. 4 years after the first neurosurgical procedure), PR undertook an 18-month course of chemotherapy, in order to prevent the glioma from invading deeper structures. In 2010, a second neurosurgical operation was performed (under "wide-awake" conditions) because of the DLGG's progression into the left prefrontal cortex. The entire left prefrontal cortex was removed at this time. In 2014, PR underwent a third operation (again under "wide-awake" conditions) because of progressive