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TRACING THE BOUNDARIES OF EXECUTIVE FUNCTION FRACTIONATION: EVIDENCE FROM LESION-SYMPTOM MAPPING IN BRAIN TUMOR PATIENTS

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To my family and Lex-Mea mates, thank you.

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Abstract

Historically, the prefrontal cortex (PFC) has been considered as the cognitively "silent" part of the brain. Owing to the rapid advancements in neuroimaging techniques that revealed its extraordinary complexity and widespread connections with nearly all other brain regions, the PFC has been recognized as the central region in human cognition. However, one of the first approaches that brought knowledge about the functions of the PFC relied on the behavioural consequences observed in brain-damaged patients. Today, it is probably still the most powerful method for establishing the causal involvement of a brain region in the assumed cognitive function. Yet, mapping the PFC functions has been a difficult enterprise mainly because the underlying processes are closely interrelated and share common information resulting from lower-level processes. In neuropsychology, this issue has been even more problematic given the frequent use of clinical tests, which are often unable to isolate specific cognitive control components. Moreover, only recently the neuropsychological approach started to make use of objective, statistical methods similar to those employed in functional magnetic imaging, which however are not bias-free and therefore should be used with caution. Finally, in order for lesion-behavior relationship investigations to shed light on the putative specialization of different prefrontal areas, it is fundamental to address the issues arising across different cognitive neuroscience research methods.

The purpose of the present research project was to investigate, by means of different lesion-symptom mapping techniques, the behavioral consequences of focal frontal lobe injuries in order to tackle the currently debated issues regarding the PFC organization. In particular, in the first two studies we aimed at delineating the observed impairments as possible disruptions of common and/or distinct processes in order to test the dissociability of putatively distinct cognitive control processes. We focused on switching and response inhibition abilities, which according to the literature rely on left

and right prefrontal areas, and tested whether their impairments could be accounted for by more general task-setting and/or sustained attention impairments. In particular, we tested brain tumor patients with left and right prefrontal damage, and compared their performance with non-prefrontal patients and healthy controls. Critically, in order to exclude eventual lower-level processing difficulties known to emerge after lateralized brain lesions, verbal and spatial features of the employed tasks were mostly balanced. The results from both studies suggest that there is probably no specialized inhibitory or switching module hosted by a particular brain area; instead they show how performance on tasks requiring both inhibitory and switching abilities can be disrupted by a more general task-setting impairment supported by left prefrontal areas and their connections with posterior regions. Furthermore, inhibitory impairments, previously observed in patients with right prefrontal lesion, might alternatively be explained by sustained attention impairments.

In the last study, instead, we focused on finding out whether lesions in specific prefrontal areas could account for a general cognitive decline, as supported by unitary models of the PFC organization. In particular, we applied a latent variable analysis on distinct neuropsychological test scores in order to minimize the influence of low-level processing requirements and thus obtain a more pure measure of general cognitive functioning. Additionally, we examined the impact of surgical tumor removal on general cognitive functioning across different tumor histological types. The results confirmed previous findings on the impact of surgery on low-grade glioma. However, they also extend them by showing that surgery in left dorsolateral frontal areas causes a more prominent cognitive decline, regardless of the tumor histology. Taken together, the findings across all the three studies have highlighted a critical involvement of left-lateralized prefrontal areas in most of the high-level cognitive tasks we employed, event though the precise localization was somewhat different. However, the involvement of right prefrontal areas seemed critical in more sustained type of processing required to maintain attention to task-relevant events. This observation is in line with a more integrative, albeit lateralized, view of the PFC organization according to which higher,

associative types of processes rely on the interaction between frontal and posterior brain regions, but their left and right lateralizations reflect separate, specialized type of processing probably involved in more phasic type of processing, necessary to form and flexibly implement task-relevant associations, and sustained type of processing, needed to maintain the relevant features of the task in an active state.

CHAPTER 1

GENERAL INTRODUCTION

1.1 Organization of executive functions

Organizing and controlling our thoughts and actions are essential human abilities that allow us to cope with complex but also ordinary everyday life activities. Without them, learning new skills like playing an instrument, or simply creating a daily schedule, would become difficult or even impossible tasks. The processes underlying these abilities fall under the umbrella term of executive functions (EFs). EFs have been defined as a set of high-level cognitive processes that, by coordinating and controlling other lower-level processes, allow goal-directed behavior (Koechlin, Ody, & Kouneiher, 2003; Miller & Cohen, 2001; Stuss & Alexander, 2000). Almost two centuries ago, with the first descriptions of patients with lesions in the frontal lobes (Harlow, 1999; Luria, 1966), the prefrontal cortex (PFC) was posited as the seat of the goal-directed behavior. Today, however, it is clear that the neural processes underlying this type of adaptive behavior rely on the interactions between the prefrontal and other cortical and subcortical regions (Bonelli & Cummings, 2007; Dosenbach, Fair, Cohen, Schlaggar, & Petersen, 2008; Heyder, Suchan, & Daum, 2004). Different models have been put forward to explain the functional organization of EFs and how they are implemented within the PFC and its interactions with the rest of the brain. According to one view, EFs can be fractionated into distinct cognitive functions, which rely on partially segregated PFC networks. On the contrary, alternative accounts suggest a more unitary view of the PFC, which assumes undifferentiated roles of PFC areas.

1.1.1 Executive function integration within the prefrontal cortex

One of the most influential unitary models of the PFC was suggested by Duncan and colleagues (Duncan & Owen, 2000), according to whom most of PFC regions are part of a "multiple-demand system" that supports a variety of novel and complex tasks. In particular, they suggest that neurons in a large part of the PFC are programmable or adaptable on the basis of currently relevant behavioral demands. This adaptive coding hypothesis has been corroborated by a great amount of neurophysiological and neuroimaging evidence. For example, it has been observed that with behavioral training in monkeys, the activity of neurons across distributed lateral prefrontal regions start to code information relevant for the current task after relatively little experience (Freedman, Riesenhuber, Poggio, & Miller, 2001). Moreover, the neural responses can be easily adapted to code different information, relative to the current task demands (Asaad, Rainer, & Miller, 2000). According to the authors, this flexibility and adaptability of PFC neurons may explain the fact that different neuroimaging studies have observed similar patterns of PFC engagement during tasks with very different cognitive demands. Recently, based on functional imaging in humans, they demonstrated that selected regions within the fronto-parietal cortex exerted multiple-demand coding of all task features that were necessary to complete the task (Woolgar, Thompson, Bor, & Duncan, 2011). Moreover, when task demands were made more difficult, the representations within the same regions were adjusted so as to cope with an increase in perceptual (Woolgar, Hampshire, Thompson, & Duncan, 2011) and task rule complexity (Woolgar, Afshar, Williams, & Rich, 2015), in line with the adaptive coding hypothesis. Finally, it was also observed that brain regions throughout the multiple-demand system were broadly engaged across a wide range of tasks, thus providing strong evidence for a functional generality of those areas (Fedorenko, Duncan, & Kanwisher, 2013). In line with this evidence, the authors proposed another application of the adaptive coding function of the PFC according to which the multiple-demand system provides a processing basis for general (i.e., *'g'*) fluid intelligence factor, assumed to contribute across different cognitive abilities (Duncan, 2005; Duncan et al., 2008). In particular,

they hypothesize that most of the EF impairments observed in prefrontal patients can be accounted for by a fluid intelligence loss (Roca et al., 2010); however, as discussed later on (paragraph 1.2.1), this is not always the case (Barbey et al., 2012; Cipolotti et al., 2016).

1.1.2 Executive function segregation within the prefrontal cortex

Several other theories supporting the segregation of EFs have proposed that different PFC regions are recruited under various task demands and contexts. For instance, different suggestions have been made regarding the functional organization of the PFC along the rostral-caudal axis, in terms of hierarchical gradients of abstraction (David Badre & D'Esposito, 2009; Christoff, Keramatian, Gordon, Smith, & Mädler, 2009; Nee & Brown, 2012), rule complexity (Burgess, Dumontheil, & Gilbert, 2007; Koechlin & Summerfield, 2007) and degree of automaticity (Jeon & Friederici, 2013, 2015). Others have argued for a ventral-dorsal functional organization that associates lower-level executive functions, like maintenance of information in short-term memory, with more ventral prefrontal areas, and other complex information-processing operations with dorsal prefrontal areas (O'Reilly, 2010; Michael Petrides, 2005; Rowe, Toni, Josephs, Frackowiak, & Passingham, 2000; Wagner, Maril, Bjork, & Schacter, 2001). Distinctions along the medial-lateral axis have been mostly related to affective/motivational processing differences between tasks (Chan, Shum, Toulopoulou, & Chen, 2008; O'Reilly, 2010). Finally, fractionation of the PFC functions along the left-right axis has mainly been based on domain-based specialization, which has linked the left and right prefrontal areas to verbal and spatial processing demands (Kelley et al., 1998; Wagner et al., 1998). However, more recently, drawing on studies with frontal patients, Stuss and Alexander (2007) localized three putatively independent EFs, task-setting, monitoring and energizing (not strictly executive), to left lateral, right lateral and medial prefrontal areas, respectively. Importantly, the left-lateralized task-setting, which reflects more transient, task-related processes (e.g., creating and selecting task relevant

rules) and the right-lateralized monitoring, which reflects more sustained cognitive control processes (e.g., maintaining and evaluating goal-directed behavior) have shown to maintain their prefrontal lateralization regardless of the verbal and spatial characteristics of the task (Ambrosini & Vallesi, 2016a, 2016b, Capizzi, Ambrosini, Arbula, Mazzonetto, & Vallesi, 2016a, 2016b; Vallesi, Arbula, Capizzi, Causin, & D'Avella, 2015).

1.1.3 Towards a common segregation and integration framework

A theoretical line that investigates common and shared variance among putatively distinct EF components has forged the "unity and diversity" EF framework (Friedman & Miyake, 2000). By means of a latent variable approach, the authors of this framework showed that distinct components of EFs, although being robustly correlated to one another (i.e., showed unity), were nevertheless tapping separate construct (i.e., also showed diversity). Importantly, fluid intelligence has shown to be only partially related to the Common EF (i.e., unity) factor and to one of the three separable EF factors (N. P. Friedman et al., 2006), thus adding evidence against the hypothesis that EFs and fluid intelligence are mostly overlapping constructs. Although the relevance of this framework in denoting the fractionation of EFs is considerable, it is however relatively blind to the anatomo-functional organization of these components within the PFC (but see (Reineberg, Andrews-Hanna, Depue, Friedman, & Banich, 2015; Reineberg & Banich, 2016).

With recent advancements of methods exploring correlations in neural activity between distant brain regions (i.e., functional connectivity), the segregated (i.e., modular) and integrated (i.e., unitary) views of the PFC, and brain functional organization in general, have been shown to be complementary (Bertolero, Yeo, & D'Esposito, 2015; Cohen & D'Esposito, 2016; Friston, 2009). In particular, some brain regions were found to be tightly coupled and densely interconnected, thus forming brain modules, whilst others were found to be coupled across multiple brain modules

(i.e., network hubs), allowing communication and integration among them (Sporns, 2013). It has been observed that hubs within the fronto-parietal network, which were integrating information and coordinating connectivity across distinct brain modules, were located in regions whose activity was associated with many different cognitive functions (Bertolero et al., 2015; Cole et al., 2013; Yeo et al., 2015). Conversely, activity in regions that reflected modular connectivity did not increase during the engagement of different cognitive functions, thus confirming their functional autonomy and modularity (Bertolero et al., 2015). Moreover, balancing between network segregation and integration was found to be associated with cognitive demands of the current task (Cohen & D'Esposito, 2016). In particular, the authors observed that increased network segregation and local, within-network communication was related to motor execution, whereas integrative, between-network communication was associated with working memory.

Sophisticated functional connectivity analyses have made a qualitative leap in understanding the complexity of brain functional organization and recently these techniques have started to unveil the neural mechanisms underlying behavioral deficits after brain damage. In the next section I will review different neuropsychological studies that investigated the PFC functional organization, with a focus on some recent advancements in the neuropsychological approach, and how they further increased the knowledge of the way the brain mediates EFs.

1.2 The contribution of neuropsychological studies in mapping higher cognitive functions

The valuable information derived from neuropsychological studies resides in uncovering the necessity of the affected region for the ability under investigation. Indeed, mapping of putatively distinct/common EFs to specific/broad PFC regions has often been achieved within prefrontally lesioned patients. However, the heterogeneity of findings

regarding the PFC processes (e.g., Stuss et al., 2002) made evident the complexity behind behavioral consequences of prefrontal lesions. On one side, low correlation between EF tests across different prefrontal patient groups, single-case and group EF dissociations brought strong evidence for a fractionated view of PFC functions (Burgess, Alderman, Evans, Emslie, & Wilson, 1998; Hamilton & Martin, 2005; Geddes, Tsuchida, Ashley, Swick, & Fellows, 2014; Godefroy, Cabaret, Petit-Chenal, Pruvo, & Rousseaux, 1999; Robbins, Weinberger, Taylor, & Morris, 1996). On the other side, broader deficits across a range of EF measures have been proposed to reflect common, unitary function impairments, related to goal maintenance (Duncan, 1986) and fluid intelligence loss (Duncan, Emslie, Williams, Johnson, & Freer, 1996).

1.2.1 Insights into executive function segregation and integration based on lesion studies

Fluid intelligence is known to suffer after frontal lobe damage (e.g., Gläscher et al., 2009) and also to correlate positively with performance on EF tests (Duncan et al., 1996; Salthouse, 2005). However, studies investigating the relationship between fluid intelligence loss and EF impairments in patients with prefrontal damage do not suggest a complete overlap between these two constructs (Barbey et al., 2012; Roca et al., 2010). In particular, while impairments on some widely used EF tests were thoroughly accounted for by fluid intelligence loss, other deficits remained even after the *g* factor was partialled out (Roca et al., 2010). Furthermore, the investigation of brain-behavior relationships of fluid intelligence and executive function in brain-damaged patients (Barbey et al., 2012) showed that although both measures seemed to rely on a shared distributed fronto-parietal network, other distinct regions were recruited selectively by each domain, suggesting partial independence of the two constructs. Finally, in a recent study focusing on different measures of inhibitory control, the authors investigated whether fluid intelligence was a substantial contributor to impairments on those tasks (Cipolotti et al., 2016). Although they found significant correlations between the

performance on inhibitory tasks and fluid intelligence measures, patients with prefrontal lesions remained more impaired with respect to healthy controls even when fluid intelligence impairments were controlled for. Altogether, these findings suggest that differences observed among patients with PFC damage cannot be accounted for entirely by fluid intelligence or a common EF loss.

A larger number of studies on brain-damaged patients focused on isolating distinct component processes of EFs and testing their segregation both behaviorally and in relation to their PFC localization (Aron, Fletcher, Bullmore, Sahakian, & Robbins, 2003; Aron, Monsell, Sahakian, & Robbins, 2004; Reverberi, Lavaroni, Gigli, Skrap, & Shallice, 2005; Robinson et al., 2015; Robinson, Shallice, Bozzali, & Cipolotti, 2012; Shallice, Stuss, Picton, Alexander, & Gillingham, 2007; Swick, Ashley, & Turken, 2008; Vallesi et al., 2007). One of the most fruitful investigations of PFC functional fractionation was based on systematic and exhaustive neuropsychological assessments conducted on patients with refined PFC lesion localizations (Alexander et al., 2005; Stuss et al., 2005; Stuss & Alexander, 2007). By using a simple reaction time (RT) task and modifying it progressively, the authors managed to isolate distinct impairments and associate them with specific PFC lesions. For instance, throughout different tasks, patients with superior medial PFC lesions showed a consistent RT slowing, which did not improve even with a warning signal, suggesting a disruption of an energization process needed to initiate and sustain the responses during the task. On the other hand, as briefly mentioned in the previous section, left-lateralized and right-lateralized PFC lesions were associated with distinct impairments, the former observed as deficit in setting up stimulus-response contingencies, and the latter as deficit in monitoring and adjusting ongoing performance. Regardless of their different hemispheric lateralization, these higher-order prefrontal processes are assumed to be domain general because of their interaction with and coordination of domain-specific, lower-level processes, which was also recently confirmed in healthy adults (Ambrosini & Vallesi, 2016a, 2016b; Capizzi, Ambrosini, Arbula, Mazzonetto, & Vallesi, 2016a, 2016b; Vallesi et al., 2015). However, other more recent neuropsychological studies report some contrasting results regarding

this domain-general nature of lateralized PFC functions (Geddes et al., 2014; Tsuchida & Fellows, 2012). In particular, the authors of these studies observed that, even though lesions to left and right PFC areas caused distinct EF impairments, as predicted by the fractionation view, the impairments were strongly related to verbal and spatial domain-specific characteristics of the tasks, supporting a fractionated albeit material-specific cognitive control organization within the PFC. Still, not many lesion studies on prefrontal patients investigated or controlled for the influence of low-level (i.e., verbal and spatial) processing on different higher-level executive functions, and this was one of the research questions in the first two studies presented in this thesis (chapters 2 and 3).

1.2.2 Implications from lesion induced changes in functional connectivity on executive function organization

Recently, it has been recognized that physiological and functional changes in anatomically intact brain regions distant from the lesion (i.e., diaschisis) play an important role in investigating brain functional organization through lesion studies (see Carrera & Tononi, 2014 for recent review). As introduced in the previous section, advancements in neuroimaging techniques uncovering brain functional connectivity, have brought important findings on how focal brain lesions modify larger-scale brain networks and how these network modulations affect behavior (see Baldassarre, Ramsey, Siegel, Shulman, & Corbetta, 2016 for recent review). Importantly, it has been observed that lesions in critical areas, important for communication between distinct, more specialized brain regions, can cause disruptions of network organization throughout the brain (Gratton, Nomura, Pérez, & D'Esposito, 2012). Moreover, patients with lesions in those areas exhibit more widespread cognitive deficits with respect to patients whose lesions cover brain regions involved in more local processing networks (Warren et al., 2014). These findings are in line with the emerging complementary view of functional segregation, reflecting the specialization of localized brain areas, and functional integration, relying on interactions between and coordination of distinct

brain areas (Bullmore & Sporns, 2012; Deco, Tononi, Boly, & Kringelbach, 2015; Park & Friston, 2013).

Even though there are not many studies that investigated the fractionation of EFs by means of functional connectivity, there is some recent evidence that different EF components are supported by distinct resting-state networks in healthy individuals (Reineberg et al., 2015; Reineberg & Banich, 2016). However, up till now there is no evidence of whether abnormal functional connectivity in prefrontal patients is associated with impairments on distinct EF measures. Nevertheless, results from previous neuropsychological studies clearly show that no unitary cognitive control process can account for different EF deficits observed in prefrontal patients, and, based also on functional connectivity evidence, it is supposable that delimited PFC regions support broader albeit dissociable EF processes.

1.3 Project overview

The present research project is devoted to understanding the behavioral consequences of focal frontal lobe injuries and how they can shed light on the previously outlined and still debated issues regarding the EF organization within the PFC. The main approach was to assess few relatively well-defined cognitive control processes, which according to the literature rely on distinct prefrontal regions, and to try to relate them to other broader, but closely related processes in order to investigate their common or dissociable neural underpinnings. In the first two studies we investigated the processes underlying task-switching and response inhibition which, at least according to some literature, rely on left and right prefrontal areas, respectively. By means of different lesion-symptom mapping techniques, we investigated whether their disruption could be accounted for by more general decisional and/or attentional impairments. It is important to underline that in all of the tasks we employed, verbal and spatial features were mostly balanced so as to be able to fairly compare patients with left and right frontal lesions, while controlling for lower-level material- or task-

specific processes. In the last study, instead, we focused on finding out whether lesions in specific prefrontal areas could account for a general cognitive decline, as supported by unitary models of the PFC organization. Additionally, we examined the impact of surgical tumor removal on general cognitive functioning across different tumor histological types, which previous studies have shown to be determinant for post-surgical cognitive decline. Since all three studies were carried out on brain tumor patients, an important aspect that needs to be addressed is the reliability of this population to study and localize brain functions. Recently, this issue has been debated within the neuropsychological approach (Duffau, 2011; Karnath & Steinbach, 2011; Shallice, Mussoni, D'Agostino, & Skrap, 2010; Shallice & Skrap, 2011) and even though a systematical investigation across different etiologies has proven no significant difference in performance on "frontal" executive tests (Cipolotti et al., 2015), grouping of tumor and stroke patients for more fine-grained localization studies was not investigated. However, due to a different distribution of stroke and tumor lesions across cortical and subcortical areas, their grouping might bias the location of the critical region if not well balanced (see Mah, Husain, Rees, & Nachev, 2014, for a discussion on stroke patients). Therefore, our choice was to limit our sample to patients who had to undergo brain surgery for tumor resection, excluding recurrence. Even though all patients were tested before and after the operation, we did not expect to find the effect of surgery since it was mainly reported in low-grade tumor types, due to their slowly growing and infiltrative activity. Still, the effect of surgery on general cognitive functioning after tumor resection in particular areas was never explored by means of lesion-symptom mapping techniques, and this was one of the aims of the last study.

Altogether, the main findings of this work point toward an integrative PFC organization, even though functional specializations have been observed mainly between left and right PFC regions.

CHAPTER 2

QUESTIONING THE SELECTIVE ROLE OF DISTINCT PREFRONTAL AREAS IN RESPONSE INHIBITION

2.1 Introduction

Even though it is well acknowledged that executive functions (EFs) depend on the integrity of the prefrontal cortex (PFC), it has been a difficult enterprise to causally map distinct cognitive processes to dedicated brain regions within the frontal lobes. Partly this is due to the difficulty in defining separable functions and their presumed underlying processes. Moreover, the majority of the tests aimed at investigating a certain EF lack the specificity required to identify unequivocally the process of interest and its neural correlates. Inhibition is an important example of a widely accepted EF for which there is still an ongoing debate regarding its discreteness as a cognitive construct and its underpinning neural mechanisms (Aron, Robbins, & Poldrack, 2014a; Hampshire & Sharp, 2015; Swick & Chatham, 2014).

A major problem in studying response inhibition is that it occurs alongside different related control processes like response selection, sustained attention and working memory (Chambers, Garavan, & Bellgrove, 2009). The adequacy of classic inhibitory paradigms, such as Go/No-Go (GNG) and Stop Signal Task (SST), in assessing response inhibition without entangling other closely related processes has been controversial (Criaud & Boulinguez, 2013; Mostofsky & Simmonds, 2008). Although these paradigms have brought considerable evidence for a sub-set of frontal areas specialized in inhibiting behavior, results from lesion and functional imaging studies do not show consistent results regarding the localization of a putative inhibitory module (see Bari & Robbins, 2013, for a comprehensive review).

One of the most prominent models of inhibitory control highlights the critical role of the right inferior frontal cortex (rIFC), along with that of pre-SMA and the sub-thalamic nucleus, in response inhibition tasks (Aron, Robbins, & Poldrack, 2004). According to this model, the rIFC is proposed to suppress a motor response in a top-down manner once a relevant environmental or internal signal has been captured. In support of this model, many neuroimaging studies show reliable activations of rIFC during both GNG and SST paradigms (Aron et al., 2004; Buchsbaum, Greer, Chang, & Berman, 2005; Nakata et al., 2008; Rubia et al., 2001; Rubia, Smith, Brammer, & Taylor, 2003). Evidence also comes both from virtual and real lesions studies that suggest a critical involvement of the rIFC in response inhibition (Aron et al., 2003; Chambers et al., 2006; Molenberghs et al., 2009).

Other studies have, however, challenged the rIFC exclusive role in response inhibition by providing evidence that the same areas are also being recruited when the environment needs to be monitored for infrequent stimuli that require response initiation, and not only response inhibition (Braver, Barch, Gray, Molfese, & Snyder, 2001; Chatham et al., 2012; Dodds, Morein-Zamir, & Robbins, 2011; Hampshire, Thompson, Duncan, & Owen, 2009; Sharp et al., 2010; Walther, Friederich, Stippich, Weisbrod, & Kaiser, 2011). This raised the issue of whether the engagement of rIFC areas in GNG and SST tasks may be due to "oddball" effects (Mostofsky & Simmonds, 2008) and more generally to the recruitment of the ventral attentional network involved in detecting behaviorally relevant stimuli (Corbetta & Shulman, 2002). Two recent studies have explored the involvement of the rIFC in paradigms similar to GNG and SST tasks that require a response to be initiated as opposed to inhibited when an infrequent target is presented within a sequence of more frequent distractors (Erika-Florence, Leech, & Hampshire, 2014; Hampshire, 2015). By varying systematically attentional and inhibitory demands of the tasks, both studies found that target detection and response inhibition activated to the same level the rIFC area and increased functional connectivity between sub-regions within that area. Based on these results the authors suggested that the rIFC regions are unlikely to host a specific inhibitory module but instead support a broader set of cognitive control functions through dynamic interactions within distributed functional networks.

In support of this idea, multiple neuropsychological studies failed to find SST or GNG impairments in patients with brain damage including rIFC (Dimitrov et al., 2003; Floden & Stuss, 2006; Krämer et al., 2013; Picton et al., 2007). While the study by Kramer and colleagues (2013) did not find unilateral PFC areas to be critically involved in response inhibition, they reported more frequent Go omissions in right versus left prefrontal patients in a condition with infrequent No-Go trials. This result goes in line with a more general target detection function of right lateral PFC areas (Shallice, Stuss, Alexander, Picton, & Derkzen, 2008; Stuss et al., 2005; Vallesi, 2012). In other studies, however, the authors observed different areas to be involved in inhibitory impairments. In particular, Picton and colleagues (2007) have found that patients with left superior medial PFC damage made significantly more false alarms in a GNG task with respect to right inferior frontal patients and healthy controls. Conversely, Floden and colleagues (2006) demonstrated that damage to right superior medial frontal regions impaired inhibitory control in the SST. Finally, the study by Swick and colleagues (2008) examined the performance of patients with left IFC damage on a GNG task in comparison with a group of orbitofrontal patients and healthy controls. The authors found that left IFC patients responded more often to No-Go stimuli than controls and interpreted this result as evidence against the dependence of inhibitory control exclusively on rIFC or superior medial areas. Based also on the results from their meta-analysis, these authors suggested that the left IFC role is also critical in suppressing prepotent responses. However, this finding was recently rebutted by Aron and colleagues' argument (2014b) that left frontal patients might have been impaired because of the task's No-Go frequency (50% and 10%), which required more decision-making processes, and because of its verbal WM demands (not responding to one letter of the alphabet).

As discussed earlier, a possible explanation of these contrasting results could reside in the weakness of the currently used inhibitory tasks to disentangle other intrinsically related cognitive processes (Criaud & Boulinguez, 2013). While the typically found right prefrontal lateralization of inhibitory processes could be accounted for by a more general role of right prefrontal areas in detecting critical events (Langner & Eickhoff, 2013; Shulman et al., 2009; Vallesi, 2014), the finding of an engagement of left prefrontal areas in the same tasks

(Meffert, Hwang, Nolan, Chen, & Blair, 2016; Swick et al., 2008; Zhang & Li, 2012) may have risen from more left lateralized co-occurring processes like task setting and response selection, or verbal WM requirements (Fletcher, Shallice, & Dolan, 2000; Mostofsky & Simmonds, 2008; Smith, Jonides, & Koeppe, 1996; Vallesi, Mcintosh, Crescentini, & Stuss, 2012). Moreover, given the correlational nature of the evidence from neuroimaging studies, the hypothesis of a specialized inhibitory module localized in the rIFC can unlikely be ruled out solely based on this methodological approach. Therefore additional lesion studies covering appropriately left and right prefrontal areas and investigating both inhibitory and other potentially related processes are critical for determining whether successful response inhibition depends critically on one specific lateralized prefrontal area.

To test this hypothesis, in the present neuropsychological study we adopted a simple GNG task design in which there was a single Go stimulus and a single No-Go stimulus and their presentation was equiprobable. We chose to use a 50% GNG probability design for two reasons. First, we wanted to avoid ”oddball” effects so that failure in inhibiting responses to infrequent No-Go stimuli would not be confounded with a No-Go detection problem. The second reason was to separate eventual response selection deficits from inhibitory ones, since the former should be observed as both frequent false alarm and target omission errors, while the latter only as a higher false alarm rate. Even though the majority of the task designs requiring inhibitory control build a prepotent response tendency by reducing the frequency of No-Go trials, this has been shown as an unnecessary manipulation in simple GNG task designs since different studies observed a strong motor activation related to No-Go events regardless of their frequency (Boulinguez et al., 2008; Boulinguez et al., 2009; Jaffard et al., 2007; see Criaud & Boulinguez, 2013 for a discussion). Furthermore, in order to assess a possible target detection deficit, and to be able to dissociate it from an inhibitory impairment, we administered a simple RT task in which a target stimulus, requiring a fast response, was preceded by a warning stimulus, which did not require a response. The rationale for the selection of this task, also known as the Foreperiod (FP) task, was twofold. First, it is a simple target detection task in which sustained attention is crucial for fast and accurate responses, and during which sustained

attention lapses should be seen as failures in target detection. Second, it has been observed that warning stimuli, even if completely predictable, induce motor activation and can cause false alarms (Boulinguez et al., 2008). Therefore possible inhibitory difficulties could be observed also as responses to warning stimuli and/or anticipations of the target stimuli. Moreover, different neuropsychological studies have shown a specific target occurrence monitoring impairment in right prefrontal patients in terms of RTs (Stuss et al., 2005; Vallesi et al., 2007). In particular, when the time interval between the warning and the target stimuli varies randomly and equiprobably (as in the typical variable FP paradigm), RTs get faster as the FP increases, given that the probability of target occurrence increases (i.e., FP effect). Right prefrontal patients do not show this typically found FP effect, probably because they do not keep track efficiently of the increasing probability of target occurrence. However, when the FP duration is kept constant (i.e., fixed FP paradigm), this FP effect is not observed and thus right prefrontal patients' RT performance is in the normal range, while superior medial frontal regions seem to be critically involved in maintaining a relatively short RT even for long fixed FPs (Stuss et al., 2005). Therefore, in our FP task design, we included both fixed and variable FP durations in order to verify and eventually replicate this FP effect reduction in right prefrontal patients.

These two tasks were administered to two groups of patients with either right prefrontal (RPF) or left prefrontal (LPF) lesions and their performance was compared to that of a group of patients with non-prefrontal (NPF) lesions and that of a carefully matched healthy control group. Since all of our patients had to undergo a surgical tumor removal, they were all tested twice (as well as the controls, for the sake of comparability and to take into account possible learning effects): a few days before and a few days after the operation, in order to disentangle tumor effects from possible surgery effects. Based on the two diverging hypotheses outlined in the introduction, we predicted two possible types of impairment in the RPF group of patients (Figure 1A presents the predictions of the two hypotheses): 1) more frequent responses to both warning and No-Go stimuli and normal target and Go detection, if the damaged areas are critically involved in response inhibition; 2) frequent Go and target omissions and normal warning and No-Go stimuli response

withholding, if the damaged areas support more general target detection processes. Given the above reviewed neuropsychological and imaging findings of a possible left PFC involvement in response inhibition, it can be supposed that alternatively the LPF patients will be the ones exhibiting more response withholding errors. However, if those areas underlie processes related more to task setting and response selection, LPF patients should produce equally often false alarms and target omissions. Figure 1B presents the predictions for the LPF lesions hypotheses.

An important aspect that needs to be taken into account when studying performance of patients with lateralized lesions is the type of material used to detect their impairments. It has been acknowledged that some of the prefrontally mediated processes (e.g., working memory) might rely critically on left and right regions when verbal/non-spatial and spatial material is employed, respectively (Babcock & Vallesi, 2015; Kelley et al., 1998; Robinson, Shallice, Bozzali, & Cipolotti, 2012; Sandrini, Rossini, & Miniussi, 2008). To the best of our knowledge, this possible aspect of inhibitory control has not been well controlled in many of the previous neuropsychological studies. Therefore, patients in the current study were tested on two versions of a GNG task that employed identical stimuli (i.e., letters) presented above or below a central fixation point. In the verbal/non-spatial task they had to attend to the identity of the letter rather than to its position, whereas the spatial task required them to attend to the location of the letter, regardless of its identity. In this way, we could disentangle possible impairments in general spatial or non-spatial processing from inhibitory ones, while controlling for other lower-level processes.

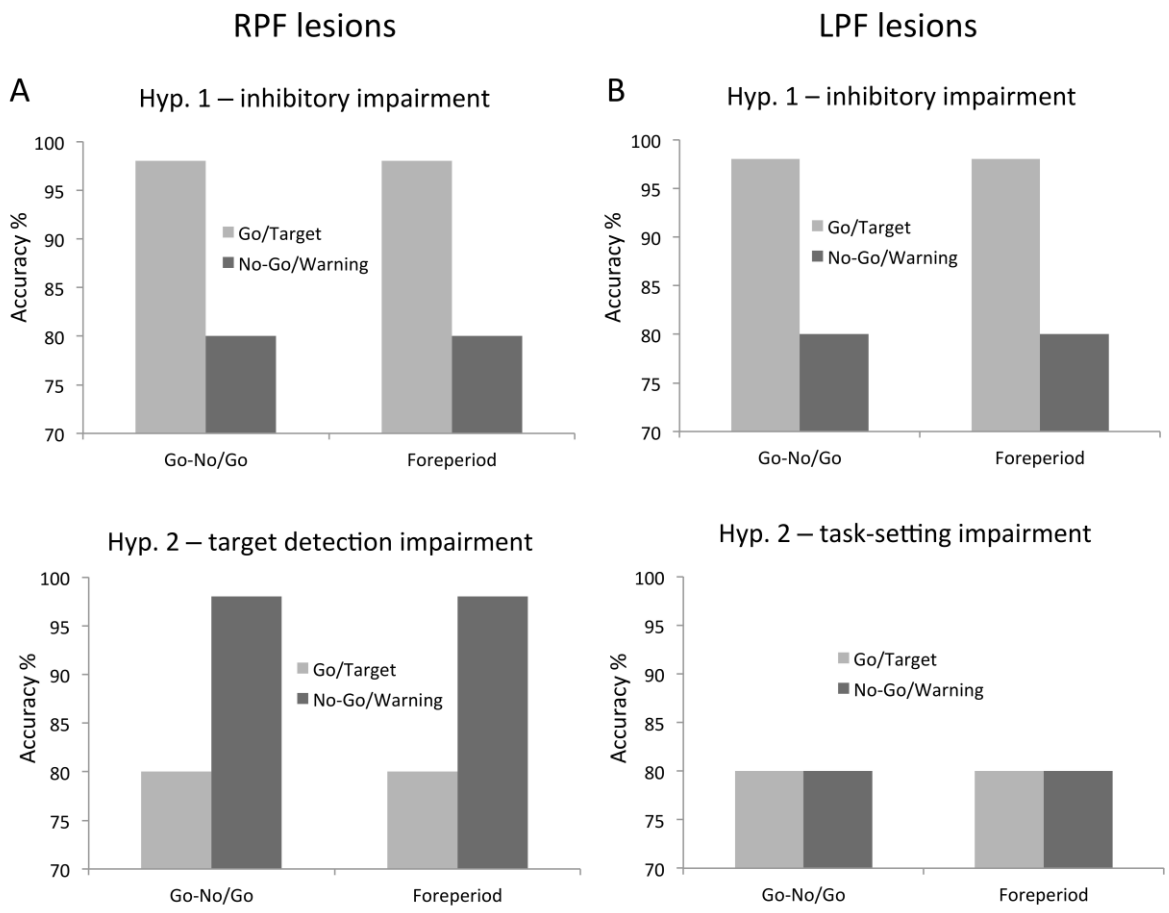

Figure 1. Predictions of the inhibitory impairment and target detection impairment hypotheses after RPF damage (A), and the inhibitory impairment and task-setting impairment hypotheses after LPF damage (B).

2.2 Materials and methods

2.2.1 Participants

Forty-four patients undergoing a brain tumor operation at the University Hospital of Padova participated in the study. The inclusion criteria were: the presence of an age ranging from 18 to 85 years, no previous neurological or psychiatric disorders and absence of recurring brain lesions. A posteriori, we excluded seven patients who were not able to complete the second testing session for post-surgical complications or organizational reasons. According to their histopathological exam, the remaining thirty-seven patients had high-grade gliomas (n = 18), low-grade gliomas (n = 7), meningiomas (n = 8) and metastases

(n = 4). Patients were divided in three groups: left prefrontal (LPF, n = 10), right prefrontal (RPF, n = 11) and non-prefrontal (NPF, n = 16), according to the reconstructed tumor location that was established by taking into account the area with the highest number of lesioned voxels and the location of the lesion center of mass. Figure 2 shows the lesion overlap maps for LPF, RPF and NPF patients. For two patients without the MRI scans the localization of the lesion was based on the clinical neuroradiological report. Tumor grade distribution (high vs. low) was not significantly different across the three groups of patients (p = .3, Fisher's exact test), nor was the volume of the lesion [$F(2, 32) = 2.82$, p = .07, η^2_p = .15]. Additionally, 41 neurologically intact participants, matched for age (t-test's p = .34), sex (χ^2 = 2.33; p = .13) and years of education (t-test's p = .13), were tested as control participants[1]. All but two participants were right-handed (one from the RPF group and one from the control group), as assessed by the Edinburgh Handedness Inventory (Oldfield, 1971). Patients' demographical and etiological data are reported in supplementary material Table S1.

All participants performed two identical testing sessions, in between which patients underwent the surgical operation. During both testing sessions all participants underwent a neuropsychological evaluation on general cognitive status, premorbid intelligence, memory, language, attention and executive functions (scores reported in supplementary material Table S1), after which the experimental tasks were administered. All participants gave their written informed consent before the beginning of the first testing session. The study was approved by the Bioethical Committee of Azienda Ospedaliera di Padova and was conducted according to the guidelines of the Declaration of Helsinki.

[1] Due to technical issues 3 control participants did not perform all tasks in the second session. Missing data from these subjects were replaced with values predicted from regression derived from observed data. Control analyses were performed by excluding these 3 subjects and none of the significant results reported changed.

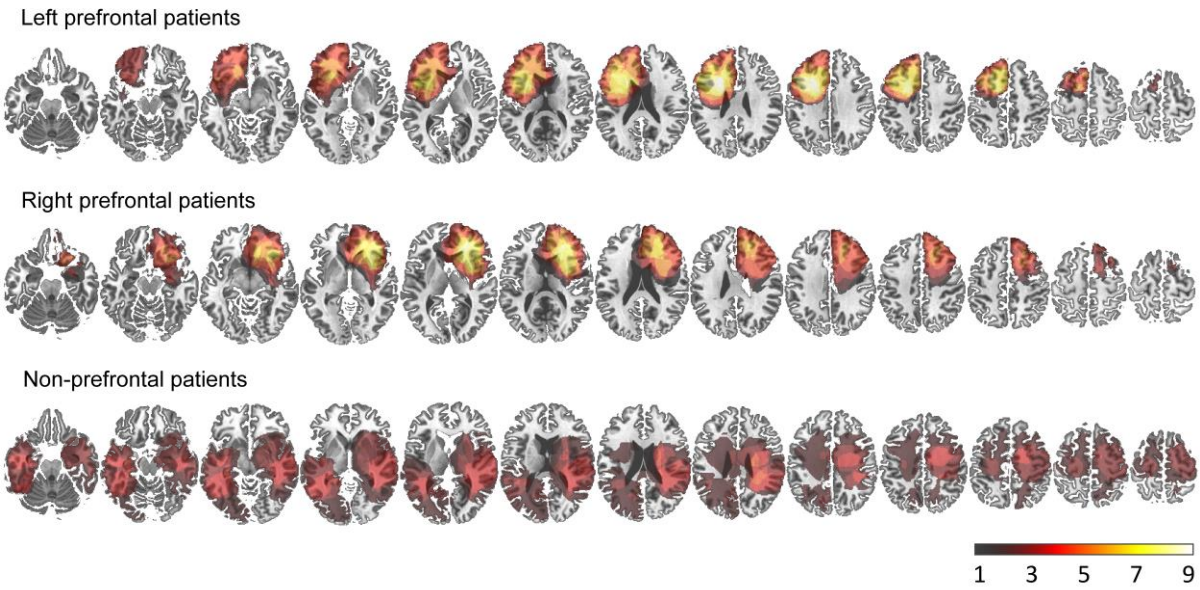

Figure 2. Lesion overlap maps for left prefrontal, right prefrontal and non-prefrontal patient groups. The color bar indicates the number of patients whose lesions overlap on one voxel.

2.2.2 Experimental investigation

The experimental testing session consisted of a Foreperiod task and a Go/No-Go task. The order of presentation was counterbalanced between subjects. All tasks were presented on a Dell Intel Core laptop with a 17 inch screen using E-Prime 2 software (Schneider, Eschman, & Zuccolotto, 2002). Participants were seated in front of the computer screen at approximately 60 cm in a quiet and normally illuminated room. Three patients, one from each group, were tested after the surgery in their hospital room due to transport limitations.

Go/No-Go task. Two uppercase letters (A and E), subtending an average visual angle of 0.8° x 0.8°, were presented individually, approximately 2.8° above or below a centrally positioned fixation point (asterisk) that constantly remained on the screen. The stimulus was presented for 1000 ms, followed by a 2500 ms inter-stimulus interval. Response collection lasted for 3000 ms from stimulus appearance. Participants had to respond according to specific task instructions that varied across two task conditions: a letter identity task required them to press the spacebar for one specific letter (Go stimulus) and

to withhold the response for the other (No-Go stimulus) while ignoring their position, whereas the letter position task required them to respond to one specific position of the letter and not to the other, regardless of the letter identity (Figure 3). The two tasks were presented separately and each task comprised two blocks of trials that had reversed Go and No-Go stimuli. Each block consisted of 24 trials, preceded by 4 practice trials, for a total of 96 trials. Both letters and both positions were equally distributed across trials, which resulted in an equal number of Go and No-Go stimuli. Data from one RPF patient were discarded due to technical issues.

Foreperiod task. At the beginning of each trial, a visual cue (2 cm × 2 cm 'XX') was displayed at the center of the screen together with an auditory warning stimulus (a 1500 Hz pure tone) presented for 50 ms through laptop internal speakers with the volume set at a constant level for all participants. The double X remained on the screen for 1000 or 3000 ms. The duration of the FP was variable (i.e., equiprobable and random) in one block of 60 trials, and fixed in two blocks of 30 trials, one per each FP duration. The order of presentation of the three blocks was counterbalanced between participants. The target stimulus, which appeared at the end of the FP, was a downward pointing white arrow (with maximum length and width of 2 cm) and the participants were instructed to respond to it by pressing the spacebar as quickly as possible. Figure 4 describes the variable FP paradigm. The target remained on the screen for 2000 ms or until the response was detected, and was followed by a 2000 ms long inter-trial interval (ITI). Responses were collected until the end of the ITI.

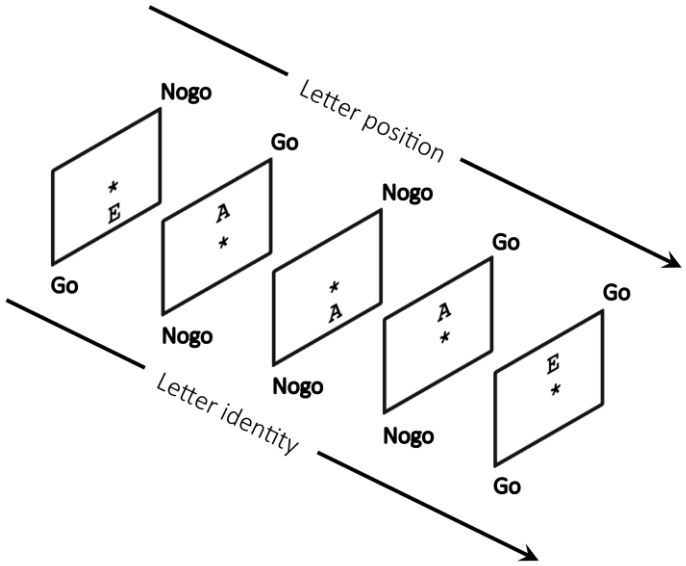

Figure 3. Letter position and letter identity Go/No-Go tasks.

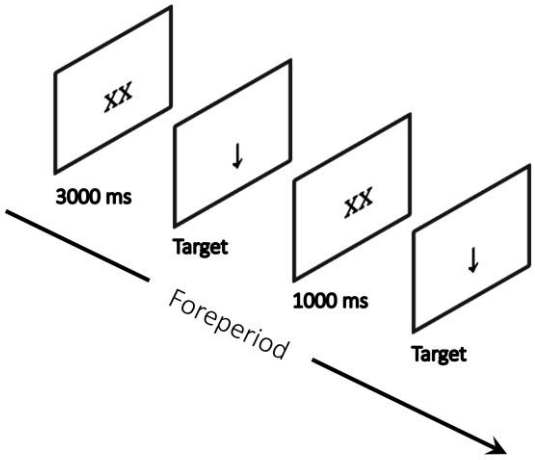

Figure 4. Variable Foreperiod task.

2.2.3 Analyses of the behavioral data

Analyses were performed on accuracy and reaction time (RT) data, filtered for anticipations (RT<150ms) and arcsine- and log-transformed, respectively, in order to improve normality. Accuracy data were analyzed by means of a repeated measures ANOVA separately for the GNG task and the FP task. In both analyses, Task (letter identity vs. letter position for the

GNG task; fixed FP vs. variable FP for the FP task), Stimulus type (Go vs. No-Go for the GNG task; warning vs. target for the FP task; withheld responses for No-Go and warning stimuli are considered as correct) and Surgery (pre- vs. post-surgery performance) were included as within subject variables, and Group (LPF, RPF, NPF and Controls) as a between subjects variable. The RT analyses were performed separately for the GNG task and the FP task only on Go and target trials, respectively. In both analyses, Task (letter identity vs. letter position for the GNG task; fixed FP vs. variable FP for the FP task) and Surgery (pre- vs. post-surgery performance) were used as within subject variables and Group (LPF, RPF, NPF and Controls) as a between subjects variable. The FP task analysis included an additional within subject FP duration variable (short vs. long).

Additionally, we focused our analysis on the sensitivity and response bias measures from the Signal Detection Theory (SDT), which are usually confounded in standard performance measures, in order to better characterize possible impairments observed in terms of false alarms and target misses (Snodgrass, Levy-Berger, & Haydon, 1985). In particular, the sensitivity measure *d'* provides an estimate of the ability to distinguish Go and No-Go stimuli while controlling for possible differences in response bias, with a *d'* of 0 representing chance performance. The response bias measure *c* on the other hand, reflects a general tendency in initiating or withholding the response without the impact of stimulus discriminability, with low and high values indicating liberal and conservative response bias, respectively. In case of perfect hit rates (1) or perfect false alarm rates (0), a correction factor was applied (Stanislaw & Todorov, 1999). Sensitivity and response bias measures were computed separately for the letter identity GNG task, the letter position GNG tasks and the FP task. Two separate repeated measures ANOVAs were conducted for each measure with Task as within subject factor and Group as a between subjects factor. In cases where ANOVA assumptions were violated on some dependent variables, significant effects were also assessed with a non-parametric test. For all the reported analyses, significant effects were followed by Newman–Keuls post-hoc tests corrected for multiple-comparison.

2.2.4 Lesion mapping and analysis

The aim of this analysis was to determine more precisely specific brain areas associated to behaviorally relevant differences between the three groups of patients, without any a-priori grouping. In order to proceed with the voxel-based lesion-symptom mapping analysis (VLSM), pre-operative contrast-enhanced T1-weighted, T2-weighted and/or FLAIR scans were collected. For each patient, the tumor lesion was drawn on the MRI axial slices and reconstructed as a 3D region of interest (ROI) with MRIcroN (Rorden & Brett, 2000). The MRI scans and the ROIs were then spatially normalized to a MNI template by means of SPM8 (Statistical Parametric Mapping; http://www.fil.ion.ucl.ac.uk/~spm)**.** Once the normalization of each lesion was acquired, the VLSM was performed on NPM software of MRIcroN. On a voxel-by-voxel basis, patients were divided in two groups according to whether their lesion affected that voxel or not, and their performance was compared by means of a *t*-test with a statistical threshold set at $p < .01$ with the False Discovery Rate (FDR) correction applied. Only voxels damaged in three or more patients were included in the analysis, in order to minimize possible outlier effects.

2.3 Results

2.3.1 Behavioral results

Go/No-Go task. For the accuracy data, the analysis revealed a main effect of Group [$F(3, 73) = 11.75$, $p < .001$, $\eta^2_p = .33$], an interaction between Group and Stimulus type [$F(3, 73) = 4.99$, $p = .003$, $\eta^2_p = .17$] and an interaction between Group and Task type [$F(3, 73) = 2.9$, $p = .041$, $\eta^2_p = .11$]. Post-hoc test for the Group main effect showed that LPF and RPF patients' accuracy was significantly lower than NPF and control group accuracy (all *p*s < .001), and they did not differ between each other ($p = .11$). Post-hoc tests for the Group × Stimulus type interaction showed that performance on No-Go trials was impaired in LPF patients only, compared to all the three other groups (*p*s < .01; Figure 5A), whereas on Go trials both LPF and RPF patients made significantly more omissions than NPF patients and

controls (*p*s < .01; Figure 5B), and did not differ between each other (*p* = .65)[2]. By looking separately at the stimulus type effect in each group, LPF's, NPF's and control group's accuracy did not differ significantly between No-Go and Go trials (all *p*s > .14), whereas only RPF patients showed significantly lower accuracy on Go trials with respect to No-Go trials (*p* = .004). When this accuracy difference between No-Go and Go trials was compared between the four groups, only RPF patients differed significantly from all the three other groups (all *p*s < .036). The task type instead modulated the performance only in RPF patients by reducing their accuracy for the letter position task with respect to the letter identity task (post-hoc test *p* = .003)[3].

The RT analysis showed a main effect of Group [$F(3, 73) = 16.29$, $p < .001$, $\eta^2_p = .4$], Session [$F(3, 73) = 20.66$, $p < .001$, $\eta^2_p = .22$] and Task [$F(3, 73) = 20.56$, $p < .001$, $\eta^2_p = .22$]. Post-hoc tests on the main effect of Group showed a similar RT performance between LPF and RPF patients (*p* = .9) and significantly higher RTs in these two groups with respect to NPF patients and controls (all *p*s < .001). Significant Group × Session [$F(3, 73) = 5.86$, $p = .001$, $\eta^2_p = .19$] and Group × Task [$F(3, 73) = 4.09$, $p = .01$, $\eta^2_p = .14$] interactions were better explained by a significant 3-way Group × Session × Task interaction [$F(3, 71) = 6.31$, $p < .001$, $\eta^2_p = .21$]. Post-hoc tests showed a significant surgery related increase of RTs in the RPF group specific for the letter position task (*p* = .0001), in the NPF group in the letter identity task (*p* = .044) and in the LPF group in both tasks (*p*s < .001). In the control group the RTs did not change across the two sessions (*p*s > .28).

Foreperiod task. Analyses on the accuracy data revealed a main effect of Group [$F(3, 74) = 10.32$, $p < .001$, $\eta^2_p = .29$], Task [$F(3, 74) = 6.03$, $p = .016$, $\eta^2_p = .08$] and more critically, an interaction between Group and Stimulus type [$F(3, 74) = 6.59$, $p < .001$, $\eta^2_p = .21$]. Post-hoc

[2] The additional assessment of accuracy scores comparing the four groups with non-parametric Kruskal-Wallis H test confirmed significant group differences in the No-Go condition [$H(3) = 11.95$, $p = .007$], with a mean rank accuracy score of 21.1 for the LPF group, 30.3 for the RPF group, 41.7 for the control group and 48.6 for the NPF group. Group differences were also confirmed for the Go condition [$H(3) = 14.26$, $p = .003$], with a mean rank accuracy score of 24.6 for the RPF group, 25.6 for the LPF group, 37.6 for the NPF group and 46.3 for the control group.

[3] Wilcoxon Matched Pairs test did not replicate the Task type difference in performance for the RPF group (*p*=.12).

tests for the main effect of Group showed that both LPF and RPF patients had lower accuracy when compared to NPF and control groups (all *p*s < .034), and also LPF patients were less accurate than RPF patients (p = .033). Post-hoc tests for Group × Stimulus type interaction showed that for the warning stimuli only the LPF group differed significantly from all the three other groups (all *p*s < .001; Figure 5C), whereas for the target stimuli both LPF and RPF patients performed significantly worse than NPF and control groups (all *p*s < .01; Figure 5D), with no difference between each other (p = .91)[4]. Given that only the LPF patients made significantly more frequent responses to the warning stimuli, an apparently similar performance of LPF and RPF patients on target stimuli could have been driven by a different behavioral deficit. Therefore we additionally examined the effect of stimulus type separately for each group. While LPF, NPF and control group accuracy was significantly lower on warning stimuli with respect to the target stimuli (all *p*s < .01), the RPF group did not show this pattern (p = .58). Moreover, when comparing this effect of stimulus type (i.e., accuracy difference between warning and target stimuli) between the four groups, only RPF patients' pattern of accuracy differed significantly with respect to the three other groups (all *p*s < .01). On the other hand, the finding of frequent warning responses in the LPF group could instead of false alarms reflect target anticipations. In order to exclude this alternative hypothesis we compared the RT distributions between warning and target responses, since false alarms should mostly have similar RTs as responses to target. Target anticipations instead should show up with longer RTs, mainly between 2000 and 3000 ms, which was the long FP duration. In line with the false alarm hypothesis, the majority of responses to the warning were committed within the first 1000 ms (≈ 70%), similarly as responses to the target.

Analyses performed on RT data for the FP task produced the following significant results: main effect of Task [$F(3, 74) = 86.35$, $p < .001$, $\eta^2_p = .54$], Session [$F(3, 74) = 10.57$, *p*

[4] A Kruskal-Wallis H tests comparing the four groups' accuracy on warning stimuli replicated the ANOVA result only as a trend [$H(3) = 7.22$, $p = .065$], with a mean rank accuracy score of 24 for the LPF group, 39.5 for the RPF group, 39.8 for the control group and 48.5 for the NPF group. Differences in accuracy on target stimuli between the four groups were significant [$H(3) = 22.88$, $p < .001$], with a mean rank accuracy score of 19.3 for the LPF group, 23.9 for the RPF group and 41.7 for both the NPF and the control group.

= .002, η^2_p = .13], FP [F(3, 74) = 18.46, p < .001, η^2_p = .2] and Group [F(3, 74) = 10.68, p < .001, η^2_p = .30]. Post-hoc tests on the main effect of Group showed how both LPF and RPF patients were generally slower than NPF patients and controls (all ps < 0.02), but did not differ between each other (p = .57). In agreement with common findings in this type of task (Niemi & Näätänen, 1981), there was a significant interaction between Task and FP duration [F(1, 74) = 212.14, p < .001, η^2_p = .74]: when the FP was fixed within a block, RTs were slower on the long FP than on the short one (p < .001), whereas the opposite occurred when the FP was variable (i.e., FP effect; p < .001). Also in line with previous neuropsychological studies (Stuss et al., 2005; Vallesi et al., 2007), the significant interaction found between Session, FP and Group [F(3, 74) = 3.47, p = .02, η^2_p = .12] was due to a RT slowing on long FPs after surgery selectively in the RPF group (post-hoc p = .037). Given that these previous studies mainly found a FP effect reduction (i.e., RT increase on long FPs when the FP is variable) in RPF patients, we performed an additional ANOVA on the FP effect (i.e., short FP - long FP RTs) in the variable FP task with Session as a within subject variable and Group as a between subjects variable. This analysis yielded a significant Group × Session interaction [F(3, 74) = 2.79, p = .046, η^2_p = .1] and post-hoc tests confirmed that the FP effect was reduced only in the RPF patients (p = .045).

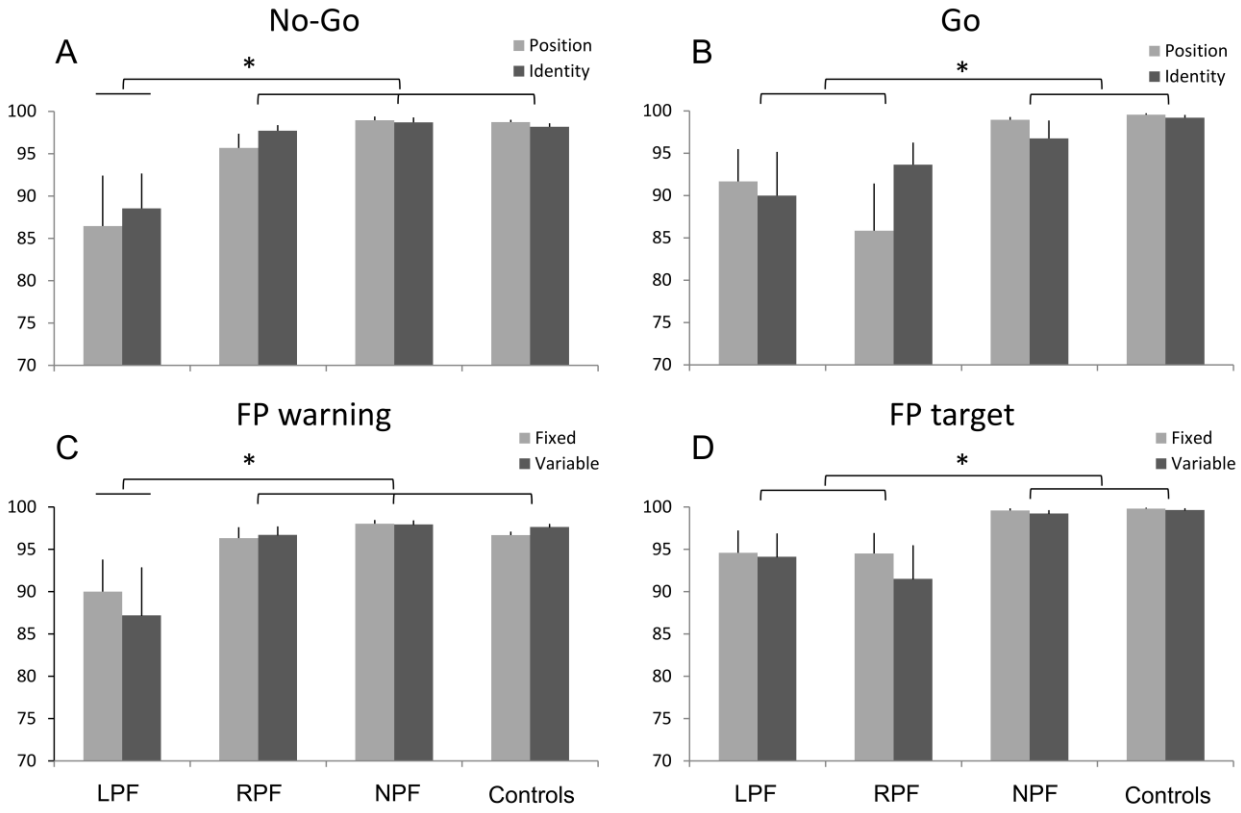

Figure 5. Accuracy scores (sessions collapsed) with standard error (vertical lines) for the No-Go (A) and Go (B) stimuli across the two GNG tasks (letter position and letter identity) and for the warning (C) and target (D) stimuli across the fixed and variable FP tasks. The asterisks denote significant group differences for each stimulus type.

SDT measures. The analysis of the sensitivity scores showed a main effect of Group [$F(3, 71) = 12.86$, $p < .001$, $\eta^2_p = .35$] and Task [$F(6, 142) = 19.73$, $p < .001$, $\eta^2_p = .21$]. Post-hoc analysis revealed significantly lower scores for both LPF and RPF patients with respect to NPF patients and controls (*p*s < .01; Figure 6A). Critically, LPF patients also had a significantly lower sensitivity score with respect to RPF patients (p = .049). For the response bias scores there was a main effect of Group [$F(3, 71) = 6.05$, $p < .001$, $\eta^2_p = .20$] and Task [$F(6, 142) = 22.47$, $p < .001$, $\eta^2_p = .24$]. Post-hoc tests showed that response bias scores were higher in RPF patients with respect to all the three other groups (*p*s < .01; Figure 6B). As for the main effect of Task in both analyses, higher sensitivity scores and a more liberal response bias was found in the FP task with respect to the GNG task (*p*s < .001).

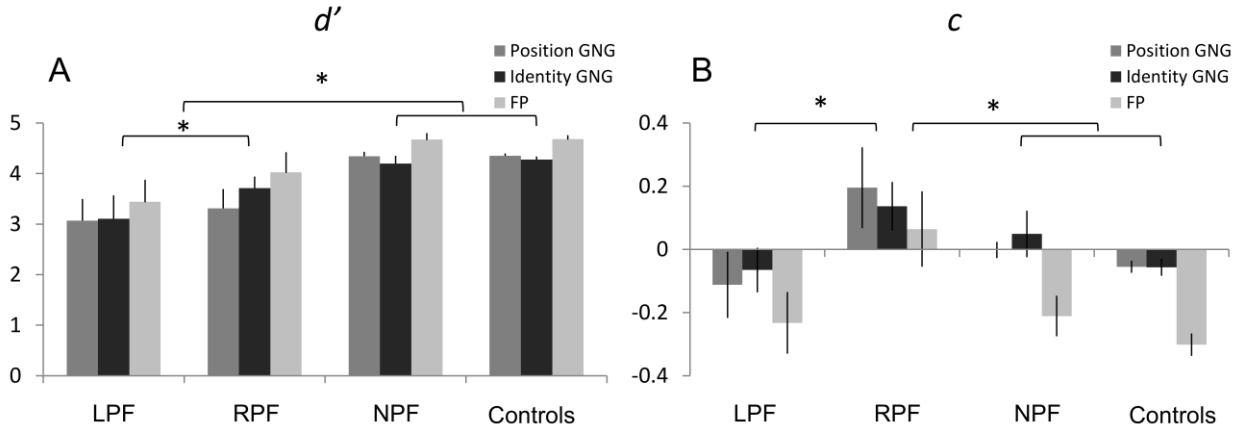

Figure 6. Signal Detection Theory (SDT) measures of sensitivity *d'* (A) and response bias *c* (B), across the three tasks (letter position GNG, letter identity GNG and FP task). Significant group differences are indicated with an asterisk.

2.3.2 Voxel-based lesion-symptom mapping results

The VLSM analysis was performed on the average *d'* and *c* measures from the three tasks which were included in the SDT analysis, since these measures were found to represent better the specific impairments in LPF and RPF patients. The results of this analysis confirmed that, regardless of any a priori patient grouping, the areas significantly associated with lower *d'* scores are located in the left prefrontal cortex, with the highest number of damaged voxels in the left ventrolateral and dorsolateral prefrontal cortex, and with a peak *z*-score in the left basal ganglia structures (see Figure 7A and Table 1). Conversely, the areas significantly associated with a more conservative response bias *c* (i.e., more frequent target misses) are found in the right ventrolateral and medial prefrontal cortex, and in the right basal ganglia structures (see Figure 7B and Table 2).

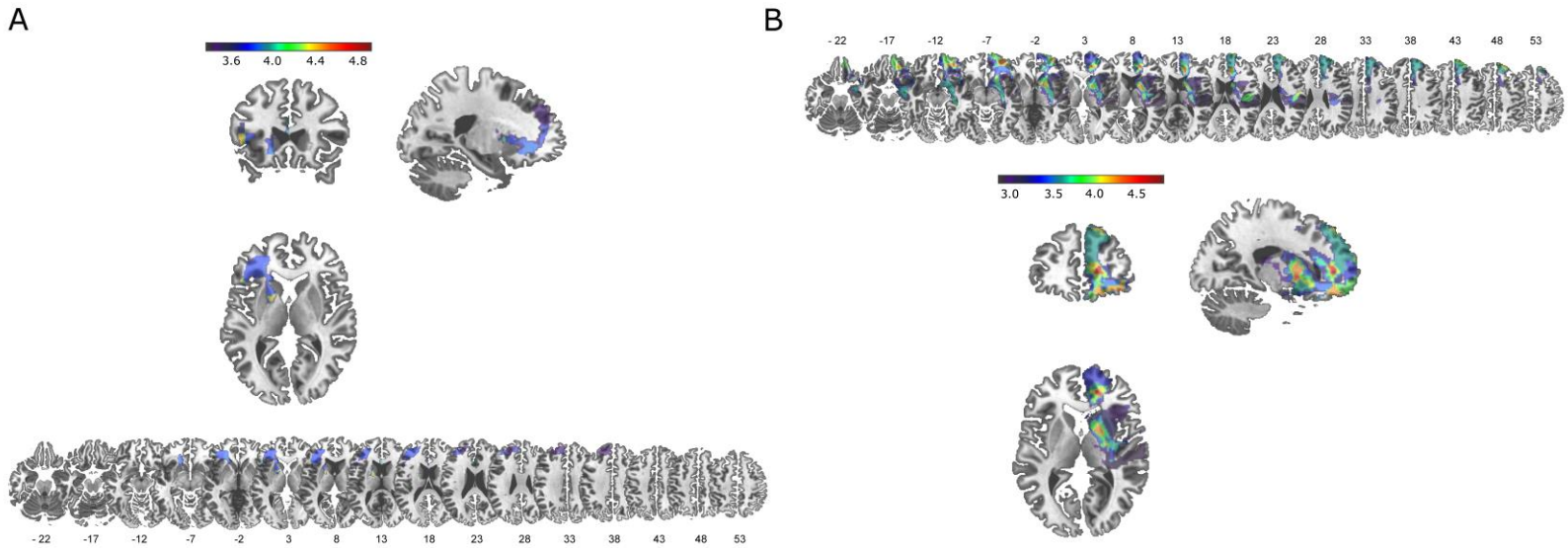

Figure 7. VLSM analysis results showing only significant voxels at $p < .01$, with False Discovery Rate correction applied. Color bars indicate Z-scores. Panel A: areas significantly associated to lower *d'* scores are located in the left ventrolateral and dorsolateral prefrontal cortex, and in the left basal ganglia structures. Panel B: areas significantly associated with a more conservative response bias *c* (i.e., more frequent Go and target misses) are found in the right ventrolateral and medial prefrontal cortex, and in the right basal ganglia structures.

Table 1. Exploratory VLSM results for sensitivity measures (*d'*)

Region	AAL label	Hemisph.	N° sign. voxels	% sign. area	Mean Z-score	Max Z-score	MNI coordinates		
							Max X	Max Y	Max Z
Left ventrolateral prefrontal cortex	Inferior frontal pars triangularis	L	11341	56.4	2.457	4.397	-48	24	-1
	Inferior orbitofrontal gyrus	L	1663	12.2	1.404	4.397	-48	24	-2
	Inferior frontal pars opercularis	L	3053	36.9	2.086	3.984	-52	20	11
Left dorsolateral prefrontal cortex	Middle frontal gyrus	L	10048	25.9	1.564	3.783	-36	43	-2
	Superior frontal gyrus	L	7908	27.3	1.342	3.783	-28	48	0
Left orbitofrontal cortex	Middle orbitofrontal gyrus	L	1047	14.7	1.456	3.802	-29	39	-6
	Superior orbitofrontal gyrus	L	1609	21.0	1.356	3.856	-21	28	-12
	Medial orbitofrontal gyrus	L	1254	21.7	1.849	3.856	-12	34	-10
	Olfactory cortex	L	33	1.5	1.477	4.098	-8	24	-8
	Gyrus rectus	L	418	6.1	1.440	3.856	-16	18	-10
Medial prefrontal cortex	Medial superior frontal gyrus	L	8786	36.8	1.917	3.851	-2	22	44
	Medial superior frontal gyrus	R	288	1.7	1.192	3.720	2	54	22
	Supplementary motor area	L	131	0.8	0.462	3.525	-2	22	45
	Anterior cingulate cortex	L	5095	45.1	2.473	4.294	2	35	24
	Anterior cingulate cortex	R	710	6.8	1.732	4.294	2	38	22
Basal Ganglia	Putamen	L	3318	41.8	2.341	4.397	-22	6	2
	Caudate nucleus	L	2440	31.8	2.238	4.397	-18	0	18
	Pallidum	L	547	23.9	1.384	4.887	-14	6	2
Subcortical white matter	Subcortical	L	20146	0.4	0.035	4.397	-14	8	4
Insula	Insula	L	4517	30.1	2.101	3.856	-26	30	3

Voxels significant at threshold of $p < .01$, using a *t*-test, with False Discovery Rate correction applied.

Table 2. Exploratory VLSM results for response bias measures (*c*)

Region	AAL label	Hemisph.	N° sign. voxels	% sign. area	Mean Z-score	Max Z-score	MNI coordinates		
							Max X	Max Y	Max Z
Right ventrolateral prefrontal cortex	Inferior frontal pars triangularis	R	10695	62.4	1.788	3.915	54	32	26
	Inferiror orbitofrontal gyrus	R	8976	65.3	2.185	4.421	52	28	-4
	Inferior frontal pars opercularis	R	7102	63.6	1.950	3.915	58	16	32
Right dorsolateral prefrontal cortex	Middle frontal gyrus	R	25179	62.4	1.886	4.244	30	57	-1
	Superior frontal gyrus	R	17493	54.5	1.948	4.119	18	66	16
Orbitofrontal cortex	Medial orbitofrontal gyrus	R	5766	83.9	2.630	3.998	14	40	-4
	Middle orbitofrontal gyrus	R	5022	62.3	2.555	4.244	19	42	-18
	Superior orbitofrontal gyrus	R	5174	65.8	2.520	4.244	16	42	-18
	Medial orbitofrontal gyrus	L	321	5.5	0.686	3.126	2	58	-9
	Olfactory cortex	R	1623	71.0	2.550	4.103	4	10	-12
	Gyrus rectus	R	4439	74.9	2.583	4.244	14	38	-16
	Olfactory cortex	L	135	6.0	0.891	2.945	0	7	-9
	Gyrus rectus	L	970	14.1	1.169	2.899	-2	21	-25
Medial prefrontal cortex	Medial superior frontal gyrus	R	12974	76.4	2.737	4.572	18	46	5
	Medial superior frontal gyrus	L	580	2.4	0.227	3.915	2	62	32
	Supplementary motor area	R	2580	13.7	0.685	3.608	8	24	47
	Anterior cingulate cortex	R	8709	83.4	3.072	4.572	18	43	4
	Middle cingulate cortex	R	5485	31.4	1.229	3.608	10	18	30
	Anterior cingulate cortex	L	1610	14.3	0.992	3.125	2	36	12
Right parietal lobe	Postcentral gyrus	R	1165	3.8	0.313	4.103	56	-4	20
	Precentral gyrus	R	5725	21.2	0.909	4.103	54	0	22
	Rolandic operculum	R	7664	71.4	2.460	4.103	54	-10	16
	Supramarginal gyrus	R	3382	21.4	0.909	3.872	50	-16	26
Right temporal lobe	Superior temporal gyrus	R	15130	59.9	1.899	3.324	48	-14	-9
	Middle temporal gyrus	R	1013	2.9	0.492	3.324	48	-16	-12
	Middle temporal pole	R	124	1.3	0.117	2.976	45	10	-24
	Superior temporal pole	R	3704	34.8	1.216	4.353	42	16	-20

Insula	Insula	R	13438	95.1	2.828	4.103	38	-12	18
	Heschl gyrus	R	1879	97.1	2.714	3.858	35	-22	16
Basal Ganglia	Caudate nucleus	R	7562	95.2	3.070	4.794	14	14	16
	Pallidum	R	2188	100.0	3.712	4.757	16	10	-2
	Putamen	R	8510	100.0	3.497	4.421	16	8	-6
Subcortical white matter	Subcortical	R	83226	1.5	0.052	4.572	22	40	2
Other subcortical structures	Thalamus	R	1652	19.7	0.687	3.464	22	-17	8
	Hippocampus	R	4941	65.0	2.292	4.353	34	-18	-16
	Parahippocampal gyrus	R	1308	14.5	0.802	4.103	34	-30	-14
	Fusiform gyrus	R	16	0.1	0.054	3.278	39	-30	-14
	Amygdala	R	1887	96.0	3.307	3.657	30	-2	-24

Voxels significant at threshold of $p < .01$, using a *t*-test, with False Discovery Rate correction applied.

2.4 Discussion

The main aim of this study was to try to dissociate co-occurring processes like response selection and target detection from inhibitory ones by assessing them separately in patients with different brain lesion locations. In particular, we focused on patients with left prefrontal and right prefrontal damage in order to verify whether previous discordant neuropsychological findings of a critical inhibitory involvement of these prefrontal areas can be conciliated by assessing other processes closely related to inhibition.

The impairments that emerged in RPF and LPF patients were dissimilar and remained consistent irrespective of the task context. Specifically, when the task required Go and target detection in an inhibitory task context and in a simple target detection task context, patients with RPF lesions showed a higher number of omissions than NPF patients and healthy controls. Even though LPF patients showed a similar rate of omissions, their also higher false alarm rate to both No-Go and warning stimuli suggested a different type of underlying impairment. Post-hoc tests confirmed that the accuracy pattern was affected differently in LPF and RPF patients in both tasks: while RPF patients' accuracy reduction was specific for the type of stimuli (i.e., Go and target), patients with LPF damage showed an unspecific accuracy reduction, which reflects a probable underlying difficulty in creating stable response and non-response associations to different stimuli. In line with these assumptions, indices of target/non-target discriminability and response bias, computed according to the SDT, were found to be more sensitive for distinguishing the impairments of LPF and RPF groups. Namely, LPF patients' discriminability index was significantly lower than that of the other three groups, suggesting the effects of the lesion on decisional processes rather than on inhibitory ones. Conversely, RPF patients showed a pronounced tendency of not responding, with respect to all other three groups that showed a common response bias towards responding. This finding suggests a more general deficit in maintaining attention to critical events.

The target detection impairment observed in RPF patients was confirmed and extended by the VLSM analysis showing a critical involvement of right inferior and medial frontal areas, right ACC and right basal ganglia structures across both GNG and FP tasks. Critically, these areas have previously been implicated in inhibitory regulation of motor response (Aron & Poldrack, 2006; Congdon et al., 2010; Garavan, Ross, & Stein, 1999). Yet, our study shows that lesions of these regions are significantly associated to a generic target detection deficit and do not cause inhibitory impairments. In relation to previous lesion studies, a general difficulty in maintaining attention to relevant stop signals could have caused also longer SSRT, which in the work by Aron and colleagues (2003) was interpreted as an inhibitory impairment in patients with rIFC damage. Unfortunately, the accuracy data were not reported and it is not possible to know whether these patients also made more frequent Go omissions, which could have given us a more accurate picture of their impairment. In line with this hypothesis, in another more recent study no evidence of inhibitory impairment in terms of SSRT was found in rIFC lesion patients compared to LPF patients and healthy controls (Krämer et al., 2013). However, similarly to our results, the authors observed that patients with prefrontal lesions omitted a significantly higher number of Go trials across three different inhibitory tasks and this omission rate was significantly higher in RPF with respect to LPF patients in a GNG task with more frequent Go trials. Although their performance was comparable in terms of false alarms, and this result is not completely in line with the differences we found between LPF and RPF patients, more frequent omissions of Go stimuli observed in RPF patients confirms their more general target detection impairment rather than an inhibitory one. It is possible that the lack of a significant difference between RPF and LPF patients in terms of false alarms was due to their small sample size (RPF n = 4, LPF n = 8).

With a somewhat different task using verbal initiation and suppression measures (i.e., Hayling Sentence Completion Test), Robinson and colleagues (2015) recently showed a link between right PFC lesions and suppression deficit. However, this deficit was also accompanied by a significant slowness in the suppression condition and by

more frequent semantically related errors, which made the authors hypothesize impairment in strategy generation and implementation rather than an inhibitory failure per se. Hornberger and Bertoux (2015), in their commentary on this study, suggested that a failure in maintenance of task goals could account for both action cancellation and strategy use impairments observed in patients with right PFC damage. Similarly, the right ventrolateral prefrontal area has been found several times as being involved in maintenance and representation of task rules (e.g., Bengtsson, Haynes, Sakai, Buckley, & Passingham, 2009; Reverberi, Görgen, & Haynes, 2012). Moreover, such a task maintenance ability has already been shown to rely on right-lateralized sustained control processes (Ambrosini & Vallesi, 2016a; Braver, Reynolds, & Donaldson, 2003; Cieslik, Mueller, Eickhoff, Langner, & Eickhoff, 2015; Langner & Eickhoff, 2013). The deficit we observed in RPF patients could also be interpreted as a difficulty in task-goal maintenance, however this process is highly intertwined with sustained attention processes and our tasks were not suited to untangle them.

Similar findings emerged from a more detailed lesion localization study (Picton et al., 2007) where patients with right ACC damage made more errors of omission while patients with left superior medial frontal damage made more false alarms. While the former result was interpreted as a general difficulty in allocating attentional resources, the latter one was seen as a deficit in setting stimulus-response rules and response selection. Our finding of decisional process impairment in the LPF group goes in line with this observation. Areas that were significantly associated to a lower discriminability index (i.e., left ventrolateral and dorsolateral PFC) are those reported in the literature as implicated in stimulus-response learning and rule based response selection (Fletcher et al., 2000; Vallesi et al., 2009; see Bunge, 2004 for a review). Moreover, different neuropsychological and neuroimaging studies evidenced a strong involvement of left lateral prefrontal areas in setting up response criteria in task-switching and strategy-shifting contexts (Aron, Monsell, et al., 2004; Brass & von Cramon, 2004; Campanella, Skrap, & Vallesi, 2016; Shallice, Stuss, Picton, Alexander, & Gillingham, 2008; Vallesi et al., 2015). In contrast with our results, in the study by Swick and colleagues (2008) the

authors did not observe an increase of Go omissions associated with a higher false alarm rate committed by LPF patients, even though they adopted a frequent (50%) and un-frequent (10%) No-Go design. This discrepant finding could be potentially explained by their different task design that had a high number of different Go stimuli and only one No-Go stimulus, which renders the response association more difficult to No-Go than Go stimuli, given that they are under-represented.

Although the majority of voxels identified by the VLSM analysis were clearly lateralized, some of the areas were found to be associated both to discrimination and detection failures, in particular those around the medial wall, such as bilateral superior medial frontal areas and bilateral ACC. Results from the behavioral analysis, with a priori grouped patients, showed a significant decrease of the discriminatory index in both RPF and LPF patients, although the latter group was significantly more impaired than the former. This could partially account for the finding of common areas in the VLSM analysis: lesions in ACC and medial frontal areas might have caused both response selection and response initiation difficulties, which is in line with the energisation account that ascribes a supporting role in both processes to these areas (Stuss et al., 2005). Basal ganglia were another brain region found to be involved in both processes, even though with distinct lateralization. This significant association could be explained by its critical role in feedback-mediated learning, as suggested by accounts of cognitive deficits in Parkinson disease (Frank, 2005). In particular, positive and negative reinforcements modulate Dopamine release in the Basal ganglia that leads to response learning. Lesions in these regions therefore might impair this reinforcement-based response adjustment, incrementing both discrimination and detection errors.

The anatomical lateralization of different processes within the PFC could depend on the domain-related components of the task. In this study we also aimed at exploring whether LPF and RPF patients would show different performance in the GNG task depending on the verbal or spatial characteristics of the stimuli they had to attend to. The only group whose performance was modulated by this manipulation was the RPF group. Patients with RPF lesions showed a greater impairment in the letter position task

with respect to the letter identity task, although this result should be taken with caution since non-parametric tests did not replicate this result. Importantly, the localization of the letters was not lateralized (displayed on the left-right axis) and therefore this plausible impairment observed in RPF patients cannot be explained by their possible sub-clinical neglect. Instead, it probably reflects a more pronounced decrement in attention to the task when the task requires attending to spatial rather than verbal attributes of the stimuli. This result underlines the importance of controlling for the type of material used in neuropsychological studies. With a similar task design, Malhotra and colleagues (2009) found both sustained attention and spatial impairments in a group of neglect patients. The authors argue that even though both of these impairments are often concurrently observed in neglect patients, their finding could be explained by a disconnection between right prefrontal areas and parietal areas, which are involved separately in maintaining attention and coding spatial locations, respectively (Bartolomeo, 2007; Doricchi & Tomaiuolo, 2003).

Even though the main aim of the study was to try to dissociate co-occurring decisional and sustained attention processes from inhibitory ones, neither the LPF patients nor the RPF ones tested here showed any specific inhibitory impairment. We argue that the specific failures in response selection and target detection found in these two groups of patients can account for previous discordant neuropsychological findings on inhibition. Still, one could argue that in our GNG task, given the equal frequency of Go and No-Go trials, the demands were more on response selection than on inhibitory control. However, as already addressed in the introduction, previous studies have shown that regardless of the Go – No-Go ratio, motor activation on No-Go trials is equally strong (Boulinguez et al., 2008, 2009; Jaffard et al., 2007). Besides, in this study we found that in all the tested groups, except in the RPF group, the response was biased towards responding, which confirms that regardless of the Go and target frequencies and their predictability, patients with no target detection difficulties and healthy controls have developed a prepotent responding tendency. Finally, although this could be seen as a possible limitation to our study, it also allowed us to reduce maximally any

sort of “oddball” or novelty effect, which has shown to be an important confounding effect in the inhibitory research field (e.g., Dodds et al., 2011; Hampshire et al., 2009; Mostofsky & Simmonds, 2008). Future studies should however consider including an additional un-frequent No-Go condition in order to clarify better whether the impairments observed in our study can account for frequent false alarms found in both LPF and RPF patients.

None of the observed accuracy impairments were affected by surgery. Although surprising, this result is in line with a previous study of acute surgery effects on cognitive functioning in brain tumor patients reporting a significant post-operative decline only for patients with low-grade glioma (Campanella, Fabbro, Ius, Shallice, & Skrap, 2015) due to its slowly growing and infiltrative activity, which in our sample were least represented (7/37). RTs instead increased after surgery and particularly in patients with prefrontal damage. However, this increase was different in LPF and RPF patients, the former ones showing an unspecific slowing after surgery, while in the latter group RTs increased mostly on long FP durations and in the letter position task. This selective RT increase observed in RPF patients is in line with a more pronounced impairment in maintaining attention to spatial locations observed in accuracy, although it is not clear why in terms of RTs emerged only after the surgery. One possible explanation could be that, since RTs are measured only on correct trials, a surgery-induced lesion caused an extra disruption (in terms of slowing) of the relative processes. Additionally, in line with previous neuropsychological studies we found a post-surgery decrease of the FP effect in RPF patients only, which is believed to be due to deficiencies in monitoring for the stimulus occurrence over time (Stuss et al., 2005; Vallesi et al., 2007).

In summary, we found that when explicitly assessing response selection and target detection across different response suppression contexts, left and right prefrontally lesioned patients show distinct impairments of the former and the latter, respectively. These results suggest that the areas involved in these lesions, in particular the left ventrolateral and dorsolateral prefrontal areas, and the right ventrolateral and medial prefrontal areas, are unlikely to host a specialized inhibitory module, but rather support

a broader set of cognitive control processes which work together in guiding successful response inhibition, among other executive abilities. From a clinical perspective, a wider assessment of inhibitory related processes, like the ones explored here, across various clinical populations, could help discriminate potentially different underlying impairments in dysfunctional inhibitory regulation.

CHAPTER 3

ARE TASK-SWITCHING IMPAIRMENTS SWITCH SPECIFIC OR TASK GENERAL?

3.1 Introduction

One of the core functions of the frontal lobes is to allow flexible behavior in response to the internal and external changes. This ability has long been investigated by means of the task-switching paradigm in which two or more task sets are presented in an intermixed fashion. By measuring the so-called switching costs (i.e., decrease in performance for switch vs. repeat trials), scientists have gained insight into the cognitive control processes required to shift between different tasks and their neural underpinnings. Different models have been put forward in order to explain the nature of the switch cost. According to one group of accounts, the switch cost reflects the time needed for an endogenous control process to reconfigure the task set (e.g., Mayr & Kliegl, 2000; Rogers & Monsell, 1995). An important aspect of the reconfiguration view is the assumption of a switch-specific process, which is not required during task repetitions since the previous task set is still active. This assumption has been heavily debated in a recent review of fMRI studies on task-switching (Ruge, Jamadar, Zimmermann, & Karayanidis, 2013) where the authors report a large number of studies that failed to find switch-specific brain activations (Brass & von Cramon, 2002, 2004; Bunge, Kahn, Wallis, Miller, & Wagner, 2003; Cavina-Pratesi et al., 2006; Gruber, Karch, Schlueter, Falkai, & Goschke, 2006; Luks, Simpson, Feiwell, & Miller, 2002; Ruge et al., 2005; Ruge, Braver, & Meiran, 2009; Vallesi et al., 2015), speaking against the existence of a switch-only process. Moreover, most of the studies reporting differences between

switch and repeat trials show the activation of the same areas, only to a different degree (Braver et al., 2003; Dove, Pollmann, Schubert, Wiggins, & von Cramon, 2000; Kimberg, Aguirre, & D'Esposito, 2000; Rushworth, Hadland, Paus, & Sipila, 2002; Smith, Taylor, Brammer, & Rubia, 2004). These findings support alternative accounts that assume a relatively greater recruitment of the same processes when switching vs. repeating the task (Altmann & Gray, 2008; Koch, 2005; see Kiesel et al., 2010 for review). On the other hand, a number of event-related potential (ERP) studies, given their high temporal resolution, reported switch-specific ERP modulations (Capizzi, Ambrosini, Arbula, Mazzonetto, & Vallesi, 2016; Nicholson, Karayanidis, Poboka, Heathcote, & Michie, 2005; Tarantino, Mazzonetto, & Vallesi, 2016; see Karayanidis et al., 2010 for review), speaking in favor of a switch-related process. However, similarly as fMRI studies, most of them report only ERP amplitude increases in switch compared with repeat trials, in line with the assumption that similar processes are being engaged during both trials (but see Karayanidis, Provost, Brown, Paton, & Heathcote, 2011; Mansfield, Karayanidis, & Cohen, 2012).

While both fMRI and ERP techniques have brought considerable evidence on the processes underlying task-switching abilities, another complementary and fundamental approach that was not so often adopted in this area, relies on the investigation of the spared abilities in brain-lesioned patients. It is important to underline that the assessment of the switching abilities in the majority of the neuropsychological studies was done by means of clinical tests, such as the Wisconsin Card-Sorting and the Extra-Dimensional Intra-Dimensional Shift test of the CANTAB battery (e.g., Owen, Roberts, Polkey, Sahakian, & Robbins, 1991; Stuss et al., 2000), which, other than switching, measure many other cognitive abilities (Stuss et al., 2000). However, there are few studies that evaluated those abilities with a task-switching paradigm, primarily on patients who suffered from stroke (Aron, Monsell, et al., 2004; Mayr, Diedrichsen, Ivry, & Keele, 2006; Pohl et al., 2007; Rogers et al., 1998; Shallice, Stuss, Picton, et al., 2008; Tsuchida & Fellows, 2012). A main finding that emerges in all of these neuropsychological studies is the critical involvement of prefrontal regions in switching

performance. Still, the localization and the type of impairment observed in patients with prefrontal damage is rather inconsistent across these studies and does not allow drawing conclusions regarding the processes underlying this capacity. For instance, some authors report an increased switch cost in both left and right prefrontal patients, with an apparently greater interference effect in the latter group during incongruent trials (i.e., when the stimulus affords different responses for the two tasks; Aron et al., 2004), others instead report both an increased switching cost and interference effect only in patients with left prefrontal damage (Mayr et al., 2006; Rogers et al., 1998; Tsuchida & Fellows, 2012). Finally, Shallice and colleagues (2008) did not replicate this switching cost increase in a study with a large sample of prefrontal patients, although they report a significant accuracy interference effect during the first block of trials in patients with left lateral prefrontal damage. Taken together, the results from the above reported studies seem to point to left-lateralized prefrontal correlates of the processes underlying task-switching, which is in line with evidence from neuroimaging studies (e.g., Badre & Wagner, 2006; Vallesi et al., 2015), but do not add evidence regarding the nature of those processes. In particular, it is not clear whether the weaker performance on task-switching is due to the patients' inability to reconfigure/activate the currently relevant task-set on switch vs. repeat trials, or to direct their attention to task-relevant and suppress task-irrelevant information, irrespective of the switching or repeating task context.

In the present neuropsychological study we approached this unanswered question by implementing a simple task-switching design that allowed us to minimize the impact of other closely related and frequently weakened processes in patients with brain damage (e.g., maintenance of stimulus-response associations in memory, verbal vs. spatial processing). Moreover, we gave the participants the possibility to prepare for the upcoming task (i.e., long cue-target interval), thus reducing the interference from the previous task set while still tapping the task reconfiguration process on switch trials. As a consequence, any switch-specific decrease in performance should be interpreted as evidence supporting a disruption of a task reconfiguration process required only during

switch trials. Conversely, if the observed deficit reflects more general interference resolution difficulties, and thus is being present on both switch and repeat trials, but only during incongruent trials, as already observed in previous studies (Aron, Monsell, et al., 2004; Mayr et al., 2006; Pohl et al., 2007; Rogers et al., 1998; Shallice, Stuss, Picton, et al., 2008), then a probable underlying cause could not be associated with a disruption of a putative reconfiguration process. Instead, an impaired suppression of task-irrelevant information would be a more plausible explanation. However, a selective decrease in performance on incongruent trials could also reflect a more severe task reconfiguration/activation impairment: patients could perseverate and follow only one task rule most of the time, and thus their performance would be reduced on the alternative task rule, independently of whether the trial was a repeat or a switch. Consequently, their performance would be high on congruent trials (i.e., when both tasks require the same response), and low on incongruent trials (i.e., when the two tasks require different responses).

Another important aspect of this study is the inclusion of a patient group without lesions in the PFC, which was not done in previous studies investigating the impact of frontal lesions on task-switching performance (Aron, Monsell, et al., 2004; Mayr et al., 2006; Pohl et al., 2007; Rogers et al., 1998; Shallice, Stuss, Picton, et al., 2008; Tsuchida & Fellows, 2012). Posterior regions are known to have a major role in task-switching performance and damage within different areas might induce similar impairments. To this extent, the relationship between damage across multiple areas and the resulting behavioral deficit was investigated by means of multivariate lesion-symptom mapping analysis, which is essential when trying to capture the neural basis of processes known to rely on more than one brain area.

3.2 Materials and methods

3.2.1 Participants

Our participant sample was selected from a series of patients that underwent a brain tumor operation at the University Hospital of Padova with age ranging from 18 to 85 years. Patients with previous neurological or psychiatric disorders and recurring brain lesions were excluded a priori. A posteriori, we excluded six patients who did not manage to complete the task because of its difficulty: five with damage in LPF and one in RPF areas. The remaining forty-one patients were divided in three groups according to the location of the tumor's center of mass and the area with the highest number of damaged voxels: LPF (n = 12), RPF (n = 10) and non-prefrontal (NPF, n = 19). Lesion overlap maps for each patients' group are shown in Figure 8. The histopathological exam of the lesions showed 15 high-grade gliomas, 8 low-grade gliomas, 14 meningiomas and 4 metastases. Tumor grade distribution was not significantly different across the three groups of patients (p = .5, Fisher's exact test). We tested also forty-four healthy participants as a control group; there was no significant difference between the four groups in terms of age (K-W test's p = .82) and years of education (K-W test's p = .5). All but four participants were right-handed (one from the RPF group, one from the NPF group and two from the control group), as assessed by the Edinburgh Handedness Inventory (Oldfield, 1971).

All participants performed two identical testing sessions, in between which patients underwent the surgical operation. One LPF patient did not perform the pre-surgical session due to time constrains, and was included only in the analysis on post-surgical data. Before each experimental testing session, all participants underwent an extensive neuropsychological assessment that included tests on general cognitive status, premorbid intelligence, memory, language, attention and executive functions, reported in chapter 3. Demographical, etiological and neuropsychological data are reported in supplementary material Table S1. All participants gave their written informed consent before the experimental testing session. The study was approved by

the Bioethical Committee of Azienda Ospedaliera di Padova and was conducted according to the guidelines of the Declaration of Helsinki.

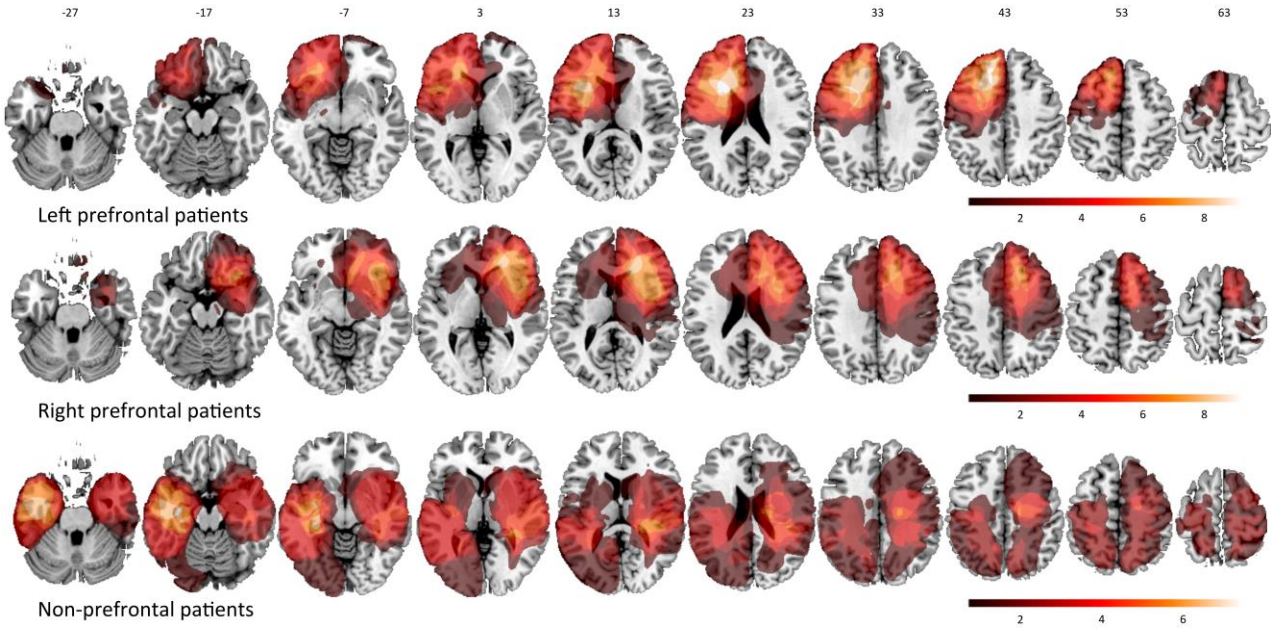

Figure 8. Lesion overlap maps for left prefrontal, right prefrontal and non-prefrontal patient groups. The color bar indicates the number of patients whose lesions overlap on one voxel.

3.2.2 Experimental investigation

The task was presented on a Dell Intel Core laptop with a 17 inch screen using E-Prime 2 software (Schneider et al., 2002). Participants were seated in front of the computer screen at approximately 60 cm in a quiet and normally illuminated room.

The schematic representation of the paradigm can be seen in Figure 9. On each trial, one out of two letters (A or E) was presented approximately 2.8° above or below a centrally positioned fixation asterisk that remained constantly on the screen. Each letter subtended a visual angle of approximately 0.8° x 0.8°. During the single-task blocks participants performed one task that remained constant throughout the block. In one

block they were asked to identify the letter (A or E) by pressing the “k” key (marked by the number 1) or the “l” key (marked by the number 2) on the computer keyboard, whereas in the other block they were asked to identify its position (above or below the fixation point) by pressing the same keys. The order of presentation of the two single-task blocks was counterbalanced between participants. During the next two blocks of trials both letter identity and letter position tasks were presented together in a pseudo-random order (i.e., task-switching blocks). At the beginning of each trial a 3000 ms long cue was presented that instructed the participant about which task to carry out. The cue was explicit, as it comprised both the name of the task (“LETTERA” – Italian for letter or “SPAZIO” – Italian for space) and the key association for that task (1: A / 2: E or 1: SOPRA / 2: SOTTO – Italian for above and below). The cue was then substituted by the target stimulus that remained on the screen until a response was detected, which was followed by a 500 ms long response-to-cue interval. During single-task trials a 1000 ms long fixation asterisk was presented instead of the cue. All four blocks consisted of 40 trials each and had equally distributed letter and position task cues that were presented randomly. During task-switching blocks on average 50% of the trials were “repeat” trials in which the task remained the same as the one performed on the previous trial, and the remaining were “switch” trials in which the task changed with respect to the one in the previous trial. Moreover, each stimulus was categorized as “congruent” if the same response had to be given whichever task had to be performed, or “incongruent” if the response for that stimulus on the current task was different than the response that should have been given under the alternative task rules. The ratio of congruent and incongruent trials was 50:50. Each single-task block was preceded by 4 practice trials, while the task-switching block was preceded by 8 practice trials, that could be repeated if necessary for a maximum of three times. A feedback message, “corretto” – “correct” in blue (for correct responses), “fai più attenzione” – “pay more attention” in red (in case of wrong responses), or “nessuna risposta rilevata” – “no response detected” in red (for null responses), was presented after each response during the practice blocks for a duration of 1500 ms. Six participants were excluded for not being able to follow the task

rules after three blocks of practice. Participants were instructed to press the keys with their index and middle fingers of their dominant hand, and to respond both quickly and accurately.

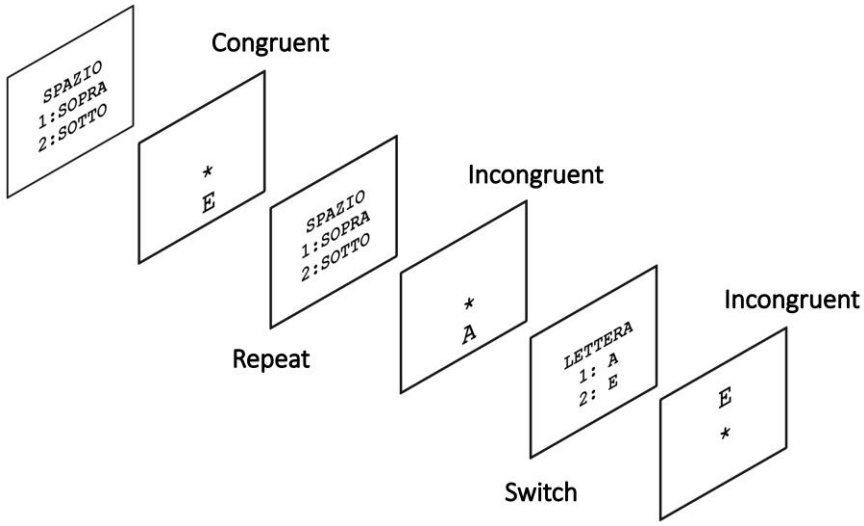

Figure 9. Switching block of the task-switching paradigm ("spazio" - space; "sopra" - above; "sotto" - below; "lettera" - letter).

3.2.3 Analyses of the behavioral data

Trials with response times (RTs) below 150 ms and above 4 standard deviations from the mean RTs of each participant in each experimental condition were excluded from all analyses, which resulted in 0.99% of excluded trials. Accuracy data were analyzed by means of non-parametric Kruskal-Wallis H test if differing significantly from the normal distribution, as assessed by Kolmogorv-Smirnov test. RT data were log-transformed in order to improve normality and reduce skewness. Group differences in accuracy were analyzed within each testing session separately for the two single tasks, congruent and incongruent trials, switching cost (i.e., accuracy difference between switch and repeat trials) and perseveration. The latter was measured as the absolute difference in accuracy between the two types of tasks (i.e., letter identity and letter position), however only on incongruent trials during which perseverative errors were observable. Follow up multiple comparisons of mean ranks were used to assess significant group differences. The reported *p*-values refer to two-sided significance levels with a

Bonferroni adjustment, as implemented in STATISTICA software (Dell Inc., 2015). The analyses on correct RT data were performed by means of a repeated measures ANOVA separately for single and task-switching blocks. For the single task blocks, Session (pre vs. post surgery) and Type of task (letter identity vs. letter position) were included as the within subject variables, and Group (LPF, RPF, NPF and Controls) as the between subjects variable. For the task-switching blocks, we included Session (pre vs. post surgery), Congruency (congruent vs. incongruent) and Trial type (repeat vs. switch) as the within subject variables, and Group (LPF, RPF, NPF and Controls) as the between subjects variable.

3.2.4 MRI preprocessing and lesion segmentation

Tumor lesions were manually drawn on pre-operative structural MRI axial slices (T1, T2 or FLAIR) with MRIcroN (Rorden & Brett, 2000). Both images and lesions were normalized to an age-appropriate template brain using the Clinical Toolbox (Rorden, Bonilha, Fridriksson, Bender, & Karnath, 2012) for SPM12 (Statistical Parametric Mapping; http://www.fil.ion.ucl.ac.uk/spm) using enantiomorphic normalization (Nachev, Coulthard, Jäger, Kennard, & Husain, 2008). In order to perform multivariate lesion-based symptom mapping, the dimensionality of voxel-wise lesion maps was reduced by calculating the proportion of damaged voxels in each brain area from the unified AAL (116 grey-matter areas; Tzourio-Mazoyer et al., 2002) and CAT (34 white-matter areas; Catani & Thiebaut de Schotten, 2008) atlases. Both lesion segmentation and the following multivariate analyses were carried out using the NiiStat toolbox written in Matlab (https://www.nitrc.org/projects/niistat/).

3.2.5 Multivariate lesion-symptom mapping analyses

The relationship between lesion maps and behavioral measures was modeled using the Support Vector Regression (SVR) algorithm (Drucker, Burges, Kaufman, Smola, & Vapnik,

1997) with linear kernel (LIBSVM Matlab library implemented in the NiiStat toolbox). The estimated linear model can be described as:

$$y_i = \boldsymbol{w}^T \varphi(x_i) + b$$

where y_i is the behavioral score of the *i*-th subject, $\varphi(x_i)$ is the kernel function transforming the lesion data contained in all brain areas of the *i*-th subject to a higher dimensional space, $\boldsymbol{w} = \left(w_{1,}\, w_{2,}, w_{3,} \ldots\right)^T$ are the fitting coefficients that describe the strength of the association between each brain area and the behavioral score (*y*), and *b* is the fitting error. Only areas that were damaged in at least three patients were considered in the analysis, which resulted in 116 out of 150 atlas areas. The estimation of the coefficients *w* and the bias *b* was done with a leave-one-out procedure. Specifically, one patient was excluded during this training phase while damage data and behavioral scores from the remaining 40 patients were used to compute the parameters of the model. The resulting model was then used to estimate the behavioral score from the left-out patient. The same procedure was repeated for all 41 patients in order to obtain 41 predicted behavioral scores. The model accuracy was determined by calculating the Pearson's correlation coefficient between predicted and actual scores. To retain only the areas that were highly predictive in all participants, the weight of each brain area was averaged across all participants. Only those areas whose average weight was 2.5 SD above the mean weight of all areas were considered as significantly predictive. We note here that the weights derived from multivariate lesion-symptom mapping techniques should be interpreted with caution because they do not necessarily reflect the level of their importance for the cognitive process under investigation (Haufe et al., 2014). A more detailed description of the training and testing phase methods can be found in the original paper (Yourganov, Fridriksson, Rorden, Gleichgerrcht, & Bonilha, 2016).

3.3 Results

3.3.1 Behavioral results

Group differences on pre-operative accuracy resulted significant only on the single letter position type of task [$H(3) = 7.89$, $p = .048$] and on incongruent trials [$H(3) = 8.57$, $p = .035$], even though post-hoc group contrasts did not yield any significant difference (all corrected ps > .07). Similarly, post-operative accuracy differed significantly across the four groups only on incongruent trials [$H(3) = 20.42$, $p < .001$]. This time, however, post-hoc tests showed that LPF and NPF patients' accuracy was significantly lower with respect to the control group's performance (both corrected ps < .031; Figure 10), while RPF patients' performance was comparable to the control group's one ($p = .21$). Since the analysis on congruent trials did not reveal a significant accuracy modulation across the four groups in either pre- or post-operative sessions, the subsequent switching cost analyses were conducted only on incongruent trials. However, contrary to our expectations, no significant group differences emerged in terms of switching cost, nor there was any interaction with session. On the other hand, the perseveration measure differentiated significantly between the four groups both on pre- and post-surgical testing sessions (pre: [$H(3) = 7.87$, $p = .049$], post: [$H(3) = 21.16$, $p < .001$]). However, only for post-operative scores there were significant post-hoc group differences (Figure 11). In particular LPF and NPF patients' perseveration score was significantly higher than the control group's score (both ps < .01). Again, RPF patients did not differ with respect to the controls ($p = .12$).

For the single tasks, the RT analysis showed a main effect of Group [$F(3, 80) = 8.42$, $p < .001$, $\eta^2_p = .24$], Session [$F(3, 80) = 23.99$, $p < .001$, $\eta^2_p = .23$] and Task [$F(3, 80) = 91.74$, $p < .001$, $\eta^2_p = .53$], and an interaction between Group and Session [$F(3, 80) = 4.56$, $p = .005$, $\eta^2_p = .15$]. Post-hoc test for the Group main effect showed longer RTs in LPF and RPF groups with respect to the control group (both ps < .025). However, RPF patients were also significantly slower with respect to all other three groups (all ps < .047). Moreover, the post-hoc test for the Group × Session interaction showed that while LPF and RPF patients were slower than controls in the second session (for

patients: after surgery; both *p*s < .01), only RPF patients were slower also before surgery when compared to the controls (*p* = .001). The analysis on RTs from the task-switching block showed a main effect of Group [$F(3, 80) = 6.87$, $p < .001$, $\eta^2_p = .2$] and an interaction between Group and Session [$F(3, 80) = 3.42$, $p = .021$, $\eta^2_p = .11$]. While the group main effect was due to a general slowing in all patient groups with respect to the controls (all *p*s < .044), post-hoc test on the session interaction showed that all three patient groups differed significantly from the control group after surgery (all *p*s < .032), however prior to surgery only RPF patients were significantly slower than the control group (p = .006). The main effects of Congruency [$F(3, 80) = 86.26$, $p < .001$, $\eta^2_p = .52$], Trial type [$F(3, 80) = 53.2$, $p < .001$, $\eta^2_p = .4$], and an interaction between the two also emerged [$F(3, 80) = 4$, $p = .049$, $\eta^2_p = .05$] due to a higher switch cost in the incongruent vs. congruent trials (average switch cost: incongruent = 140 ms, congruent = 82 ms). Since patients who followed only one task rule most of the time might have had lower or no switching costs, correlation analyses were performed between switching cost and perseveration measures. Given that a negative correlation emerged between those two measures in the post-operative session (r = -.25, *p* = .024), an additional switching cost analysis was performed with the perseveration measure as a covariate. However, even after controlling for perseveration, no interaction between Group and Trial type emerged, confirming the previous results of no specific switch cost modulation in either of the three patients' groups.

Additionally, in order to verify whether an increase in perseveration had also consequences in terms of RTs, we correlated the absolute accuracy difference (i.e., perseveration measure) with the absolute RT difference between the two tasks. Four patients whose accuracy was null on the alternative task were excluded from the analysis. A positive and significant correlation (r = .43, *p* < .001) showed that patients who perseverated on one task responded more slowly on the alternative task, even when the response was correct.

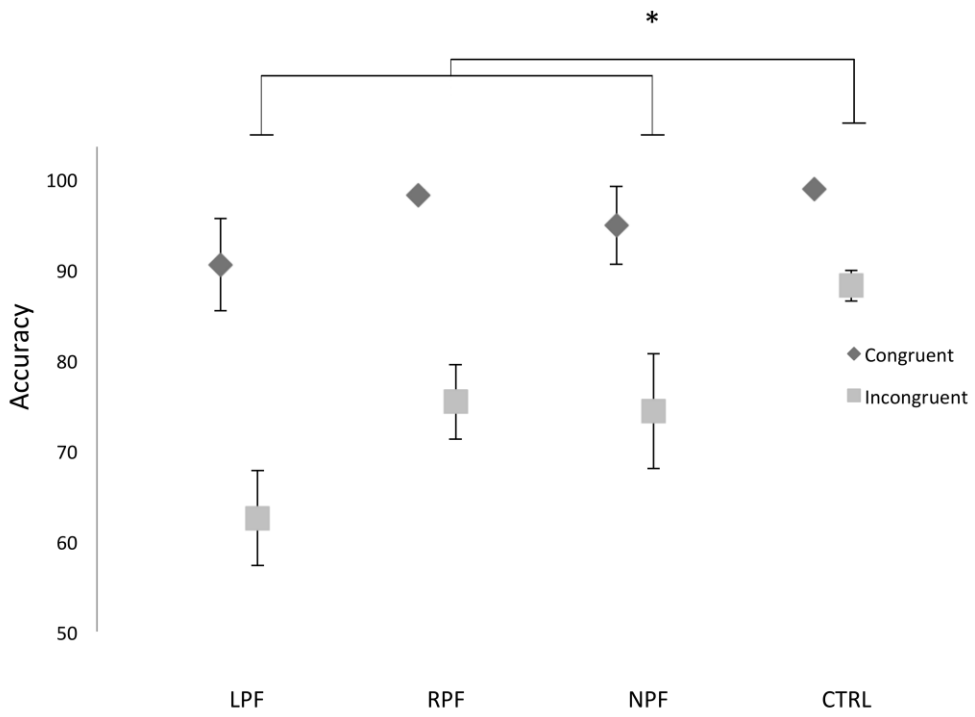

Figure 10. Accuracy (%) on congruent and incongruent trials. Significant group differences are indicated with an asterisk. The reported data are from the post-surgical session.

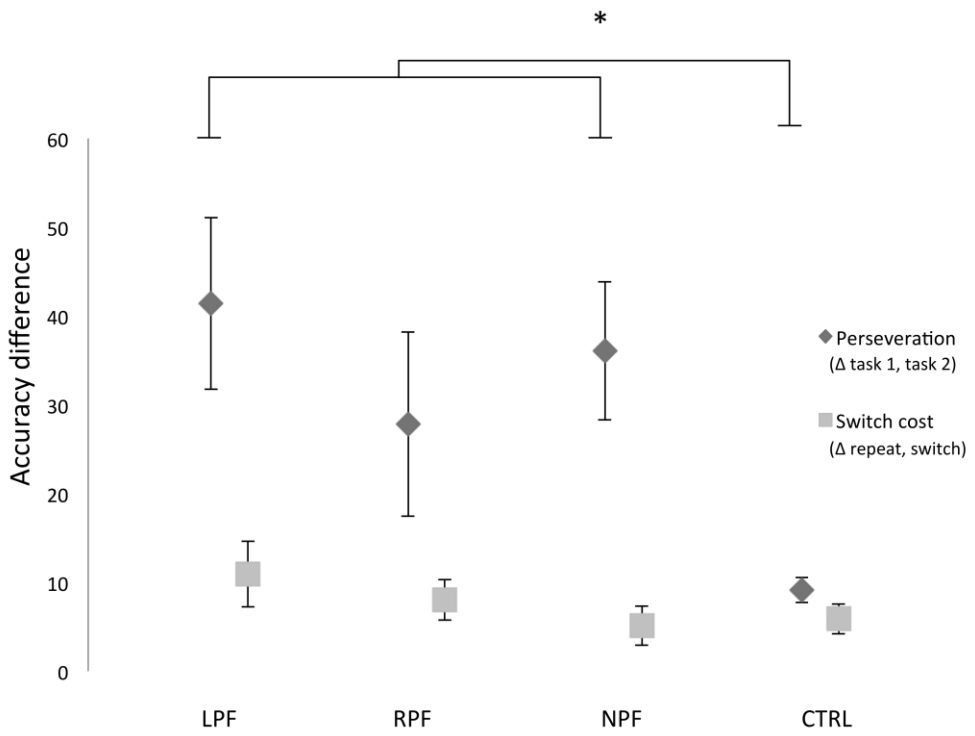

Figure 11. Absolute accuracy difference between the two types of tasks reflecting perseveration measure, and accuracy difference between switch and repeat trials reflecting the switching cost measure. Significant group differences are indicated with an asterisk. The reported data are from the post-surgical session.

3.3.2 SVR results

The brain-behavior relationship was investigated for measures that were found to significantly differentiate between the three patients' groups and the control group or that were a-priori determined. Thus, the prediction of behavioral measures from lesion data was performed for post-operative switching cost and perseveration measures, and for pre- and post-operative RTs. Only positive coefficients were considered as predictive since their higher values (i.e., more damage) corresponded to higher behavioral scores and RTs, which reflected poorer performance.

The correlation between actual scores and those predicted by the linear SVR model was significant only for perseveration (r = .3, p = 0.027). The corresponding scatter plot is shown in Figure 12. Areas that were found to be highly predictive

belonged mainly to (left) white matter pathways, in particular the anterior segment (fronto-parietal connections) and the long segment (fronto-temporal connections) of the arcuate fasciculus. Gray matter areas that contributed strongly in predicting perseveration were confined to left medial and lateral parts of the orbitofrontal cortex, left inferior frontal gyrus and left anterior cingulate cortex. The brain areas that resulted most informative in predicting the perseveration scores, together with their relative weights, are visualized in Figure 13 and reported in Table 3; only brain areas with weights > 2.5 are shown. The correlation of perseveration scores and lesion volume was non-significant (r = .13 and p = .79).

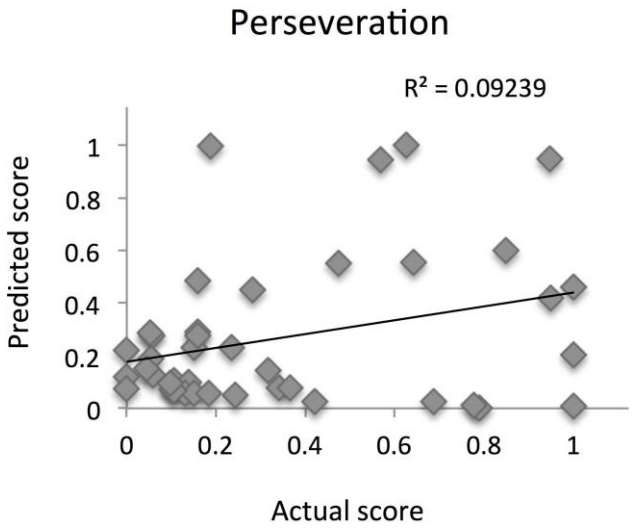

Figure 12. Correlation between actual and predicted perseveration scores obtained by means of lesion-based support vector regression predictions.

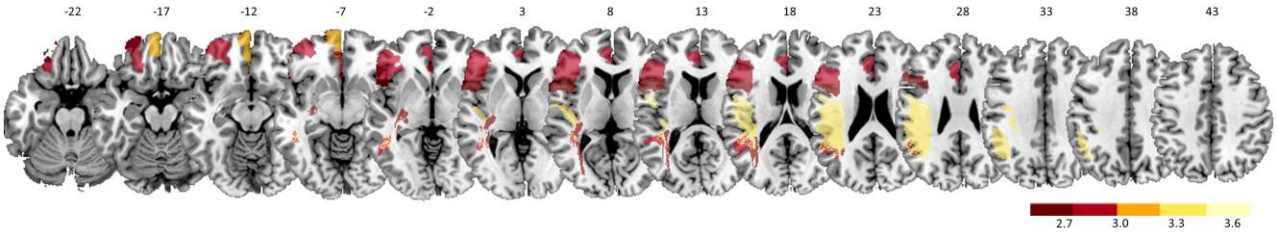

Figure 13. Brain areas with their relative weights that resulted significant in predicting the perseveration measure.

Table 3. Gray and white matter regions associated with perseveration

Measure	Actual and predicted score correlation	*p*-value	AAL/CAT label of predictive brain area	Hemisph.	Weight
Perseveration	0.304	0.027	Arcuate fasciculus anterior segment	L	3.678
			Arcuate fasciculus long segment	L	3.606
			Heschl gyrus	L	3.300
			Arcuate fasciculus	L	3.256
			Medial orbitofrontal gyrus	L	2.989
			Middle orbitofrontal gyrus	L	2.861
			Inferior frontal pars triangularis	L	2.837
			Anterior cingulate cortex	L	2.819
			Arcuate fasciculus posterior segment	L	2.776
			Optic radiations	L	2.538
			Inferior frontal pars opercularis	L	2.536

3.4 Discussion

In the present study, our aim was to individuate the cognitive and neural determinants of task-switching impairments observed in patients with prefrontal damage. In particular, by doing so, we were interested in addressing an ongoing debate regarding the processes underlying task-switching and their common vs. distinct engagement in trials that require switching vs. repeating the previous task, or that require interference control. We hypothesized that a disruption of a hypothetical switch-related process would produce a switch cost increase, probably more evidently during incongruent trials, as typically observed in task-switching paradigms (Wendt & Kiesel, 2008). Alternatively, a larger interference effect during both switch and repeat trials would suggest a disruption of a common process required to overcome conflict, probably not selectively engaged during task-switching performance, but also on other tasks demanding interference control (e.g., Stroop, Flanker, etc.; see Tsuchida & Fellows, 2012 for a similar result).

Our main finding showed a strong accuracy interference effect in patients with LPF and NPF damage, without a significant switch cost increase in any of the three patient groups, neither in terms of RTs nor accuracy. However, a more careful inspection of the patients' performance pointed to a more severe form of switching impairment: often LPF but also NPF patients applied only one task rule throughout the task, while less frequently they switched to the alternative one. This made their accuracy high on congruent trials, where both task rules required the same response. Conversely, on incongruent trials their performance was significantly reduced, but mostly on trials in which the alternative task rule had to be followed. Since the presentation of the cue, which comprised also the stimulus-response key association, allowed participants to fully prepare for the upcoming task, we suggest that the rule perseveration observed in those patients is due to their inability to use that information to bias their attention towards the alternative task stimulus attribute. Another possible interpretation of our results could be that perseverating patients, rather than being unable to switch to the alternative task, were unable to perform it because of its spatial

and verbal/non-spatial components, which are known to rely on differently lateralized brain regions (Cai, Van der Haegen, & Brysbaert, 2013; Gotts et al., 2013). This hypothesis would probably be valid if any differences between the groups emerged already on the single task, which was not the case. Moreover, a closer look at the accuracy difference between the two single tasks in the perseverating group of patients showed that only one LPF patient had a post-surgical decrease specific for the letter position task, whereas in all other cases the accuracy in the single task blocks remained similar between the two types of task.

Based on previous literature and on the evidence provided by the present work on both prefrontal and non-prefrontal involvement in task-switching execution, the brain-behavior relationship was investigated more in detail by means of a multivariate method, which takes into account the interactions between spatially distributed lesions (Zhang, Kimberg, Coslett, Schwartz, & Wang, 2014). In this more fine-grain analysis we considered switching cost and perseveration measures as two possible behavioral outcomes of more localized, albeit distributed lesions. A significant prediction of the behavioral scores from the lesioned brain areas was obtained only for the perseveration measure. In particular, damage found in left hemispheric fronto-parietal and fronto-temporal white matter tracts, inferior frontal gyrus, and orbitofrontal and anterior cingulate cortices contributed significantly in predicting perseveration.

The association between task perseveration and left prefrontal areas is in line with previous neuropsychological findings, which mainly agree upon the central role of those areas in supporting task-switching execution (Aron, Monsell, et al., 2004; Mayr et al., 2006; Rogers et al., 1998; Tsuchida & Fellows, 2012). However, the type of impairment described in each of these studies is often diverging and frequently not accountable by a pure switching deficit. Indeed, the often-reported switch cost increase is usually followed by a reduced interference control. Overall, our results could partially explain these mixed findings by showing that a difficulty in switching between tasks, other than increasing the switch cost, might emerge as a tendency to perseverate on one task and, consequently, reduce the performance on incongruent trials. Nevertheless, our results

are based only on accuracy and therefore might not resemble the effects found in other studies, which mostly report the interference effects in terms of RTs. Hence, we correlated perseveration and RT difference between the two tasks and observed that patients who often failed to switch to the alternative task showed also longer RTs when performing it correctly. This result thus demonstrates that patients attempted to switch between tasks, but probably failed because of the difficulty in implementing the weaker task set. Moreover, it elucidates how previous interference resolution and switching deficits might have a common underlying impairment.

Perseveration errors in prefrontal patients commonly emerge on the Wisconsin Card Sorting Test (WCST) (Barceló & Knight, 2002; Stuss et al., 2000), which is mostly employed during clinical neuropsychological assessment of cognitive flexibility. Typically, when perseverating, patients continue to sort the card based on the previous rule, even after they are informed that the rule has changed. The WCST is known as a complex cognitive task that entails multiple processes and therefore its specificity has been frequently debated (Nyhus & Barceló, 2009). However, it has been demonstrated that different types of perseverative errors on WCST rely on distinct frontal and non-frontal regions (Nagahama, 2005). In particular, it has been observed that stuck-in-set perseverations, which reflect the inability to shift from one task, or in this case category, to another, have been associated with left (and right) frontal regions, while recurrent perseverations, which reflect intrusions from previously abandoned tasks or categories, rely on left parietal regions. Although in our switching paradigm it was not possible to dissociate the two types of perseverations due to frequent task switches, the observation of perseverative behavior after left fronto-parietal damage is in line with the above reported findings.

A similar perseveration impairment in task-switching was previously observed in patients with lesions involving the basal ganglia (Yehene, Meiran, & Soroker, 2008) where some of them presented a no-switch behavior by applying only one rule throughout the task, while the others made some attempts to switch between tasks but often failed. Although their performance was compared to that of a group of patients

with prefrontal lesions, the authors reported no similar deficit in the latter group. These results are quite in contrast to what we found, but could be partially accounted by a small number of patients with left prefrontal damage (N=2) included in their study. However, the fact that our lesion-symptom mapping analysis did not show a significant involvement of basal ganglia and perseveration is a bit more concerning. One possible explanation could be that our patients' lesions were not so localized, especially after surgery, and therefore often involved subcortical structures, which consequently were not informative enough for this type of analysis. From the MRI scans we identified 30 out of 41 patients whose lesions involved the basal ganglia, and 9 out of 11 highly perseverating patients had lesions in those regions (8 involving the left basal ganglia). These descriptive data point to a possible association between those regions and perseveration, although it is more conceivable that the white matter pathways connecting frontal with posterior and subcortical regions might have a more critical role in the observed switching impairments. This hypothesis is also supported by recent neuroimaging studies that explored the neural dynamics during acquisition and implementation of novel task rules (Hartstra, Kühn, Verguts, & Brass, 2011; Ruge & Wolfensteller, 2010). In particular, these studies found that the initial learning phase relied more or less exclusively on fronto-parietal network activation, which decreased rapidly and was followed by a rapid increase of fronto-striatal cooperation, reflecting the early stages of task automatization. According to these findings, damage to both the fronto-parietal and fronto-striatal networks could disrupt the rule implementation ability. However, due to a relatively low number of trials in our task design, we were not able to distinguish between learning and automatization stages and future studies should try to dissociate them within patients suffering from different cortical and subcortical lesions.

Finally, the results from the RT analyses yielded a generalized slowing only in patients with RPF damage that was present both before and after surgery, and therefore cannot be interpreted as a consequence of surgery, as was seen in other patient groups. This result partially resembles the one from the first study (chapter 2) in

which RPF patients, together with LPF patients, had longer RTs on Go/No-Go and Foreperiod tasks. Moreover, the sustained attention impairment observed in that study in RPF patients, where they frequently omitted to respond to the stimuli, could have emerged as an RT increase in this study that was self-paced (i.e., the stimulus stayed on the screen until a response was detected). However, the lesion-symptom mapping analysis did not associate any pattern of lesions to higher RTs either in the pre- or in the post-surgical session. Therefore this result and its interpretation should probably be taken with caution and investigated more carefully with a specific task design.

In summary, the results from this second study confirm and extend those from the first study in which LPF regions seemed to be critically involved in creating a stable stimulus-response association. We show that lesions in LPF areas and along the left fronto-temporal and fronto-parietal white-matter tracts create a more severe task-setting impairment, which within the task-switching context is not reflected as a mere difficulty in switching between two task rules, but instead as a difficulty in activating and implementing weaker task rules. These results are in line with recent neuroimaging studies showing that learning and task automatization are associated respectively with increased and decreased fronto-parietal network activation, reflecting the respective recruitment and release of cognitive control (Cole et al., 2013; Fair et al., 2007; Mohr et al., 2016). Future neuropsychological studies should investigate whether damage across different networks involving the prefrontal regions might dissociate the acquisition and automatization stages of task rule implementation.

CHAPTER 4

CAN PREFRONTAL LESIONS ACCOUNT FOR GENERAL COGNITIVE DECLINE?

4.1 Introduction

Despite there is a general agreement that the involvement of the prefrontal cortex (PFC) is crucial in executive functioning, the organization of executive functions (EFs) within the PFC and its interaction with the rest of the brain while implementing these functions is still a highly investigated area in cognitive neuroscience. Partly this is due to the anatomical complexity of the PFC and its considerable inter-individual variability (Petrides & Pandya, 1994; Rajkowska & Goldman-Rakic, 1991). However, a major problem in studying the functional organization of the PFC is the low validity of the EF tasks (Chan et al., 2008). Since EF are a set of high-level processes that coordinate in a goal-directed manner other low-level processes, the assessment of a hypothetically distinct EF by definition implies the recruitment of other processes. This has been an even major issue in the neuropsychological approach that often employed complex tests because of their sensitivity to frontal lobe damage, hence lacking the specificity to isolate particular sub-processes. To overcome this task impurity obstacle, studies investigating EFs within neurologically healthy individuals have adopted a latent variable approach, which, by definition, extrapolates only common variance across different EF measures, while reducing the influence of low-level processes (Friedman & Miyake, 2017).

Recently, similar methods have been applied on the measures obtained from clinical neuropsychological assessments to investigate the neural substrates of high-level cognition (Barbey et al., 2012; Gläscher et al., 2010). The focus was on the general intelligence factor (*g*), which reflects the common variance shared across a variety of

cognitive tests, and the relationship with EF measures. Impairments on measures of general intelligence and executive functioning were associated with lesions to a shared left-lateralized fronto-parietal network and the relative white matter connections. Moreover, damage across most of these regions was related to poor performance on single subtests measuring both executive and non-executive functions, which clearly points to the dependence of derived, higher-order measures, like general intelligence and EFs, on the functional integration among separate brain regions supporting different cognitive processes.

Other lower-level processes including motor, language, memory and attention domains have been found to be associated with lesions in a specific set of relatively distributed regions (Corbetta et al., 2015). However, deficits across multiple domains, identified with higher-order factors, were strongly related with damage in subcortical structures and regions containing multiple white matter tracts (Corbetta et al., 2015). These findings, as well as those reported above, are all in line with the recently emerging literature that highlights the importance of inter-regional connectivity in accounting for behavioral deficits involving associative functions (Boes et al., 2015; Siegel et al., 2016).

However, these explanations are quite in contrast with plenty of neuropsychological and neuroimaging studies that brought evidence of functionally specialized prefrontal areas (Aron et al., 2014a; Botvinick, Cohen, & Carter, 2004; Muhle-Karbe et al., 2016; Robinson et al., 2012; Stuss & Alexander, 2007; Tsuchida & Fellows, 2012). Even though these studies have often assigned different cognitive processes to the same prefrontal areas, there is still some consensus regarding the involvement of distinct regions in particular EFs supported by meta-analytic reviews (Kim, Cilles, Johnson, & Gold, 2012; Nee, Wager, & Jonides, 2007; Rottschy et al., 2012), which speaks in favor of a fractionated organization of the PFC. Recently, with the advancing of large-scale network studies in patients with focal brain injuries, the integrative and modular views of brain functional organization have shown to be partially coherent (Gratton et al., 2012; Warren et al., 2014). In particular, it has been

observed that lesions in target locations (i.e., hubs), which mediate the interactions among other regions, produce more severe and widespread cognitive deficits, with respect to damage in other, peripheral regions that cause more restricted impairments.

Here we approached this issue by investigating whether surgically induced lesions, as those provoked by tumor removal, cause stronger cognitive decline if carried out in specific brain areas. In particular, we focused on brain tumor patients because of the possibility to assess the change in cognitive functioning, which in stroke patients is not possible. Moreover, the damage distribution in stroke patients follows inevitably the neurovascular architecture, and often has a subcortical topography, weakening the anatomo-functional associations in less represented cortical areas (Corbetta et al., 2015). Previous studies exploring cognitive impairments in brain tumor patients observed that most of the post-surgical decline can be accounted for by the tumor histology: patients operated for low-grade glioma show stronger effects of surgery with respect to other tumor types (Campanella et al., 2015; Desmurget, Bonnetblanc, & Duffau, 2006; Talacchi, Santini, Savazzi, & Gerosa, 2011), probably because of its slow-growing infiltrative nature that allows functional activity within the tumor mass (Schiffbauer, Ferrari, Rowley, Berger, & Roberts, 2001). However, as discussed earlier, there is an emerging body of evidence supporting the fact that lesions in circumscribed areas, which interact with different networks, can give rise to multiple deficits. On that ground, we predicted that patients undergoing surgical tumor removal in certain areas, especially in confined prefrontal or subcortical regions, could reveal stronger cognitive decline, regardless of the tumor type. Finally, in order to obtain a purer measure of general cognitive functioning, and avoid localization and/or lateralization driven by low-level processing impairments (e.g., language, visuo-spatial attention), a latent-variable analysis was applied on a number of neuropsychological tests, which were selected because of their low complexity, reliance on different low-level processes and necessary involvement in higher cognitive functions.

4.2 Materials and methods

4.2.1 Participants

Patients with age ranging from 18 to 85 years and undergoing a brain tumor operation at the University Hospital of Padova were recruited on a voluntary basis to participate in the study. Recurring brain lesions and previous neurological and psychiatric disorders were considered as a priori exclusion criteria. Seventy-nine patients were tested on a comprehensive neuropsychological battery both before and after surgery. Twenty-five patients were excluded a posteriori mainly due to acute post-surgical difficulties (e.g., strong headaches, motor and language impairments) or to logistical issues. According to the histopathological exam of the lesion, from the remaining 54 patients, 24 had high-grade glioma (HGG), 9 had low-grade glioma (LGG), 14 had meningioma (MEN) and 7 had metastases (META). Additionally, according to the location of the tumor's center of mass and the area with the highest number of damaged voxels, patients were subdivided in three groups: left prefrontal (LPF, n = 15), right prefrontal (RPF, n = 14) and non-prefrontal (NPF, n = 25) groups. Tumor grade distribution was not significantly different across LPF, RPF and NPF groups of patients (p = .7, Fisher's exact test). Lesion overlap maps obtained from their MRI or CT scans are shown in Figure 14.

In order to control for learning effects, 49 healthy control participants were tested with the same procedure twice, on average after 8.1 days (SD = 3.2) from the first session. Difference in days between the two sessions was comparable across tumor type patient groups and controls (p = .1), while it was different across tumor location patient groups and controls (p = .02)[5]. Age and education were comparable in both tumor type and lesion location patient and control groupings (all ps > .05). All but three participants were right-handed (two from the RPF group and one from the control group), as assessed by the Edinburgh Handedness Inventory (Oldfield, 1971). Demographical and etiological data are reported in supplementary material Table S1.

[5] Control analyses were performed that included the temporal distance between the two testing sessions as a covariate. None of the reported results changed.

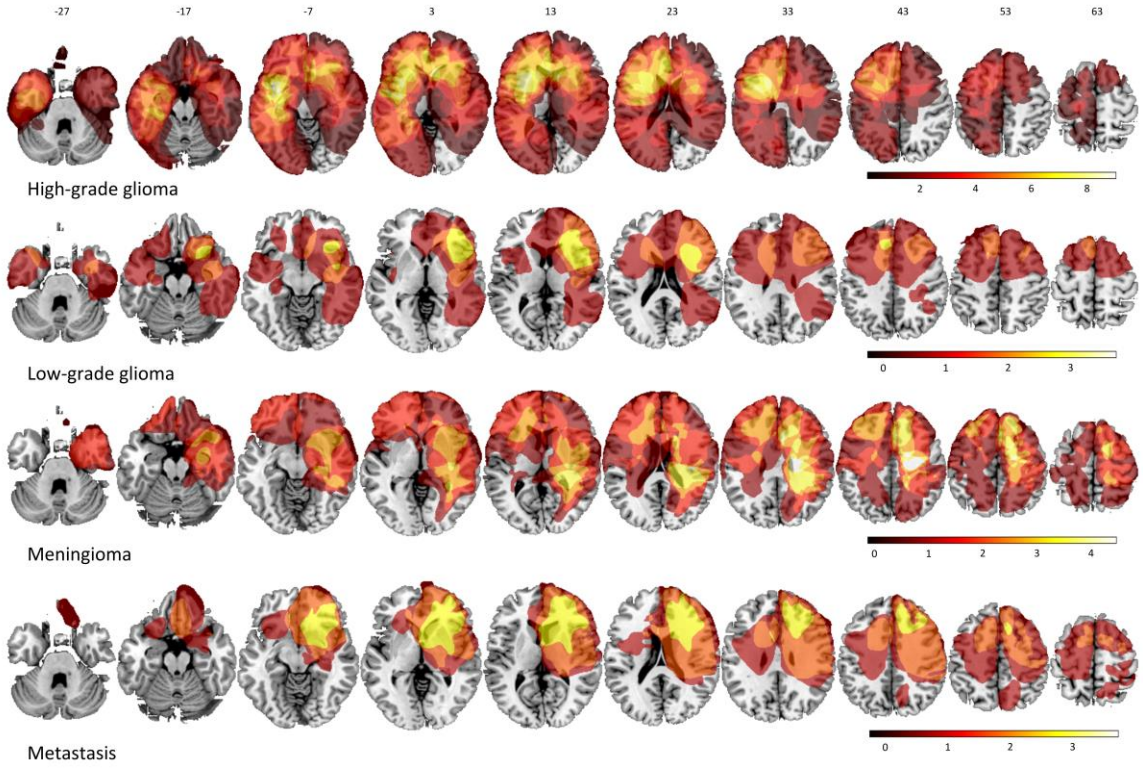

Figure 14. Lesion overlap maps across different tumor types. The color bar indicates the number of patients whose lesions overlap on one voxel.

4.2.2 Neuropsychological assessment

All patients were tested on average 4 days (SD = 7.1) before and 5.6 days (SD = 2.2) after the operation, and besides the neuropsychological tests, they completed other computerized tasks reported in the previous two studies (chapter 2 and 3). The neuropsychological assessment included the Mini Mental State Exam (MMSE) and the Italian version of the National Adult Reading Test - TIB, which provided a measure of general cognitive function and intellectual ability. We also assessed verbal and spatial short-term memory (Digit Span, Corsi), visuo-spatial abilities (Trail making test - A) and phonemic fluency. As briefly outlined in the introduction, the latter four neuropsychological tests were selected because of their low complexity and relevant

involvement in higher cognitive functions. Moreover, they all rely on distinct low-level processes, which is a fundamental requirement for latent variable extraction. Data from these six measures were included in the analysis. Data from all patients and the tests' references are reported in supplementary material Table S1. Additionally, a brief denomination and comprehension test (Rodolfi, Gasparini, & Ghidoni., 2011) was included in the assessment in order to exclude patients with language deficits that could invalidate other tests' results. All participants gave their written informed consent before the experimental testing session. The study was approved by the Bioethical Committee of Azienda Ospedaliera di Padova and was conducted according to the guidelines of the Declaration of Helsinki.

4.2.3 Data preparation and statistical analysis

Neuropsychological data from both patient and control groups were corrected for age, sex and/or education based on the normative sample data provided in the above referenced test manuals. Due to technical issues some of the participants did not perform all tests and the following imputation procedure was performed to fill the missing data (3.64%). First, we performed a multiple regression analysis on all tests but separately for each session, and excluded outlier data that had absolute standardized residuals higher than 2.5. Next, missing data were filled with values predicted from a secondary multiple regression analysis, which did not consider outliers[6]. Finally, all tests' scores were standardized with respect to the sample mean, to have the same relative scale before proceeding to the statistical analysis.

A principal component analysis (PCA) was performed on the data to obtain fewer measures (i.e., factors) that explain as much common variation between the tests' scores as possible, across all participants. Since our main aim was to quantify the impact

[6] Additional analyses revealed that the imputation procedure we used did not bias our subsequent PCA analysis. We indeed performed a PCA on the pre-operative data using the alternating least squares algorithm as implemented in Matlab, a procedure that is able to effectively handle missing data. The resulting factor scores were highly correlated to the ones obtained in our principal analysis (n = 103; r > .99, ρ > .99; both ps < 10^{-107}). We also performed additional PCA analyses with both pairwise and casewise deletion of missing data. Again, the resulting factor scores were virtually identical to those obtained in our principal analysis (in both cases, n = 89; r > .99, ρ > .99; ps < 10^{-115}).

of surgery across different tumor types and locations, a PCA was first carried out on pre-operative neuropsychological scores. The loadings from this factor solution were then used to compute the factor scores from the post-operative measurements, in order to measure the modulation of the same factors after the operation[7]. These pre- and post-operative factor scores where then compared between different groups of patients (tumor type or tumor location) and controls by means of an ANOVA for repeated measures. Additionally, the same ANOVA was performed for each test score separately, so as to potentially identify tests that are sensitive to damage in certain areas and/or to post-surgery impairments in different types of tumors. The sources of significant main effects and interactions were investigated by means of Duncan's post-hoc tests.

4.2.4 Lesion mapping and analysis

In order to obtain a more circumscribed lesion location that might be involved in greater post-surgical decline, a voxel lesion-symptom mapping (VLSM) analysis was performed with the impact of surgery (i.e., difference between pre- and post-operative scores) as the dependent variable. Additionally, the same analysis was performed on the scores averaged across the two sessions and single test measures, as control analyses. In a voxel-wise manner, we compared the performance between two groups of patients (i.e., whose lesions involved and did not involve the given voxel) by means of a t-test, with a statistical threshold set at $p < .05$ corrected for multiple comparisons (False Discovery Rate). Lesion volume effects were regressed out from the behavioral scores. In order to minimize possible outlier effects, only voxels damaged in three or more patients were included in the analysis. Tumor lesions were manually drawn on pre-operative structural MRI (T1, T2 or FLAIR) or CT axial slices with MRIcroN (Rorden & Brett, 2000). Both images and lesions were normalized to an age-appropriate template brain using the Clinical Toolbox (Rorden et al., 2012) for SPM12 (Statistical Parametric Mapping; http://www.fil.ion.ucl.ac.uk/spm) using enantiomorphic normalization (Nachev et al., 2008).

[7] A secondary PCA was conducted only on post-operative measures and control analyses were performed on the resulting scores. All reported results remained unchanged.

4.3 Results

4.3.1 Factor scores

The PCA on pre-operative scores yielded two factors with an eigenvalue > 1 (2.41 and 1.09). The optimal number of factors to be extracted was determined by carrying out a permutation-based parallel analysis (Horn, 1965) and the Velicer's minimum average partial correlation test (Velicer, Eaton, & Fava, 2000). Both procedures indicated that only one factor had to be retained, which accounted for 40.1% of variance in participants' performance. The factor loadings for each test are given in Table 4. The retention of one factor was motivated also by its methodological significance, since our main aim was not to study specific processes or functions, but instead to have a single measure that captures a more general cognitive impairment before and after brain surgery.

Tumor type. The analysis of pre and post-operative factor scores between different tumor types revealed a main effect of tumor type [$F(4, 98) = 20.78$, $p < .001$, $\eta^2_p = .46$] and critically, an interaction between tumor type and surgery [$F(4, 98) = 3.61$, $p = .009$, $\eta^2_p = .13$] (Figure 15). Post-hoc test for the main effect of tumor type showed that all four groups of patients performed significantly worse with respect to the control group (all *p*s < .01). However, the post-hoc test for the tumor type × surgery interaction showed that only LGG patients had a significant decrease in cognitive performance after surgery ($p < .001$), while in all other groups the post-operative performance did not change with respect to pre (all *p*s > .27). Moreover, the impact of surgery (i.e., pre – post-operative change in performance) in the LGG patients was significantly different when compared to all other patient and control groups (all *p*s < .012).

Tumor location. When pre- and post-operative factor scores were compared between groups with different lesion sites, only the main effect of tumor location emerged [$F(3, 99) = 26.38$, $p < .001$, $\eta^2_p = .44$] (Figure 15). All patient groups had lower performance when compared to controls (all *p*s < .001); moreover, LPF patients' performance was significantly lower with respect to NPF patients ($p = .042$) and marginally lower with respect to RPF patients ($p = .058$).

4.3.2 Neuropsychological scores

The main effects of group and group × surgery interactions for separate test score analyses are reported in Table 5; the multiple comparison False Discovery Rate correction was applied. Significant results are highlighted in bold. The post-hoc tests for the group main effects in tumor type and tumor location group comparisons showed the following significant differences. TMT-A resulted sensitive to damage in LPF and RPF areas (both control group comparison *p*s < .04), while phonemic fluency was more compromised in LPF than in RPF patients ($p = .043$). Regarding the sensitivity of each test score to the impact of surgery across different tumor types and locations, the Digit Span showed a significant post-operative decrease in LGG patients only ($p < .001$), while the MMSE score decreased significantly in LPF patients only ($p = .003$).

Table 4. Factor loadings for each test

Test	Factor Loadings
Digit Span	-0.6821
TMT-A	-0.5748
Phonemic fluency	-0.7301
Corsi	-0.5503
MMSE	-0.5807
TIB	-0.6627
Variance explained	40.13%

Table 5. Main effects and interactions for each test score analysis.

Group comparison	Test	Group main effect			Group × Surgery interaction		
		F	*p*	*η2p*	*F*	*p*	*η2p*
Tumor histology (HGG, LGG, MEN, META), Controls	Digit Span	**7.16**	**0.000042**	**0.23**	**3.68**	**0.007760**	**0.13**
	TMT-A	**4.05**	**0.004404**	**0.14**	2.13	0.082256	0.08
	Phonemic fluency	**16.65**	**0.000000**	**0.40**	1.10	0.361243	0.04
	Corsi	**6.90**	**0.000061**	**0.22**	0.80	0.528842	0.03
	MMSE	**7.51**	**0.000026**	**0.23**	2.16	0.078935	0.08
	TIB	**4.77**	**0.001473**	**0.16**	1.19	0.319973	0.05
Tumor location (LPF, RPF, NPF), Controls	Digit Span	**8.29**	**0.000057**	**0.20**	0.65	0.586490	0.02
	TMT-A	**3.31**	**0.023088**	**0.09**	1.00	0.396945	0.03
	Phonemic fluency	**18.99**	**0.000000**	**0.37**	1.52	0.212788	0.04
	Corsi	**9.85**	**0.000010**	**0.23**	3.03	0.033042	0.08
	MMSE	**8.52**	**0.000043**	**0.21**	**4.13**	**0.008359**	**0.11**
	TIB	**5.96**	**0.000891**	**0.15**	1.79	0.153168	0.05

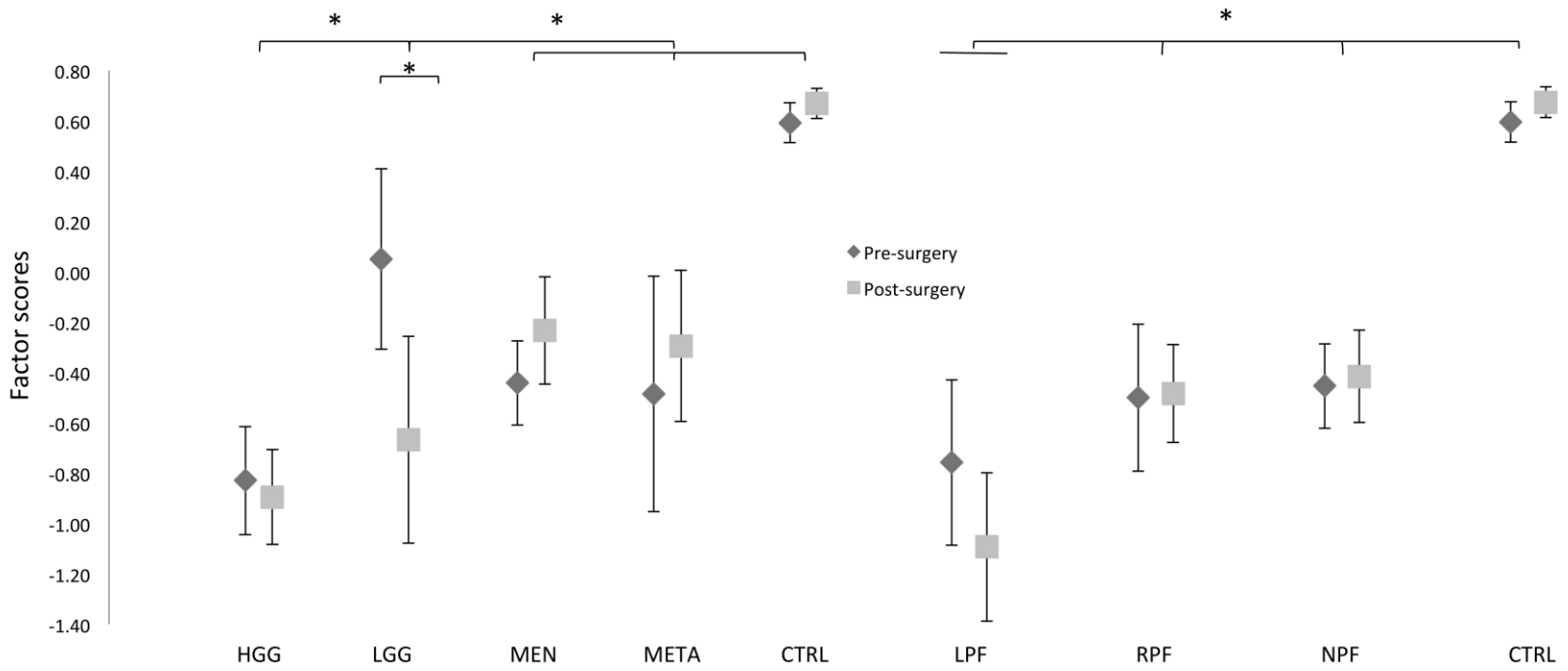

Figure 15. Factor scores on pre- and post-surgical sessions across different tumor types (left) and different tumor locations (right). Significant group and/or session differences are indicated with an asterisk.

4.3.3 Lesion-symptom mapping

The lesion-symptom mapping analysis showed a significant association between general cognitive decline due to the operation (i.e., pre-post surgical factor scores) and lesions localized to the left precentral gyrus including the inferior frontal junction (IFJ; peak z-score MNI coordinates: -52, -3, 37) and the left middle frontal gyrus (MFG; peak z-score MNI coordinates: -43, 3, 53) (Figure 16). Additional analyses on single test measures and across session impairments did not yield any significant brain correlates.

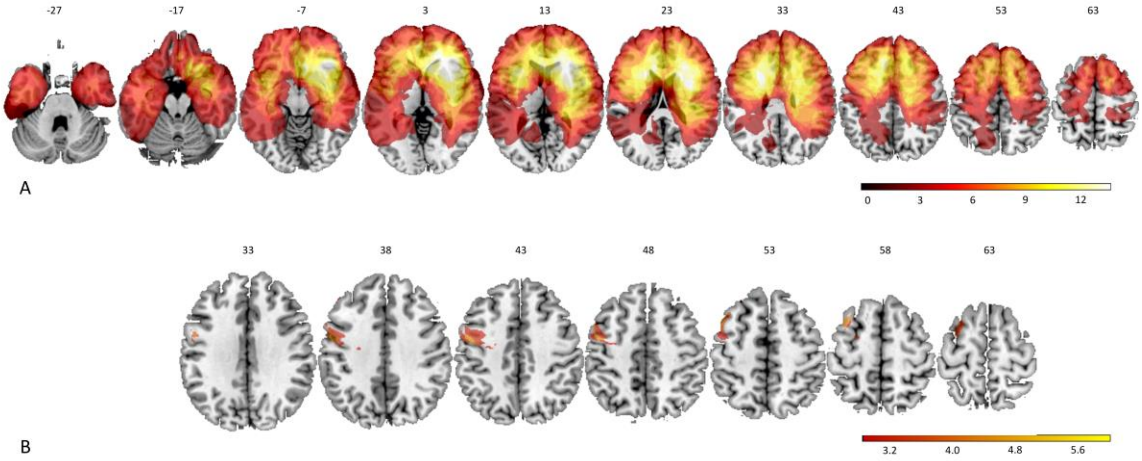

Figure 16. A) Voxels included in the lesion-symptom mapping analysis. B) Areas significantly associated with a post-surgical cognitive decline.

4.4 Discussion

In the present study, we investigated whether the impact of brain tumor surgical treatment on general cognitive functioning is mainly accounted by tumor histology as usually observed (Campanella et al., 2015; Desmurget et al., 2006; Talacchi et al., 2011), or could also be related to tumor location. Importantly, we applied a latent variable analysis on distinct cognitive test scores so as to obtain a general cognitive functioning measure while minimizing the influence of lower-level processing requirements. We also performed a lesion-symptom mapping analysis to identify brain locations associated with greater post-surgical cognitive decline.

The tumor type group comparison confirmed that patients operated for low-grade glioma (LGG) showed a stronger decrement of cognitive efficiency after surgery as compared to other patient groups. However, a finer-grained lesion location analysis showed that the effect of surgery on general cognitive functioning was significantly higher in patients with lesions involving left middle frontal and precentral gyri. Critically, out of nine LGG patients, only two had lesions in the left MFG, and one in the precentral gyrus, thus excluding the effect of tumor histology on the observed anatomical association.

The implications of these findings are relevant from both theoretical and clinical points of view. The association of rather defined cortical areas to a behavioral measure that accounts for a significant amount of variance across different neuropsychological scores supports the existence of restricted brain regions involved across multiple, specialized sub-networks, and subserving a vast range of high-level cognitive abilities (Bertolero et al., 2015). Importantly, a brain region to be characterized as such must be associated with many different cognitive functions, which is the case in literature for both left middle frontal and precentral gyrus regions. Specifically, the area within the precentral gyrus observed in our study comprised the inferior frontal junction (IFJ) (Derrfuss, Brass, Neumann, & von Cramon, 2005) that previous fMRI studies and metaanalyses have observed to be consistently involved across different cognitive control tasks (Derrfuss et al., 2005; Derrfuss, Brass, & von Cramon, 2004; Kim et al., 2012; Kim, Johnson, Cilles, & Gold, 2011), and whose functional role has been proposed to involve the integration of information across premotor, language and working memory domains (Brass, Derrfuss, Forstmann, & von Cramon, 2005). Furthermore, consistent with this hypothesis but also with our findings, a decline across various neuropsychological EF measures in early dementia has been reported as related to glucose hypometabolism in left IFJ (Schroeter et al., 2012), confirming the importance of this brain region for cognitive control processes in general. Similarly, at least one region within the posterior part of the left MFG has been identified by two different methods (i.e., lesion mapping and fMRI) as sensitive to different domains of tasks involving high

levels of executive processing (Volle et al., 2008), suggesting its global role in executive control.

Our results are also in line with recent brain lesion literature evaluating the consequences of focal damage across functional brain networks (Gratton et al., 2012; see Aerts, Fias, Caeyenberghs, & Marinazzo, 2016 for recent review). Damage to regions important for communication between networks has been shown to cause the largest disruptions in network organization. In a recent study that evaluated the neuropsychological consequences of altered functional connectivity (Warren et al., 2014), the authors found that focal lesions in regions mediating interactions among sub-networks cause more widespread cognitive impairments with respect to comparable lesions in less participating regions. Critically, one of six individuated target regions was located in the posterior part of the left MFG, in proximity to both left middle frontal and precentral gyrus regions found in our study. With a somewhat different approach in identifying the network organization following stroke, Zhu and colleagues (2016) found dysfunctional connections mainly in the left prefrontal areas. Interestingly, the altered nodal centrality (i.e., number of nodes showing correlation with a given node) of the left MFG was associated with a decline in general cognitive functioning, as indexed by a low MMSE score, a measure that was also included in our factorial analysis. Thus, findings from all these studies are well in line with the general cognitive decline that we observed after tumor resection in left prefrontal areas comprising the MFG and IFJ supporting their participation across different cognitive functions.

Within brain tumor patients, the impact of tumor location on cognitive functions was mainly explored by means of intraoperative electrical stimulation mapping of language and few other more detectable functions like sensorimotor and visuo-spatial abilities (see Duffau, 2010 for a review). Intraoperative mapping of higher-level cognitive functions has been a more difficult enterprise, given the complexity and length of the tests employed, and the fact that the patient's performance on these tests is difficult to interpret within the intraoperative setting (but see Wager et al., 2013). Moreover, the reliance of cognitive control abilities on multiple brain structures and the

plausible participation of single regions across distinct networks supporting diverse functions render the EF intraoperative mapping rather difficult.

On the other hand, studies investigating network alterations in tumor patients found that lower between-network integration and higher modularity were associated with decreased cognitive efficiency, both before (van Dellen, Douw, et al., 2012; Xu et al., 2013) and after (Bosma et al., 2009; Huang et al., 2014) tumor resection, thus resembling the functional and behavioral consequences of focal damage observed in stroke patients. However, only few studies have approached longitudinally the functional and behavioral consequences of surgery-induced lesions in brain tumor patients. Van Dellen and colleagues (2012) studied a group of ten LGG patients and observed that patients with post-surgical increase in functional connectivity showed moderate cognitive improvements across different domains (i.e., memory, attention, executive function). Similarly, in a more recent study (Carbo et al., 2017) on a larger cohort of patients (N = 28) undergoing brain surgery for different pathologies, it was observed that post-operative cognitive decline was related to the loss of dynamical patterns in functional connectivity that, according to the authors, reflect a decrease in the distribution of cognitive demands and a subsequent overload of network hubs. Altogether, these findings point to the fact that high-level cognitive deficits in brain tumor patients are mostly reflected in whole-brain network disturbances, which are mainly observed as increases in local and decreases in global functional connectivity (Derks, Reijneveld, & Douw, 2014). However, more thorough investigations, taking into account tumor type and tumor location, are needed to determine the possible causes of functional and behavioral variability observed before and after brain tumor surgery.

Clinically, defining brain regions highly involved across different sub-networks, and thus supporting a broad range of high-level cognitive abilities, may facilitate tailored tumor resections and improve cognitive surgical outcomes. Recently, findings from intraoperative electrical stimulation mapping in patients undergoing awake tumor surgery contributed to an increase of anatomo-functional associations, especially at subcortical levels (see Duffau, 2017 for recent review). In the neurosurgical approach,

this led to a hodotopical model of the brain anatomo-functional organization according to which cognitive functions are supported by extensive networks comprising both cortical functional epicenters ('topo' or sites) and white matter connections between these sites ('hodo' or pathways) (De Benedictis & Duffau, 2011). Thus, the hodotopical model could also account for our results in which surgical lesions in defined frontal regions were found to be associated with a cognitive decline across different neuropsychological measures. Nevertheless, according to these authors, even extensive frontal lobe resections are not supposed to cause permanent cognitive deficits (Duffau, 2012), however probably because of the compensatory mechanisms, which especially occur in slowly growing tumors. Indeed, our results show that the strongest cognitive decline is caused by surgery in defined left prefrontal areas that were however least involved in LGG patients. This highlights the importance of considering tumor histology when studying cognitive processes in tumor patients, but also the importance of individual pre-surgical planning in preserving cognitive functioning, which should take into account both tumor type and tumor location.

Several limitations, however, have to be considered in interpreting the observed results. The measures we adopted, although sensitive to frontal lobe damage, do not provide a comprehensive assessment of high-level cognitive abilities, and future studies should investigate whether the factorial solution variance relying on a large and varied test base can be accounted for by lesions in similar brain regions. Second, it is supposable that the factorial solution we obtained might be partially induced by patients whose lesions affect spatially near functional regions, even though this bias was certainly reduced with the inclusion of the control group. Finally, the fact that we observed left-lateralized prefrontal involvement in general cognitive functioning might be due to fact that three out of six measures we adopted relied on verbal abilities, even though patients with notable language impairments were excluded a priori. In particular, impairments on the phonemic fluency task, which had the highest factor loading in our study, were previously related to damage within precentral regions (Baldo, Schwartz, Wilkins, & Dronkers, 2006) but also other left frontal regions not

found in our study (e.g., inferior frontal gyrus in Robinson et al., 2012). We performed additional lesion-symptom mapping analyses on single test measures in order to control for these possible biases, but no specific area emerged as being related to phonemic fluency, nor any other measured impairment. Furthermore, the areas that were found to be associated with post-surgical decline are not always found as strictly related to language impairments. As mentioned before, the MFG has been characterized as a multimodal region underlying both verbal and spatial cognitive control processes (Volle et al., 2008), while the IFJ was associated with both verbal and non-verbal EF deficits (Schroeter et al., 2012). Moreover, the asymmetrical involvement of left prefrontal areas within different cognitive functions is rather consistent across studies that investigated the neural correlates of general intelligence and executive functioning in stroke patients, while controlling for lower-level processes (Barbey et al., 2012; Gläscher et al., 2010). Yet, the underpinnings of prefrontal asymmetries and why they emerge is still not fully understood. However, differences between inter- and intra-hemispheric interactions observed between the two hemispheres might shed some light on their processing specializations. In particular it has been observed that, while left-lateralized regions have stronger interactions within the same hemisphere, right-lateralized regions interact equally strongly with regions from both hemispheres (Gotts et al., 2013), and therefore might suffer from left-lateralized lesions as well. However, asymmetries in inter- and intra-hemispheric interactions have only recently started to be explored in brain-damaged patients and related to behavioral impairments (Siegel et al., 2016).

In summary, our finding of rather confined left prefrontal areas critically involved in cognitive decline across different neuropsychological measures is in line with the recently suggested modular and integrated view of brain functional organization, according to which restricted brain regions are highly involved across different sub-networks and subserve a vast range of cognitive abilities (Bertolero et al., 2015). Future studies should investigate whether functional network alterations after tumor resection in cohesively connected brain regions can be related to greater post-surgical cognitive decline, in order to improve cognitive surgical outcomes.

CHAPTER 5

GENERAL DISCUSSION AND CONCLUSIONS

Most of the research devoted to the study of executive functions (EFs) agrees on defining them as high-level cognitive processes that, by coordinating and controlling other lower-level processes, allow goal-directed behavior (Koechlin et al., 2003; Miller & Cohen, 2001; Stuss & Alexander, 2000). However, the definition and differentiation of EF components has forged numerous different theories and models of EF organization (Jurado & Rosselli, 2007) that are mainly split into unitary and fractionated views. Even though with recent advancements in the neuroimaging field it has become increasingly evident that the brain functional organization relies on both modular and integrated network architectures (Baum et al., 2017; Bertolero et al., 2015; Cohen & D'Esposito, 2016; Shine et al., 2016), there is still little evidence on whether segregation and integration among distinct brain regions reflect putatively distinct EF processes or a common higher-level processing mechanism (Reineberg et al., 2015; Reineberg & Banich, 2016). In the present work we aimed at extending the knowledge on the fractionation of EFs by investigating whether EF impairments observed in brain lesioned patients are separable from other closely related cognitive abilities. In particular we investigated both distinct and common EF measures and explored their relationship with broader high-level and/or lower-level processes and their association with lesions across different prefrontal regions.

The main aim of our first study was to understand whether inhibitory impairments, previously found in patients with either left or right frontal lesions, could be better accounted for by assessing other potentially related cognitive processes, like

response selection and target detection. Thirthy-seven brain tumor patients with left prefrontal, right prefrontal and non-prefrontal lesions and a healthy control group were tested on Go/No-Go and Foreperiod tasks. According to the literature, in both types of tasks inhibitory impairments are likely to cause false alarms (Boulinguez et al., 2009, 2008; Jaffard et al., 2007), although additionally the former task requires response selection and the latter target detection abilities. Irrespective of the task context, patients with right prefrontal damage showed frequent Go and target omissions, probably due to sustained attention lapses. Left prefrontal patients, on the other hand, showed both Go and target omissions and high false alarm rates to No-Go and warning stimuli, suggesting a decisional impairment rather than an inhibitory one. An exploratory whole-brain voxel-based lesion-symptom mapping analysis confirmed the association of left ventrolateral and dorsolateral prefrontal lesions with target discrimination failure, and right ventrolateral and medial prefrontal lesions with target detection failure. Results from this first study suggest that neither left nor right prefrontal areas are likely to host a specialized inhibitory module, but rather support a broader set of cognitive control processes which work together in guiding successful response inhibition, among other executive abilities.

Left prefrontal areas, that we have been found to be involved in broader task-setting/response selection processes in our first study, are frequently associated with more complex cognitive abilities required during task-switching (Badre & Wagner, 2006; Kim et al., 2012; Vallesi et al., 2015). The goal of this second study was to investigate whether these abilities rely on the employment of a specific task-reconfiguration process, which according to some models is engaged only during switch trials (Mayr & Kliegl, 2000; Rogers & Monsell, 1995), or instead are based on a common interference resolution process required during both switch and repeat trials, but also during other cognitively demanding tasks (e.g., Stroop). To that purpose, we tested a group of 41 brain tumor patients with left prefrontal, right prefrontal and non-prefrontal lesions and a healthy control group on a task-switching paradigm. Although previous neuropsychological studies report a possible involvement of both left and right

prefrontal areas in task-switching (Aron, Monsell, et al., 2004; Mayr et al., 2006; Pohl et al., 2007; Rogers et al., 1998; Shallice, Stuss, Picton, et al., 2008; Tsuchida & Fellows, 2012), they do not clarify whether the weaker performance is caused by the inability to reconfigure the currently relevant task-set, or it is driven by the difficulty in directing attention to task-relevant information and suppressing task-irrelevant information. While the former impairment is mainly associated with decreased performance on switch vs. repeat trials, the latter is observed as a switch-unspecific performance reduction on incongruent trials in which the current stimulus features afford distinct responses for the two tasks.

The accuracy pattern that was observed in left prefrontal but also non-prefrontal patients pointed to an interference resolution deficit associated with errors on incongruent trials. However, a closer inspection of the observed accuracy pattern demonstrated a more severe form of switching impairment: low-performing patients often perseverated and remained anchored to one task rule throughout the session, thus reducing their performance on the alternative task rule, a pattern that emerged only on incongruent trials. These results were also confirmed by a multivariate lesion-symptom mapping analysis in which perseveration was significantly associated with lesions in left prefrontal areas and along the left fronto-temporal and fronto-parietal white-matter tracts. Findings from this second study are in line with those from the first study in which similar left prefrontal areas were found to be critically involved in creating stable stimulus-response associations. However, they also extend them by showing that lesions across left prefrontal areas but also left fronto-temporal and fronto-parietal white-matter tracts create a more severe task-setting impairment, which within the task-switching context is not reflected as a difficulty in switching between two task rules, but instead as a difficulty in establishing and implementing task rules. On the other hand, patients with right prefrontal damage showed no specific switching or perseveration impairment, even though in terms of response latency they were generally slower, which is also somehow compatible with the sustained attention impairment associated with right prefrontal damage in the first study.

Finally, in our third study we turned to explore the unitary view of PFC organization according to which most of the PFC regions support multiple cognitive functions (Duncan & Owen, 2000). Our main focus was on the surgically induced cognitive decline which previous studies found to be associated with tumor histology rather than tumor location (Campanella et al., 2015; Desmurget et al., 2006; Talacchi et al., 2011). A latent variable analysis was performed on distinct neuropsychological test scores obtained from 54 brain tumor patients in order to derive a measure of general cognitive functioning while minimizing the influence of low-level processing requirements. The impact of surgical tumor removal on cognitive functioning across different tumor histological types was also assessed so as to identify and control for this confounding factor. Our main results showed that tumor histology, and in particular low-grade glioma (LGG), was the strongest predictor of surgery-related cognitive decline. However, when this cognitive decline was explored at a more fine-grained level of lesion location, left middle frontal and precentral gyri were significantly associated with a greater surgery-induced decline. Incidentally but critically, only two patients with LGG had lesions in the left MFG, and one in the precentral gyrus, thus making it unlikely that tumor histology could exert an effect on the observed anatomical association. The finding of PFC areas whose lesions cause a general cognitive decline related to several neuropsychological scores, might be seen as evidence in support of a unitary view of PFC organization. However, the rather confined extent of these critically involved areas is in line with both modular and integrated views of brain functional organization that suggest the existence of restricted brain regions, highly involved across different sub-networks and subserving a vast range of high-level cognitive abilities (Bertolero et al., 2015; Warren et al., 2014).

Brought together, our main findings suggest that left lateralized PFC lesions cause greater EF impairments with respect to right lateralized ones. However, we propose that the type of impairments observed in left and right prefrontal patients are driven by the different nature of processing mechanisms confined in the prefrontal cortex of the two

hemispheres. A number of studies investigating the functional hemispheric asymmetries have observed a left hemisphere specialization for analytical, fine-grained type of processing associated with rapid and sequential information such as speech production, comprehension and motor control, whereas right hemisphere specialization was found to be more related to coarse, global type of processing involved in low-frequency and configurative information (Dien, 2009; Gotts et al., 2013; Hickok & Poeppel, 2007). Transposing these processing mechanisms to higher-level cognitive functions might partially explain the different involvement of left and right prefrontal areas in the tasks we employed. Difficulties in creating stable task sets, which were found to be associated with left prefrontal lesions in our first two studies, might be caused by the disruption of a more fine-grained, phasic type of processing necessary to create temporary associations among task relevant features and to modify them flexibly. Conversely, frequently observed attentional lapses and response slowing that were observed in patients with right prefrontal damage, are probably related to impairments of more global and sustained type of processing needed to maintain the global features of the task in an active state. These findings are in line with the proposed function-based hemispheric asymmetry model of the PFC according to which criterion (or task) setting and monitoring functions are defined as phasic and sustained control process and were found to be lateralized in left and right prefrontal areas, respectively (Ambrosini & Vallesi, 2016a; Vallesi, 2012). Yet, the phasic type of processing cannot easily account for the results from our third study in which we observed that defined regions in left prefrontal areas play a crucial role in general cognitive functioning. One might speculate that this lateralization could be driven by the asymmetries observed in inter- and intra-hemispheric functional interactions. In particular it has been observed that left regions have stronger interactions within the same hemisphere, whereas right regions interact with both hemispheres (Gotts et al., 2013; Tzourio-Mazoyer, 2016) and therefore might suffer left-lateralized lesions as well. However, asymmetries in inter- and intra-hemispheric interactions have only recently started to be explored in brain-damaged patients and related to behavioral impairments (Siegel et al., 2016).

One important limitation of this research project that has to be considered in closing is the lack of psychological well-being and emotional functioning measures which, along with executive functions, are regulated by the frontal lobe. It is generally acknowledged that cognitive and affective information interact strongly in the PFC and contribute together in guiding behavior (see Pessoa, 2008 for review), and future studies should investigate to what extent general and specific cognitive decline is affected by the psychological well-being, especially after brain tumor surgery. We can only hypothesize that left-lateralized frontal injuries might have caused greater impairments in terms of well-being as there is strong evidence of asymmetrical activity in the PFC related to affective processing (Davidson, 2004).

In conclusion, evidence acquired in the present work provides support for both functional specialization and integration within the PFC. We observed that impairments across distinct EF tasks can be related to disruptions of broader left-lateralized task-setting and right-lateralized sustained attention/monitoring processes, thus supporting the integrative, albeit lateralized, view of the PFC organization. Moreover, in line with recent views of brain functional architecture suggesting that both modular and integrated brain networks support cognitive performance (Bertolero et al., 2015; Warren et al., 2014), we found that surgical lesions in defined left prefrontal areas caused cognitive decline across different neuropsychological measures. Future studies should aim at understanding whether specific EF impairments are selectively related to patterns of abnormal functional connectivity.

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Table S1 – Demographical, etiological and neuropsychological data

						MMSE[1]		IQ[2]		Digit span[3] (z-score)		Corsi[4] (z-score)		TMT-A[3] (z-score)		TMT-B[3] (z-score)		Phonemic Fluency[3] (z-score)				
ID	Sex	Education	Age	Group	Hystol.	PRE	POST	PRE	POST	PRE	POST	PRE	POST	PRE	POST	PRE	POST	PRE	POST	FP&GNG	TS	NPS
PAT_1	M	5	67	LPF	HGG	25.27	21.27	99.50	94.70	0.39	-1.63	0.24	-0.81	0.31	2.73	n.a.	n.a.	-2.35	n.a.	•		•
PAT_2	F	13	43	NPF	HGG	27.89	26.89	n.a.	n.a.	0.07	-0.84	-2.09	-1.10	-0.50	-0.27	0.13	-0.45	-0.99	-1.43			•
PAT_3	F	13	50	RPF	HGG	22.99	27.99	114.20	120.30	-0.84	0.07	-1.02	-2.04	0.02	2.10	3.22	4.77	-0.73	-0.46	•		•
PAT_4	M	13	57	RPF	HGG	28.99	25.99	115.20	115.20	-0.10	-1.04	n.a.	n.a.	0.11	0.78	0.71	n.a.	-0.35	-1.98	•		•
PAT_5	M	13	64	NPF	META	28.49	27.49	115.20	114.20	0.24	0.24	-0.77	0.02	-1.03	-0.98	-0.96	-0.53	-0.28	-0.39	•		•
PAT_6	F	5	74	RPF	META	31.03	29.03	106.14	108.00	-0.40	-0.40	-1.61	-1.61	0.22	1.99	n.a.	n.a.	-0.16	-0.16	•		•
PAT_7	M	4	74	RPF	META	21.03	22.03	87.48	82.75	-1.35	-0.40	0.77	-0.42	2.00	-0.24	n.a.	n.a.	-1.83	-1.15	•		•
PAT_8	F	8	50	LPF	HGG	26.97	29.97	103.38	98.64	n.a.	n.a.	0.00	-1.02	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	•	•	•
PAT_9	M	8	63	LPF	HGG	23.53	26.53	89.46	95.81	-2.64	-1.63	-1.55	-1.55	2.03	-0.35	n.a.	n.a.	-2.88	-2.62	•		•
PAT_10	F	18	56	LPF	META	28.31	26.31	119.44	119.44	-0.10	-0.10	-1.02	-1.02	0.18	1.92	1.21	11.32	-2.11	-3.10	•	•	•
PAT_11	F	23	43	LPF	HGG	28.21	23.21	122.74	104.74	0.07	-0.84	-0.11	-0.11	-0.78	-0.90	-0.77	-0.27	-0.46	-2.66	•	•	•
PAT_12	M	18	35	NPF	MEN	27.10	28.10	117.55	117.55	-0.11	-0.11	-0.11	-1.10	-0.71	0.08	-0.77	1.06	-1.44	-1.54	•	•	•
PAT_13	M	13	52	RPF	LGG	27.99	28.99	114.25	115.86	-0.10	-1.97	2.04	0.00	-1.43	-1.50	-1.55	-2.02	0.98	0.70	•	•	•
PAT_14	M	13	70	NPF	HGG	26.86	28.86	n.a.	103.84	0.24	-0.90	-0.42	-0.42	-0.58	-0.54	0.28	0.83	-1.61	-2.19	•	•	•
PAT_15	M	18	52	NPF	META	28.31	28.31	116.60	118.50	-0.10	-0.10	1.02	-2.04	0.24	-0.29	-1.44	-0.15	-0.21	0.55	•	•	•
PAT_16	F	18	29	LPF	LGG	n.a.	27.07	n.a.	116.31	0.59	-0.33	n.a.	-0.11	-0.49	-1.05	-0.56	-1.31	-2.76	-1.51		•	•
PAT_17	F	5	82	NPF	LGG	24.03	22.03	87.50	84.31	-2.18	-1.14	n.a.	-1.47	-0.33	-0.41	n.a.	n.a.	-0.50	-0.18			•
PAT_18	M	13	37	RPF	LGG	26.75	27.75	111.41	111.41	-0.11	-0.11	-0.11	-1.10	-1.11	-0.87	-0.99	2.60	-0.22	-0.78	•	•	•
PAT_19	M	13	47	NPF	HGG	27.89	26.89	114.24	116.15	-0.84	-0.84	-0.11	-2.09	-0.78	1.40	-0.12	0.77	n.a.	-1.61	•	•	•
PAT_20	M	8	38	NPF	HGG	29.42	27.42	103.30	109.06	n.a.	n.a.	-2.09	-2.09	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	•		•
PAT_21	M	11	44	NPF	LGG	28.89	24.89	95.90	93.05	n.a.	-1.76	-1.10	-0.11	n.a.	0.08	n.a.	4.30	n.a.	-2.66	•	•	•
PAT_22	F	18	59	LPF	LGG	28.31	22.31	119.40	118.50	n.a.	-2.91	-1.02	-1.02	n.a.	6.40	n.a.	n.a.	n.a.	-2.53	•	•	•
PAT_23	M	8	54	NPF	HGG	28.97	19.97	81.60	n.a.	-1.35	-1.35	0.00	-1.02	1.09	1.09	0.18	1.99	-2.18	-2.35	•	•	•
PAT_24	F	5	78	LPF	HGG	30.03	25.03	97.62	90.04	-1.35	-0.40	-1.12	-0.22	-0.93	-0.56	n.a.	n.a.	-1.44	-2.04	•		•
PAT_25	F	12	46	NPF	MEN	27.89	28.89	n.a.	n.a.	-1.76	-1.76	-0.11	-1.10	-0.09	0.25	1.24	7.00	-2.14	-1.59	•	•	•
PAT_26	M	13	65	NPF	HGG	26.49	27.49	108.57	110.47	-0.90	0.24	-1.86	1.29	-0.54	0.14	1.66	n.a.	-1.42	-0.85	•	•	•
PAT_27	M	13	59	LPF	HGG	22.99	18.99	106.68	111.41	-1.97	-1.04	-3.06	-2.04	5.26	1.72	n.a.	n.a.	-3.02	-3.17	•	•	•
PAT_28	M	8	76	LPF	HGG	19.20	19.20	92.02	96.75	-1.35	-2.30	-1.12	-1.12	0.49	n.a.	n.a.	n.a.	-1.62	-2.04	•		•
PAT_29	M	5	71	LPF	MEN	29.03	30.03	102.35	n.a.	-1.35	-0.40	-0.42	n.a.	-0.90	-0.83	n.a.	n.a.	0.55	n.a.	•	•	•
PAT_30	M	20	53	NPF	HGG	28.31	28.31	118.87	118.87	-0.10	-0.10	0.00	1.02	-1.16	-1.63	-0.76	-0.47	-1.33	0.89	•	•	•
PAT_31	F	16	41	NPF	HGG	28.21	27.21	n.a.	n.a.	-0.84	-0.84	0.88	-0.11	0.60	3.13	4.66	5.13	-2.48	-1.85	•		•
PAT_32	M	13	39	RPF	MEN	27.75	28.75	105.73	107.62	-1.86	-0.98	-1.10	-1.10	0.48	-1.03	1.21	0.14	-1.44	-0.78	•	•	•
PAT_33	M	5	83	RPF	MEN	29.03	30.03	101.41	107.09	1.95	1.95	-0.51	-1.47	1.20	n.a.	1.72	n.a.	-0.61	-1.35	•	•	•
PAT_34	M	13	67	NPF	MEN	27.49	29.49	110.47	111.41	-2.03	-2.03	-1.86	-0.81	-0.40	0.18	-0.21	5.88	-0.93	-1.42	•	•	•
PAT_35	M	18	26	NPF	LGG	28.07	26.07	117.54	118.50	1.52	0.59	0.88	1.87	-0.56	-0.91	-1.06	0.68	1.95	-0.10	•	•	•
PAT_36	M	13	56	NPF	HGG	26.99	n.a.	n.a.	n.a.	-1.97	-1.97	-1.02	n.a.	-0.09	5.53	1.64	4.55	-2.68	-2.53		•	•
PAT_37	M	13	33	RPF	LGG	27.75	26.75	101.94	101.94	-0.11	-1.86	-0.11	-0.11	-0.32	1.27	1.69	5.75	-1.68	-2.52	•	•	•
PAT_38	M	8	62	NPF	MEN	29.53	30.53	110.01	110.01	-0.62	0.39	-0.77	0.02	0.12	-1.45	1.23	-1.21	-1.90	-0.95	•	•	•
PAT_39	M	11	47	RPF	HGG	27.89	27.89	n.a.	n.a.	-1.76	-1.76	-1.10	-1.10	1.12	1.92	5.02	5.20	-2.21	-1.95	•	•	•
PAT_40	M	8	46	NPF	HGG	26.62	27.62	103.38	102.40	-0.48	-2.28	-1.10	-2.09	-0.57	0.37	0.02	0.25	-1.66	-1.19	•	•	•
PAT_41	F	8	70	RPF	MEN	24.20	26.20	109.06	106.20	-1.63	-1.63	-1.61	-1.61	-0.45	-0.10	n.a.	n.a.	-1.56	-2.19	•	•	•
PAT_42	F	18	53	RPF	MEN	27.31	27.31	117.50	117.50	-0.10	-0.10	0.00	-1.02	-0.96	-1.03	-0.58	-0.51	0.07	0.49		•	•
PAT_43	F	11	53	NPF	HGG	27.99	28.99	113.90	113.90	-1.04	-1.04	0.00	0.00	-1.23	-1.30	-1.05	-1.59	0.00	-1.05		•	•
PAT_44	M	18	53	RPF	META	27.31	28.31	117.55	116.60	-0.10	-0.10	-1.02	-2.04	10.68	-0.36	n.a.	9.17	-1.77	-2.19		•	•
PAT_45	M	13	20	NPF	HGG	27.59	27.59	101.90	103.80	-0.30	-0.30	-1.10	-0.11	1.87	1.87	1.81	1.30	-2.09	-1.75		•	•
PAT_46	F	8	74	NPF	MEN	31.20	31.20	103.40	107.20	-0.40	0.55	0.77	0.77	-0.84	-1.08	-0.74	-1.05	-0.64	-0.46		•	•
PAT_47	F	13	48	LPF	LGG	27.89	26.89	112.40	113.30	-1.76	-1.76	-1.10	-1.10	-0.44	-0.84	-1.20	-0.23	1.00	0.66		•	•
PAT_48	F	13	47	NPF	MEN	28.89	28.89	106.70	106.70	-0.84	0.07	-0.11	-0.11	-0.09	0.77	-0.48	0.24	-1.61	-1.17		•	•
PAT_49	M	8	62	LPF	MEN	30.53	24.53	107.20	106.20	-0.62	-0.62	-0.77	-1.55	-0.41	1.31	0.51	3.26	-2.19	-2.88		•	•
PAT_50	M	13	62	NPF	HGG	27.49	26.49	104.80	109.50	0.24	1.38	-0.77	0.02	1.04	0.18	4.94	0.77	-1.85	-1.99		•	•
PAT_51	F	11	27	NPF	MEN	28.59	25.59	100.62	104.41	-1.26	-2.19	-1.10	-1.10	2.34	1.65	5.49	7.69	-1.35	-1.51			•
PAT_52	M	13	20	LPF	MEN	27.59	28.59	100.99	105.73	-1.22	-0.30	-0.11	-0.11	0.40	-0.16	0.74	-0.24	-0.87	2.05		•	•
PAT_53	F	13	59	LPF	MEN	n.a.	27.99	n.a.	110.40	n.a.	-1.04	n.a.	-1.02	n.a.	0.44	n.a.	3.83	n.a.	-2.32		•	
PAT_54	M	11	52	LPF	META	26.99	27.99	113.00	113.90	0.83	0.83	-1.02	-1.02	0.11	-0.16	-1.41	-1.44	-0.14	-0.42		•	•
PAT_55	M	13	50	RPF	HGG	28.99	28.99	116.50	116.50	0.07	-0.84	0.00	-1.02	0.14	0.66	-0.70	1.28	-1.51	-1.87		•	•

Abbreviations: ID = identification code, PAT = patient, M = male, F = female, Edu = years of education, LPF = left prefrontal, RPF = right prefrontal, NPF = non-prefrontal, Histol. = histology of the lesion, HGG = high grade glioma, LGG = low grade glioma, MEN = meningioma, META = metastasis, PRE = pre-surgery performance, POST = post-surgery performance, n.a. = data not available. Occasionally, not all neuropsychological tests were administered due to time limits or because the patient was not able to perform the task.

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