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Addressing the selective role of distinct prefrontal areas in response suppression: A study with brain tumor patients

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ABSTRACT

The diverging evidence for functional localization of response inhibition within the prefrontal cortex might be justified by the still unclear involvement of other intrinsically related cognitive processes like response selection and sustained attention. In this study, the main aim was to understand whether inhibitory impairments, previously found in patients with both left and right frontal lesions, could be better accounted for by assessing these potentially related cognitive processes. We tested 37 brain tumor patients with left prefrontal, right prefrontal and non-prefrontal lesions and a healthy control group on Go/No-Go and Foreperiod tasks. In both types of tasks inhibitory impairments are likely to cause false alarms, 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 rather than an inhibitory impairment. 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 study show how left and right prefrontal areas, which previous research has linked to response inhibition, underlie broader cognitive control processes, particularly involved in response selection and target detection. Based on these findings, we suggest that successful inhibitory control relies on more than one functionally distinct process which, if assessed appropriately, might help us to better understand inhibitory impairments across different pathologies.

1. Introduction

Everyday life activities require the ability to willingly refrain from unwanted actions and implement goal-directed ones. Without these abilities it would be difficult to imagine driving a car, playing sports or even crossing the street safely. The processes underlying these essential human abilities fall under the umbrella term of executive functions. Even though it is well acknowledged that executive functions 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 executive function lack the specificity required to identify unequivocally the process of interest and its neural correlates. Inhibition is an important example of a widely accepted executive function for which there is still an ongoing debate regarding its discreteness as a cognitive construct and its underpinning neural mechanisms (Aron et al., 2014a; Hampshire and Sharp, 2015; Swick and 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 et al., 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

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(Criaud and Boulinguez, 2013; Mostofsky and 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 and 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 et al., 2004b). 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., 2004b; Buchsbaum et al., 2005; Nakata et al., 2008; Rubia et al., 2001, 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 et al., 2001; Chatham et al., 2012; Dodds et al., 2011; Hampshire et al., 2009; Sharp et al., 2010; Walther et al., 2011). This raised the issue of whether the engagement of rIFC areas in GNG and SST tasks may be due to “oddball” effects (Mostofsky and Simmonds, 2008) and more generally to the recruitment of the ventral attentional network involved in detecting behaviorally relevant stimuli (Corbetta and 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 et al., 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 and Stuss, 2006; Krämer et al., 2013; Picton et al., 2007). While the study by Krämer 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 et al., 2008a; 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 Stuss (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 (2014b) argument 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 and 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 and Eickhoff, 2013; Shulman et al., 2009; Vallesi, 2014), the finding of an engagement of left prefrontal areas in the same tasks (Meffert et al., 2016; Swick et al., 2008; Zhang and Li, 2012) may have risen from more left lateralized co-occurring processes like task setting and response selection, or verbal WM requirements (Fletcher et al., 2000; Mostofsky and Simmonds, 2008; Smith et al., 1996; Vallesi et al., 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, 2009; Jaffard et al., 2007; see Criaud and 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: 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.

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 and Vallesi, 2015; Kelley et al., 1998; Robinson et al., 2012; Sandrini et al., 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.

2. Materials and methods

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. Fig. 1 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 [$F(2, 32) = 2.82$, $p = .07$, partial $\eta^2 = .15$]. Additionally, 41 neurologically intact participants, matched for age (t-test's $p = .34$), sex ($\chi^2 = 2.33$; $p = .13$) 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). Demographical and etiological data for the four groups 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.

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 in. 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. Three patients, one from each group, were tested after the surgery in their hospital room due to transport limitations.

2.2.1. Go/No-Go task

Two uppercase letters (A and E), subtending an average visual angle of .8° × .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 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 position task required them to respond to one specific position of the letter and not to the other, regardless of the letter identity. 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.

2.2.2. 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,

[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.

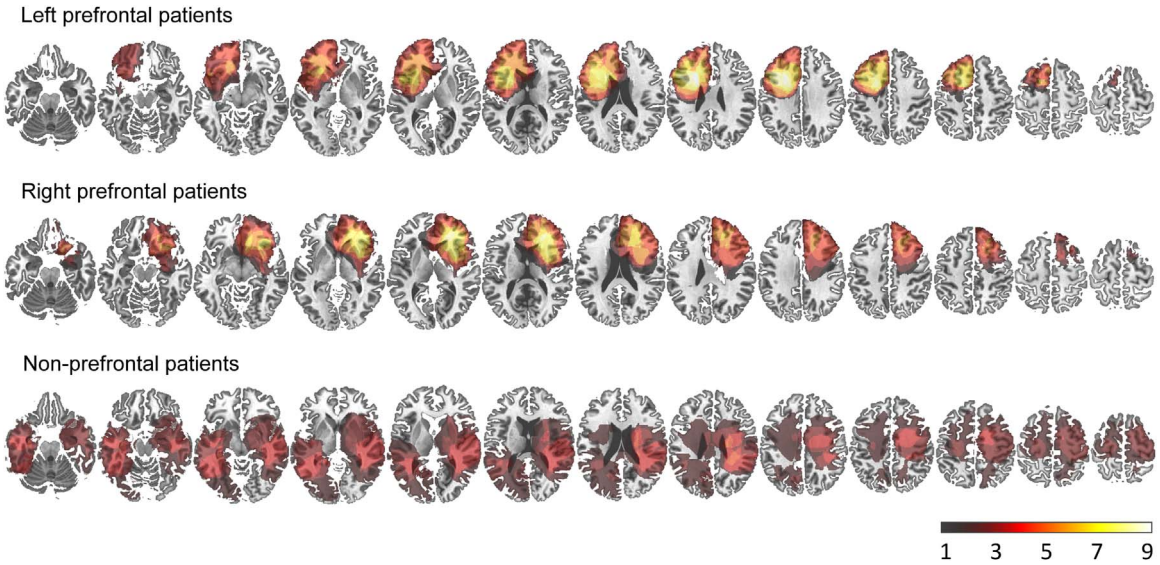

Fig. 1. Lesion overlap maps for left prefrontal, right prefrontal and non-prefrontal patient groups. The color bar indicates the number of patients whose lesions overlap on one voxel. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article).

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. 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.

2.3. Analyses of the behavioral data

Analyses were performed on accuracy and reaction time (RT) data, filtered for anticipations (RT < 150 ms) 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) 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 et al., 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 and 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 multiple-comparison post-hoc analysis.

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 location of the tumor was determined by mean of the digital format of 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 and 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 (for included voxels see Supplementary material: Fig. S1).

3. Results

3.1. Behavioral results

3.1.1. Go/No-Go task

For the accuracy data, the analysis revealed a main effect of Group [$F(3, 73) = 11.75$, $p < .001$, partial $\eta^2 = .33$], an interaction between Group and Stimulus type [$F(3, 73) = 4.99$, $p = .003$, partial $\eta^2 = .17$] and an interaction between Group and Task type [$F(3, 73) = 2.9$, $p = .041$, partial $\eta^2 = .11$]. Post-hoc test for the Group main effect showed that

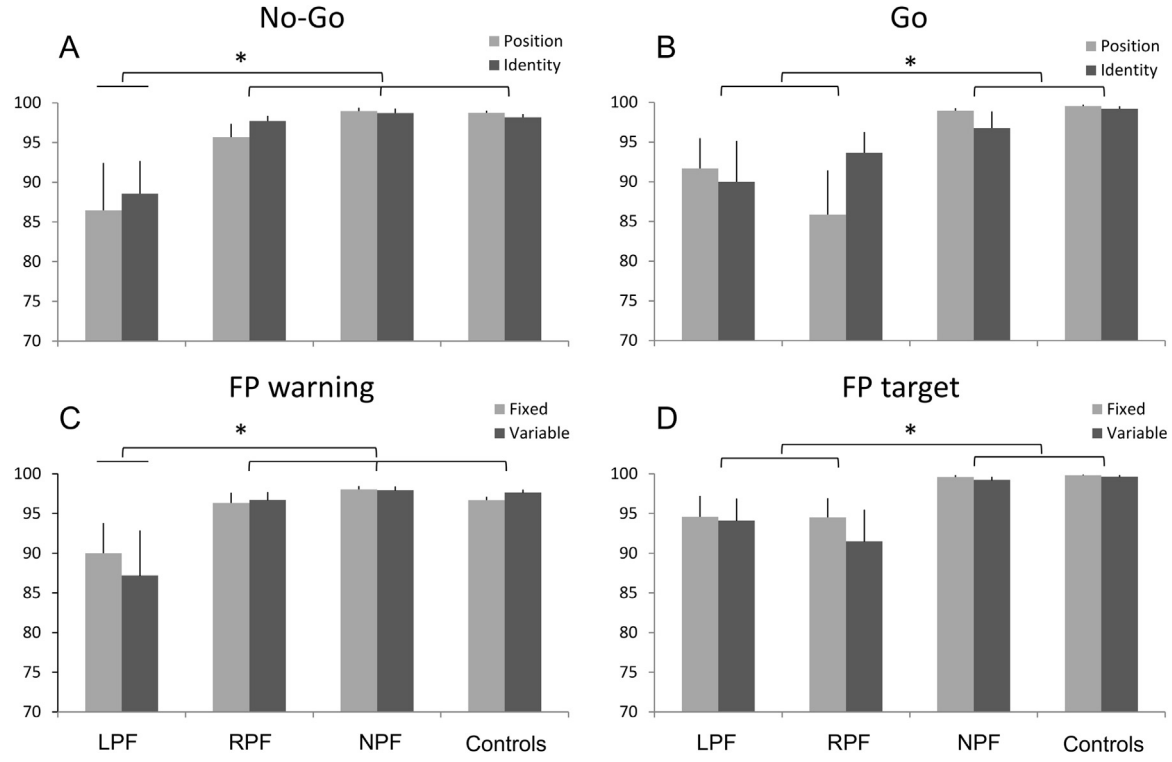

Fig. 2. Accuracy scores (sessions collapsed) with standard error (vertical lines) for the No-Go (A) and Go (B) stimuli across the two GNG tasks (letter position and letter identity) and for the warning (C) and target (D) stimuli across the fixed and variable FP tasks. The asterisks denote significant group differences for each stimulus type.

LPF and RPF patients' accuracy was significantly lower than NPF and control group accuracy (all *ps* < .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 (*ps* < .01; Fig. 2A), whereas on Go trials both LPF and RPF patients made significantly more omissions than NPF patients and controls (*ps* < .01; Fig. 2B), 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 *ps* > .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 *ps* < .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 [$F(3, 73) = 16.29$, $p < .001$, partial $\eta^2 = .4$], Session [$F(3, 73) = 20.66$, $p < .001$, partial $\eta^2 = .22$] and Task [$F(3, 73) = 20.56$, $p < .001$, partial $\eta^2 = .22$]. 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 *ps* < .001). Significant Group × Session [$F(3, 73) = 5.86$, $p = .001$, partial $\eta^2 = .19$] and Group × Task [$F(3, 73) = 4.09$, $p = .01$, partial $\eta^2 = .14$] interactions were better explained by a significant 3-way Group × Session × Task interaction [$F(3, 71) = 6.31$, $p < .001$, partial $\eta^2 = .21$]. 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 (*ps* < .001). In the control group the RTs did not change across the two sessions (*ps* > .28). All mean RT data are reported in Supplementary material: Table S2.

3.1.2. Foreperiod task

Analyses on the accuracy data revealed a main effect of Group [$F(3, 74) = 10.32$, $p < .001$, partial $\eta^2 = .29$], Task [$F(3, 74) = 6.03$, $p = .016$, partial $\eta^2 = .08$] and more critically, an interaction between Group and Stimulus type [$F(3, 74) = 6.59$, $p < .001$, partial $\eta^2 = .21$]. Post-hoc 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 *ps* < .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 *ps* < .001; Fig. 2C), whereas for the target stimuli both LPF and RPF patients performed significantly worse than NPF and control groups (all *ps* < .01; Fig. 2D), 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

[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).

[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.

was significantly lower on warning stimuli with respect to the target stimuli (all *ps* < .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 *ps* < .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 visually the RT distributions between warning and target responses (Supplementary material: Fig. S2), 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 [$F(3, 74) = 86.35$, $p < .001$, partial $\eta^2 = .54$], Session [$F(3, 74) = 10.57$, $p = .002$, partial $\eta^2 = .13$], FP [$F(3, 74) = 18.46$, $p < .001$, partial $\eta^2 = .2$] and Group [$F(3, 74) = 10.68$, $p < .001$, partial $\eta^2 = .30$]. 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* < .02), but did not differ between each other (*p* = .57). In agreement with common findings in this type of task (Niemi and Näätänen, 1981), there was a significant interaction between Task and FP duration [$F(1, 74) = 212.14$, $p < .001$, partial $\eta^2 = .74$]: 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 [$F(3, 74) = 3.47$, $p = .02$, partial $\eta^2 = .12$] 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 [$F(3, 74) = 2.79$, $p = .046$, partial $\eta^2 = .1$] and post-hoc tests confirmed that the FP effect was reduced only in the RPF patients (*p* = .045). All mean RT data are reported in Supplementary material: Table S2.

3.1.3. SDT measures

The analysis of the sensitivity scores showed a main effect of Group [$F(3, 71) = 12.86$, $p < .001$, partial $\eta^2 = .35$] and Task [$F(6, 142) = 19.73$, $p < .001$, partial $\eta^2 = .21$]. Post-hoc analysis revealed significantly lower scores for both LPF and RPF patients with respect to NPF patients and controls (*ps* < .01; Fig. 3A). 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 [$F(3, 71) = 6.05$, $p < .001$, partial $\eta^2 = .20$] and Task [$F(6, 142) = 22.47$, $p < .001$, partial $\eta^2 = .24$]. Post-hoc tests showed that response bias scores were higher in RPF patients with respect to all the three other groups (*ps* < .01; Fig. 3B). 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 (*ps* < .001).

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 Fig. 4A 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 Fig. 4B and Table 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 different groups of prefrontally damaged patients. In particular, we focused on differences between left prefrontal and right prefrontal patients 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

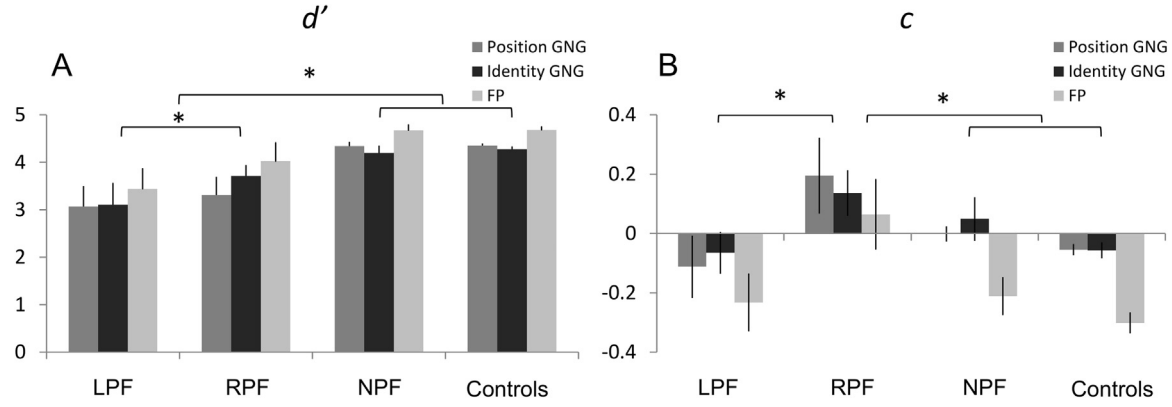

Fig. 3. Signal Detection Theory (SDT) measures of sensitivity *d'* (A) and response bias *c* (B), across the three tasks (letter position GNG, letter identity GNG and FP task). Significant group differences are indicated with an asterisk.

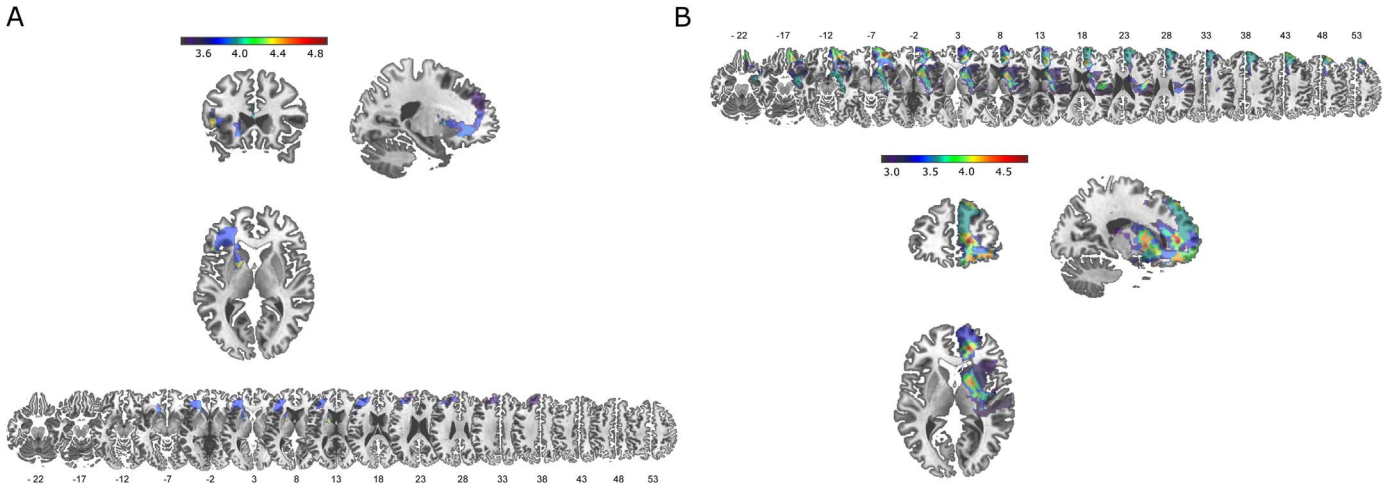

Fig. 4. VLSM analysis results showing only significant voxels at $p < .01$, with False Discovery Rate correction applied. Color bars indicate Z-scores. Panel A: areas significantly associated to lower d' scores are located in the left ventrolateral and dorsolateral prefrontal cortex, and in the left 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. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article).

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

Region	AAL label	Hemisph.	No. 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	11,341	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	10,048	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	.8	.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	20,146	.4	.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.

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 and Poldrack, 2006; Congdon et al., 2010; Garavan et al., 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

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

Region	AAL label	Hemisph.	No. 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	10,695	62.4	1.788	3.915	54	32	26
	Inferior 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	25,179	62.4	1.886	4.244	30	57	−1
	Superior frontal gyrus	R	17,493	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	.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	.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	12,974	76.4	2.737	4.572	18	46	5
	Medial superior frontal gyrus	L	580	2.4	.227	3.915	2	62	32
	Supplementary motor area	R	2580	13.7	.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	.992	3.125	2	36	12
Right parietal lobe	Postcentral gyrus	R	1165	3.8	.313	4.103	56	−4	20
	Precentral gyrus	R	5725	21.2	.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	.909	3.872	50	−16	26
Right temporal lobe	Superior temporal gyrus	R	15,130	59.9	1.899	3.324	48	−14	−9
	Middle temporal gyrus	R	1013	2.9	.492	3.324	48	−16	−12
	Middle temporal pole	R	124	1.3	.117	2.976	45	10	−24
	Superior temporal pole	R	3704	34.8	1.216	4.353	42	16	−20
Insula	Insula	R	13,438	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	83,226	1.5	.052	4.572	22	40	2
Other subcortical structures	Thalamus	R	1652	19.7	.687	3.464	22	−17	8
	Hippocampus	R	4941	65.0	2.292	4.353	34	−18	−16
	Parahippocampal gyrus	R	1308	14.5	.802	4.103	34	−30	−14
	Fusiform gyrus	R	16	.1	.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.

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. Moreover, such a task maintenance ability has already been shown to rely on right-lateralized sustained control processes (Ambrosini and Vallesi, 2016; Braver et al., 2003; Cieslik et al., 2015; Langner and 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 et al., 2004a; Brass and von Cramon, 2004; Campanella et al., 2016; Shallice et al., 2008b; 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 (see Supplementary material: Fig. S3). 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 and 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 and 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 et al., 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.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.neuropsychologia.2017.04.018.

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