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Speed-accuracy strategy regulations in prefrontal tumor patients

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ABSTRACT

The ability to flexibly switch between fast and accurate decisions is crucial in everyday life. Recent neuroimaging evidence suggested that left lateral prefrontal cortex plays a role in switching from a quick response strategy to an accurate one. However, the causal role of the left prefrontal cortex in this particular, non-verbal, strategy switch has never been demonstrated. To fill this gap, we administered a perceptual decision-making task to neuro-oncological prefrontal patients, in which the requirement to be quick or accurate changed randomly on a trial-by-trial basis. To directly assess hemispheric asymmetries in speed-accuracy regulation, patients were tested a few days before and a few days after surgical excision of a brain tumor involving either the left ($N=13$) or the right ($N=12$) lateral frontal brain region. A group of age- and education-matched healthy controls was also recruited. To gain more insight on the component processes implied in the task, performance data (accuracy and speed) were not only analyzed separately but also submitted to a diffusion model analysis. The main findings indicated that the left prefrontal patients were impaired in appropriately adopting stricter response criteria in speed-to-accuracy switching trials with respect to healthy controls and right prefrontal patients, who were not impaired in this condition. This study demonstrates that the prefrontal cortex in the left hemisphere is necessary for flexible behavioral regulations, in particular when setting stricter response criteria is required in order to successfully switch from a speedy strategy to an accurate one.

1. Introduction

We are often required to flexibly switch between rapid and accurate decision-making. When we adopt a rapid response strategy, we inevitably sacrifice accuracy, whereas a harsh response criterion will typically slow down performance. The cognitive nature of this so-called speed/accuracy trade-off has been heavily investigated for more than a century (e.g., Woodworth, 1899; Fitts, 1966; Zelaznik et al., 1988). Experimentally, it is well established that we are able to flexibly trade speed for accuracy and vice versa, depending on instructions (Hick, 1952; Howell and Kreidler, 1963), payoffs (Swensson, 1972) and deadlines (Garrett, 1922; Pachella et al., 1968).

Given the ongoing interest in speed/accuracy strategies from the cognitive viewpoint, it is surprising that the neural mechanisms underlying these strategies, and particularly the capacity to dynamically switch between them, are still poorly understood. Two previous functional magnetic resonance imaging (fMRI) studies (Ivanoff et al., 2008; Van Veen et al., 2008) found that the middle frontal gyrus (i.e., dorsolateral prefrontal cortex) is involved in adjusting baseline activity in decision-related cortical regions to prioritize speed or accuracy. In both studies, however, speed-accuracy instructions were manipulated block-wise, making it impossible to unveil switch-related mechanisms. Another study (Forstmann et al., 2008) instead adopted an event-related fMRI design, and showed that speed instructions activated the pre-supplementary motor area and the striatum, two regions associated with the adjustment of response threshold. The authors, however, did not focus on conditions with a switch between response strategies.

A more recent fMRI study pointed at fronto-parietal regions for speed/accuracy tradeoff regulations (Vallesi et al., 2012). This study adopted a diffusion model approach (e.g., Ratcliff, 1978; Voss and Voss, 2007), which allows combining both response times and accuracy data in the same analytical steps, in order to estimate parameters linked to both decisional and non-decisional processes. The results of this fMRI study showed that the level of activation in the left middle frontal gyrus, during a cue phase

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preceding the target-related implementation of a perceptual decision-making task, was positively correlated with the adoption of a stricter response criterion, as estimated with diffusion models (Voss and Voss, 2007), when switching from a hasty response strategy to an accurate one.

While a previous study already showed that lesions to ventromedial frontal cortex impair the accuracy of value-based decision-making and not response speed (Henri-Bhargava et al., 2012), to the best of our knowledge, no other neuropsychological study has more specifically investigated how damage to frontal lobes may impair the capacity to switch from a quick to an accurate decision. Given the above reviewed neuroimaging evidence (Vallesi et al., 2012), a candidate region for this capacity within the frontal lobes is the left lateral prefrontal cortex. Left prefrontal patients suffer from cognitive flexibility problems, including the failure to set a criterion for a response, especially when other non-relevant but prepotent responses need to be suppressed (Vallesi, 2012). Examples of tasks in which this left-lateralized frontal deficit has been found include color-word Stroop interference (Perret, 1974; Stuss et al., 2001), verbal fluency by first letter (Baldo et al., 2006; Stuss et al., 1998), random number generation (Knoch et al., 2005; Jahanshahi et al., 1998), and task-switching (Stablum et al., 1994; Rogers et al., 1998; Mecklinger et al., 1999; Shallice et al., 2008). Most of these tests strongly tax verbal processing, and the left lateralization of the criterion-setting function could be a side effect of these demands (e.g., Mecklinger et al., 1999). For this reason, it would be particularly important to test whether criterion-setting critically requires the left prefrontal cortex even in a task with minimal verbal requirements.

In this neuropsychological study, we tested whether the left prefrontal cortex is not only associated to the flexible regulation of speed-accuracy strategy switching in decision-making (Vallesi et al., 2012), but also *necessary* for this high-level executive process. A further goal was to demonstrate the specificity, within the prefrontal cortex, of left hemispheric lesions to cause a deficit in this type of cognitive ability as compared to right homologous ones, even in a test with low verbal demands. To test these hypotheses, we administered a perceptual decision-making task that required continuous speed-accuracy regulation (modified from Vallesi et al., 2012) to patients with unilateral tumors located in either the left or the right lateral frontal cortex. We tested patients both a few days before and a few days after the surgical removal of the brain tumor. We expected left prefrontal patients, but not right ones or a group of well-matched healthy controls, to be selectively impaired in switching from speed to accuracy. Capitalizing on the benefits derived from the use of drift diffusion models in understanding behavioral effects, primarily the fact that they provide a more integrated and insightful picture of the processes involved in a task than speed or accuracy measures separately, which are also starting to emerge in patient studies (e.g., Moustafa et al., 2015; Vallesi et al., 2015), we analyzed our data using this approach. In particular, based on previous fMRI evidence (Vallesi et al., 2012), we expected that the most sensitive performance index for a left-prefrontal impairment in speed-to-accuracy response strategy shift would be a diffusion model parameter marking the conservativeness of the adopted response strategy.

2. Material and methods

2.1. Participants

Twenty-five patients with brain tumors, who were hospitalized at the Santa Maria della Misericordia Hospital, Udine, were included in this study. Inclusion criteria were: age between 18 and 75 years and the presence of a single brain tumor involving either the left or the right lateral prefrontal cortex (i.e., BA 9, 10, 11, 44, 45, 46 or 47) but could also extend to temporal or parietal regions. The sample of patients mainly suffered from High Grade Gliomas ($n=12$), Low Grade Gliomas ($n=8$), but also Meningiomas ($n=4$) and Metastases ($n=1$). Apart from the 25 included patients, other patients were excluded a posteriori. These comprised: patients with multiple separate lesions ($n=1$); patients who did not complete both experimental sessions ($n=5$) or who were not able to understand the instructions ($n=2$); patients with lesions involving frontal lobes only in their motor/premotor components (i.e., BA 4, 6 and/or 8; $n=8$, 4 in the left hemisphere and 4 in the right one). Due to time constraints, the latter information became available only after an accurate tumor reconstruction, which was usually performed after data collection. Thirteen of the included patients had a lesion involving left prefrontal areas, while twelve other patients had tumors located in the right prefrontal areas. The mean age was 45.92 years (sd=14.25) and the mean education was 13.44 years (sd=3.23). No differences in either age (*t*-test's $p=0.786$) or education ($p=0.638$) were found between the two groups of patients. Female/Male ratio was 5/8 for the left frontal group and 4/8 for the right frontal group. A summary of all the demographic and etiological characteristics of the participants is detailed in Table 1. Apart from one ambidextrous left frontal patient, all the other patients were right handed, as assessed with the Edinburgh Handedness Inventory (Oldfield, 1971).

Patients were tested with a computerized speed-accuracy task (described below) in two separate sessions: a few days (range: 1–5 days) before the operation and a few days (range: 4–21 days) after the surgery. The lag between the two sessions was 9.09 days on average (sd=3.41) and no significant differences were reported in the lag across the two patient groups ($p=0.401$). In both occasions patients were also administered a comprehensive neuropsychological assessment covering the main cognitive domains: language, attention, executive function, memory and perception, together with the computerized experimental task.

A control group of 37 healthy volunteers was also recruited (mean age=45.1 years, sd=14.8, range: 23–67 years; mean education=13.7 years, sd=3.7, range=8–21 years; females/males=15/22). All of them were right handed as assessed with the Edimburgh Handedness Inventory. Each control participant was

Table 1
Demographic and etiological characteristics of the three samples of participants.

	Etiology[a]									
	N	Low-Grade Glioma	High-Grade Glioma	Metastasis	Meningioma	F/M	Age (range)	Education years (range)	Mean lesion volume: cc (sd)	Handedness
Left prefrontal	13	4	8	0	1	5/8	45.1 (19–69)	13.8 (8–17)	118.1 (78.6)	12 right-handed, 1 ambidextrous
Right prefrontal	12	4	4	1	3	4/8	46.7 (32–64)	13 (8–17)	123.7 (58.9)	All right-handed
Healthy controls	37	–	–	–	–	15/22	45.1 (23–67)	13.7 (8–21)	–	All right-handed

[a] Definitive etiological data were provided about two weeks after surgical operation, when the results of the histopathological examination became available.

also tested in two separate sessions separated by a time distance which was similar to that used for the patients (average = 8.1 days, range = 6–30 days). Although the events between the two sessions were clearly different for the patient groups and controls (i.e., only the former underwent surgical brain lesions), we included a healthy group of participants to control for time-related effects (such as learning).

No differences were found between each of the two patient groups and controls either for age (for both comparisons, *t*-test's $p > 0.73$) or education (for both, $p > 0.56$). All the participants gave their written consent before taking part in this study, which was previously approved by the Bioethical Committee of Azienda Ospedaliera di Padova.

2.2. Experimental design

Participants viewed the screen at a distance of approximately 60 cm. Visual stimuli were squares of 100 mm^2 presented centrally against a constantly gray background. A first familiarization block with no speed-accuracy instructions (32 trials) was performed before the beginning of the real test. Orange and green pixels were randomly dispersed in the square in various ratios (44/56, 47/53, 53/47, 56/44) to form target stimuli (see Voss et al., 2004; Vallesi et al., 2012). The task was to judge whether the predominant color in the target square was orange or green by responding with the index and middle fingers of the right hand (keys 'B' and 'N' of the laptop keyboard, appropriately covered with orange and green labels, respectively). The association between prevailing color and response button was counterbalanced between subjects. In the first familiarization run, participants were asked to simply perform this task.

Two experimental blocks with speed-accuracy cues and performance feedback were subsequently performed (64 trials each). In these blocks, lighter and darker gray pixels randomly dispersed in the square frame (50% each) were used to form the fixation space, which was shown centrally for 1000 ms during the initial cue presentation. Cues were strings of capital letters appearing on the top of the cue stimulus at the beginning of the trial and disappearing with the target offset: VEL ("velocità", that is, "speed" in Italian) and ACC ("accuratezza", that is, "accuracy" in Italian) to cue the adoption of a quick or an accurate strategy, respectively. The target lasted 2000 ms, followed by a blank screen of 1000 ms. The deadline for recording a response was 2500 ms. In each block, the four orange/green proportions were presented pseudo-randomly and equiprobably. The combination of 2 cue type (accuracy vs. speed) and 2 previous cue type (accuracy vs. speed) factors was also presented randomly and equiprobably. In these blocks, participants were required to stress either speed or accuracy according to the nature of the cue at the beginning of the trial. Visual feedback was displayed as a sentence (font: Courier New, black color) for 1000 ms after each trial, followed by a 500 ms blank screen. The provided feedback could be one of the following:

1. "Sbagliato, attenzione!" (in English: Wrong, be careful!): if participants failed to obey the accuracy instruction by making a mistake.
2. "Sii più veloce!" (in English: Be quicker!): if RT was $<$ average RT $+$ 1 SD of the familiarization run during speed trials.
3. "Tempo scaduto!" (in English: Time expired!): if no response was collected before deadline.
4. "Bene così!" (in English: Well done!): in any other case.

2.3. Data analysis

The 32 familiarization trials, trials with no response, with RTs $<$ 100 ms, and the first trial of each block were excluded from further analyses. We first decided to analyze RTs and accuracy separately, for the sake of completeness. However, given the nature of our speed-accuracy task, RTs and accuracy were then more appropriately combined together in a diffusion model analysis.

Therefore, both mean RTs (correct responses in the range = 100–2500 ms) and accuracy data were first submitted to a $2 \times 2 \times 2 \times 3$ mixed ANOVA, with session (pre- and post-operation), preceding cue (accuracy, speed) and current cue (accuracy, speed) as the within-subject factors, and group (left prefrontal, right prefrontal, controls) as the between-subjects factor. Tukey's HSD test was used as the post-hoc test to detect pair-wise differences, as a follow-up of significant effects.

The distributions of correct and incorrect RTs were then combined together in an additional analysis based on diffusion models (Ratcliff, 1978; Voss and Voss, 2007). Diffusion models are specifically conceived to analyze processing differences in speed-accuracy trade-off. The analysis of two-choice RT and accuracy data by means of the diffusion-model assumes that evidence is continuously accumulated until one of two response criteria is overcome. The analysis is based on the distributions of both correct and erroneous responses in each condition and individual subject. From these distributions a set of parameters is estimated that allows inferences about both non-decisional and decisional processes.

In particular, the model parameter t0 indicates the duration of non-decisional processes, which may comprise basic perceptual and response execution processes. The model parameter 'v' (drift rate) represents the strength of perceptual evidence accumulation that drifts the decision process from a starting point (parameter z) to one of two response thresholds (e.g., the criteria to execute a correct or a wrong response). When either response threshold is reached, a response is executed. The distance that separates the thresholds for correct and incorrect responses is captured by the parameter 'a', which indicates how much information is required before either response is initiated. Thus, 'a' is directly proportional to the conservativeness in responding and is crucial for testing the hypotheses under investigation in this study.

We used the free open-source fast-dm-29 software (Voss et al., 2004; Voss and Voss, 2007) to estimate the parameters of the diffusion model. A Simplex downhill search was used as a multidimensional optimization approach to enhance the fitting between predicted and empirical RT distributions. The Kolmogorov–Smirnov statistic (Voss et al., 2004) was used as the optimization criterion.

For each experimental session, we allowed 'a', 'v' and 'z' to vary with each of the four conditions (given by the factorial combination of the two preceding cue x two current cue), while other parameters of the diffusion model were assumed to be constant for all conditions. The choice of which parameters were left free to vary during the fit was similar to what was used in the fMRI study that directly inspired the present neuropsychological investigation (Vallesi et al., 2012). The parameters selected to vary freely according to the task conditions were compatible with what could be expected theoretically, since only decisional processes are expected to vary strategically, that is, according to task instructions, while non-decisional processes (comprised in the 't0' parameter) are expected to be much less susceptible to strategic influences. Each of the three varied parameters was treated as the dependent variable of a $2 \times 2 \times 2 \times 3$ mixed ANOVA, with session, preceding and current cue type as the within-subject factors and group (left, and right prefrontal and controls) as the between-subjects factor. To check whether there were cross-session and cross-group differences in the non-decisional processes, we also submitted the parameter 't0' to a 2×3 mixed ANOVA, with session as the within-subject factor and group as the between-subjects factor.

2.3.1. Lesion volume estimation and anatomical analyses

For all patients, high resolution gadolinium-enhanced T1 and (when available) T2-weighted and/or FLAIR scans were collected to determine tumor location (minimum number of slices: 180, voxel size $\leq 1 \times 1 \times 1\ mm^3$). Only pre-operative scans, used for neuro-navigation by the neurosurgeon, were considered in the reconstruction procedure as, after surgery, lesion locus is usually at least partially replaced by healthy neighboring tissue, possibly creating confusion in the reconstruction of the real lesion boundaries. The 3D region of interest (ROI) reconstructions of lesions were drawn for each patient from MRI slices on the horizontal plane using MRIcroN software (Rorden and Brett, 2000). Reconstructed ROIs included all the areas of altered MRI signal, including edema, which is known to have cognitive effects, as shown both in humans (e.g., Lampl et al., 1995; Steinvorth et al., 2003) and in animal models (Tominaga and Ohnishi, 1989). After ROIs reconstruction, each MRI scan underwent spatial normalization using SPM8 software, in order to match and align images on a common Montreal Neurological Institute (MNI) T1-weighted template. Once the lesion maps were normalized, overlap images were created separately for LPF and RPF patients. Lesion volume was then calculated from each ROI and compared between LPF and RPF patients in order to exclude any potential systematic difference between patient populations. Mean lesion volume (see also Table 1) for the LPF patients was 118.1 cc (sd = 73.7), while for RPF was 123.7 cc (sd = 58.9). The two groups did not differ in terms of lesion volume [$t(23) = -0.21$; $p = 0.835$].

A Voxel-based Lesion-Symptom Mapping (VLSM) analysis (Bates et al., 2003; Rorden et al., 2007) was also performed to try to better specify cortical areas most critically linked to a lower 'a' parameter in patients when switching from speed to accuracy. The VLSM analysis was performed even if only at an exploratory level, since it allows highlighting those voxels that are associated with significantly lower scores in a particular task. VLSM analysis has the advantage to avoid any a-priori grouping of patients and takes into account and compares the performance of all patients at the same time, compared voxel-by-voxel. In this procedure, all patients are classified in two groups according to whether or not the lesion affects a specific voxel. Then, the behavioral performance is compared across groups. Voxel-by-voxel statistical analyses were performed by means of NPM software (www.MRIcro.com), using *t*-tests with the statistical threshold set at $p < 0.01$ (False Discovery Rate correction applied).

2.3.2. Neuropsychological profile

Scores obtained by patients in each task of the neuropsychological battery administered were entered as the dependent variable into a repeated measures ANOVA design with "hemisphere"

Table 2
Differences in cognitive profiles of left vs. right frontal patients. Bold indicates significant differences. Apart from picture naming performance, the cognitive profile of the two groups of patients did not differ. * Degrees of freedom vary in function of the actual number of patient completing the task.

	Left frontal:		Right frontal:			
	Mean	SD	Mean	SD	*F*-value*	*p*-level
Language						
Picture naming[a]	59.231	4.851	62.458	1.271	***$F_{(1,23)} = 7.170$***	***0.013***
Language comprehension[b]	29.692	4.642	31.500	1.678	$F_{(1,23)} = 2.050$	0.166
Verbal fluency[c]	22.892	18.104	35.183	13.489	$F_{(1,23)} = 4.057$	0.056
Auditory repetition[d]	144.346	9.843	149.083	1.118	$F_{(1,23)} = 3.070$	0.093
Reading[d]	29.308	1.559	29.867	0.446	$F_{(1,22)} = 1.630$	0.215
Writing[d]	27.923	3.862	29.386	0.657	$F_{(1,21)} = 1.661$	0.211
Attention/ executive functions						
Visual search[b]	41.932	9.785	45.341	5.295	$F_{(1,20)} = 1.682$	0.210
Trail making test – A[e]	45.346	16.471	42.920	12.294	$F_{(1,22)} = 0.277$	0.604
Trail making test – B[e]	175.269	73.365	146.595	62.400	$F_{(1,22)} = 1.820$	0.191
Trail making test – B-A[e]	138.808	84.673	106.970	67.038	$F_{(1,22)} = 1.804$	0.193
Frontal assessment battery[f]	14.623	2.123	15.842	0.825	$F_{(1,23)} = 2.227$	0.149
Raven colored matrices[c]	28.062	3.409	26.967	3.890	$F_{(1,23)} = 0.825$	0.373
Visuo-spatial skills						
Rey complex figure – copy[g]	29.848	2.850	28.476	3.864	$F_{(1,22)} = 0.137$	0.715
Benton face Recognition test[h]	22.650	2.409	23.786	2.737	$F_{(1,14)} = 0.449$	0.514
Stars cancellation[i]	26.637	3.222	27.135	3.402	$F_{(1,23)} = 1.360$	0.255
Short term memory						
Digit span forward[j]	5.154	1.280	5.667	1.105	$F_{(1,23)} = 1.727$	0.202
Digit span backward	3.962	1.002	4.167	1.366	$F_{(1,23)} = 0.247$	0.623
Corsi spatial span[j]	4.769	1.047	4.396	0.985	$F_{(1,23)} = 1.061$	0.314
Long term memory						
Narrative memory[k]	14.724	4.053	14.591	3.578	$F_{(1,21)} = 0.837$	0.371
Rey complex figure – elayed[g]	15.288	3.962	17.091	6.314	$F_{(1,22)} = 0.812$	0.377

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Table 3
The regions of maximum lesion overlap within, respectively, the left and right frontal lobes. The table shows the brain areas involved, the number of voxels of the total significant together with the resective percentage and the percentage of the anatomical region involved in the significant area. BA indicates Brodmann Areas.

Patient group	Area	N. voxels	% Tot. signif.	% of area
Left frontal lobe	Insula	466	76.9	3.1
(max overlap: 10/13)	Inferior Frontal Pars Opercularis (BA 44)	140	23.1	1.7
Right frontal lobe	Subcortical (beneath BA 45)	2687	92.1	< 0.1
(max overlap: 9/12)	Caudate nucleus	165	5.6	2.1

(left vs. right) as the between-subject factor and "surgery" (pre vs. post) as the within-subject factor. Table 2 reports the main effects of hemisphere, while the effects of surgery are shown in Supplementary Table 1.

2.3.3. *Lesion overlap*

Fig. 2 shows the lesion overlap maps for both LPF and RPF patient groups. As also detailed in Table 3, the region of maximum lesion overlap (10 out of 13 patients) for the LPF group was found between the left insular cortex and the left inferior frontal gyrus, pars opercularis (corresponding to BA 44). For the RPF group (9 out of 12 patients) it was located more medially within the right prefrontal cortex, in a subcortical region beneath BA 45. These regions are shown in brighter yellow in the maps displayed in Fig. 1.

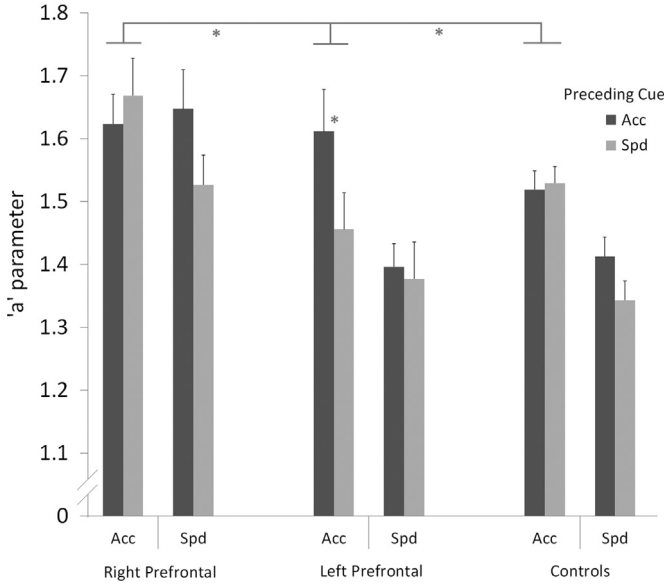

Fig. 2. Mean values for 'a' parameter of the diffusion model (i.e., distance between response criteria) according to group, cue and preceding cue (sessions collapsed). Error bars denote standard errors of the mean. The asterisks denote significant differences (see text for details).

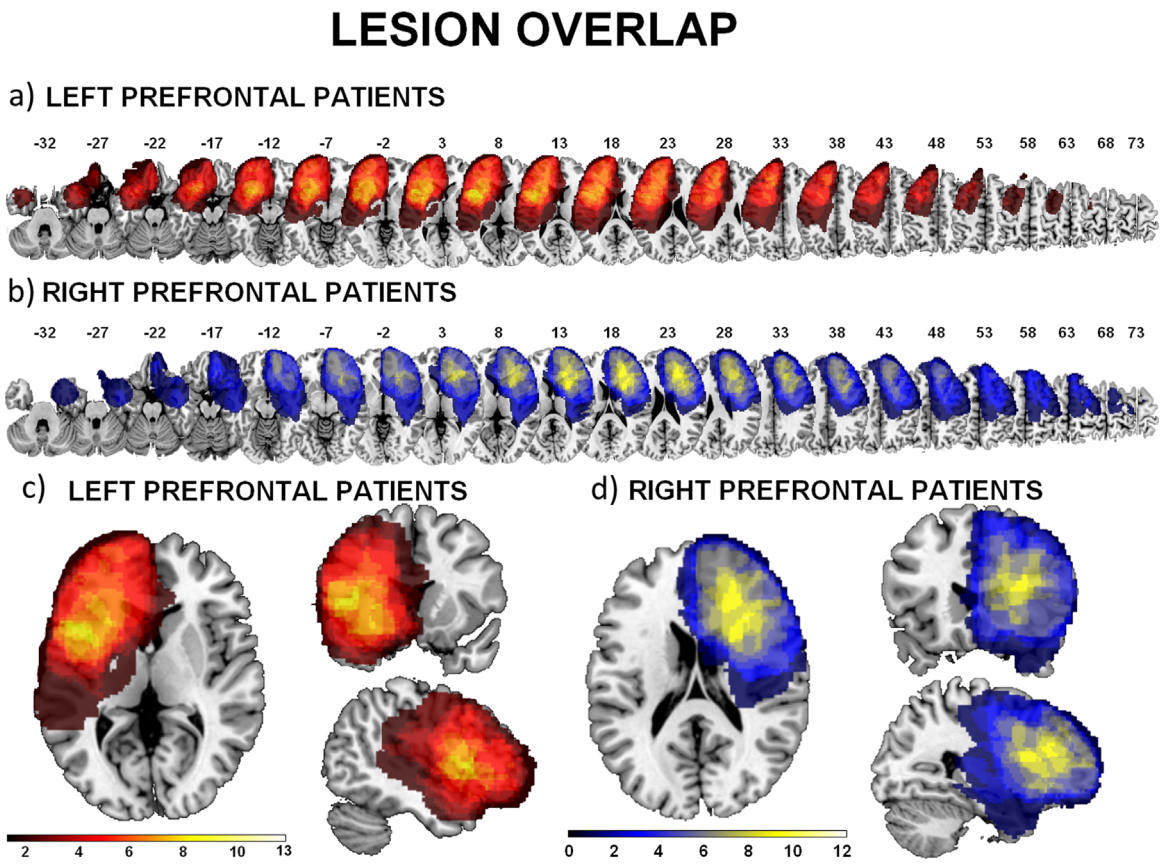

Fig. 1. Lesion overlap maps for both left and right prefrontal patient groups. The images show lesion overlaps both in axial slice series (Panels A and B, with values above slices indicating *z*-coordinates) and in the three axes (axial, coronal and sagittal, see Panels C and D), superimposed on a Montreal Neurological Institute template. The color scale indicates the number of patients with overlapping lesions at a given voxel. The region of maximum lesion overlap (10/13 patients) for the left frontal group was located between the left insular cortex and Brodmann area 44 (Panels A and C). For the right prefrontal group (9/12 patients) it was located in the white matter beneath Brodmann area 45 (Panels B and D).

3. Results

3.1. Neuropsychological profile

The scores obtained by the two groups of patients did not show any significant difference for the attentive/executive function domain in terms of number of cognitive deficits detected (Table 2). The two groups of patients were largely comparable also in terms of language skills, since the only differences detected were in terms of naming abilities (which were lower in left hemisphere patients) and, marginally, in verbal fluency. Most importantly, however, no differences in language comprehension or reading abilities were detected between the two groups, a deficit of which could have potentially limited the capacity to understand the instructions of the task. No other difference was found in any of the other cognitive domain examined. Also the effects of surgery were minimal (see Supplementary Table 1) and no significant interaction was detected between Hemisphere and Surgery in any of the cognitive tasks administered [all $F < 2.960$; $p > 0.099$].

3.2. Behavioral results

All the behavioral data are shown in Table 4.

3.2.1. Accuracy

The accuracy data were normally distributed according to the Kolmogorov–Smirnov test. There was a non-significant tendency for a session by group interaction [$F_{(2,59)}=2.86$, $p=0.065$, partial eta squared$=0.09$], which suggested that the overall accuracy increased in healthy controls from the first to the second session, while it did not change in the two prefrontal groups. No other effect was significant (for all, $p > 0.13$).

3.2.2. Response times

A session main effect [$F_{(1,59)}=23.54$, $p=0.00001$, partial eta squared$=0.28$] indicated that participants were overall faster in the second session than in the first one. The cue main effect was significant [$F_{(1,59)}=17.67$, $p=0.00009$, partial eta squared$=0.23$] indicating that participants were faster for speed cues than for accuracy ones. The session by cue interaction [$F_{(1,59)}=15.87$, $p=0.00019$, partial eta squared$=0.21$] was also significant. Although the Tukey's post-hoc test showed that responses were slower for accuracy cues than for speed ones in both sessions (for both, Tukey's $p < 0.001$), the magnitude of this difference was bigger in the first session than in the second one (90 vs. 35 ms, $p < 0.001$). There was also a trend for the preceding cue main effect [$F_{(1,59)}=3.39$, $p=0.07$, partial eta squared$=0.05$], which suggested that RTs tended to be faster after a speed cue than after an Accuracy one.

3.2.3. Diffusion model fit

The model fit, as assessed with the Kolmogorov–Smirnov statistic (Voss et al., 2004), was generally quite good (average $p=0.59$). However, two participants did not show a good model fit: one of them belonged to the right prefrontal group ($p=0.0348$) and the other one to the control group ($p=0.0002$). After checking that the results of the analyses reported in the following paragraphs did not change when we eliminated these two participants, we decided to keep them.

3.2.4. Diffusion Model parameter 'a': distance between decision criteria

The group main effect was significant [$F_{(2,59)}=6.39$, $p=0.003$, partial eta squared$=0.18$] indicating that right prefrontal patients had a higher 'a' criterion than controls (Tukey's $p=0.003$) and left prefrontal patients (Tukey's $p=0.02$), while the controls and left prefrontal patients did not show absolute differences in this parameter ($p > 0.98$). The session main effect [$F_{(1,59)}=12.33$, $p=0.00086$, partial eta squared$=0.17$] indicated that the criterion 'a' was higher in the first session than in the second one. The preceding cue main effect [$F_{(1,59)}=13.45$, $p=0.00053$, partial eta squared$=0.18$] was due to 'a' being higher when the preceding cue was accuracy than when it was speed. The cue main effect [$F_{(1,59)}=18.6$, $p=0.00006$, partial eta squared$=0.24$] indicated that participants had higher 'a' for accuracy than for speed cues. Although there was no cue by group interaction ($p=0.36$), visual inspection of the data strongly suggested that the right prefrontal patients did not modulate the response criterion according to the current cue. To corroborate this impression statistically, we contrasted accuracy and speed cues for each group separately, and found that the only group who did not show any significant modulation was the right prefrontal one ($p=0.28$), while the left prefrontal group ($p=0.007$) and the controls ($p=0.00001$) showed a clear cue effect. This effect however has to be interpreted with caution since the cue by group interaction is not significant even

Table 4
Means (and standard deviations) for all the behavioral data according to session, sequence of conditions (columns) and group (lines). AA, AS, SA and SS refer to the following sequences, respectively: accuracy-accuracy, accuracy-speed, speed-accuracy, speed-speed.

	Session 1				Session 2			
	AA	AS	SA	SS	AA	AS	SA	SS
Response times (ms)								
Right Prefrontal	1192 (222)	1114 (181)	1148 (233)	1063 (184)	1090 (266)	1048 (213)	1089 (269)	1051 (225)
Left Prefrontal	1054 (175)	963 (127)	1035 (176)	983 (176)	965 (197)	933 (182)	958 (154)	944 (257)
Controls	1087 (212)	1004 (215)	1104 (248)	958 (208)	925 (238)	898 (235)	930 (228)	874 (237)
Accuracy (% correct)								
Right Prefrontal	84.8 (12.9)	88.4 (12.5)	88.6 (15.3)	87.9 (12.1)	83.6 (17)	88.7 (9.5)	83.9 (15.4)	85.1 (12.9)
Left Prefrontal	84.0 (16.5)	84.5 (14.9)	81.9 (20.3)	79.7 (18.3)	96.2 (15.7)	84.8 (14.3)	85.5 (10.9)	83.8 (17.9)
Controls	83.9 (10.7)	83.9 (9.7)	85.5 (9.8)	83.2 (9.0)	91.1 (6.1)	89.2 (9.1)	89.0 (8.2)	88.8 (9.4)
Parameter 'a'								
Right Prefrontal	1.76 (0.23)	1.67 (0.25)	1.76 (0.25)	1.55 (0.21)	1.48 (0.22)	1.63 (0.29)	1.57 (0.26)	1.51 (0.26)
Left Prefrontal	1.68 (0.37)	1.43 (0.17)	1.52 (0.32)	1.39 (0.25)	1.55 (0.30)	1.36 (0.20)	1.39 (0.19)	1.36 (0.22)
Controls	1.64 (0.26)	1.48 (0.24)	1.67 (0.21)	1.37 (0.27)	1.39 (0.23)	1.36 (0.27)	1.39 (0.25)	1.32 (0.23)
Parameter 'v'								
Right Prefrontal	1.25 (0.84)	1.42 (0.62)	1.56 (0.73)	1.16 (0.59)	1.35 (0.73)	1.48 (0.69)	1.18 (0.84)	1.38 (0.82)
Left Prefrontal	1.60 (0.89)	1.49 (0.99)	1.24 (0.75)	1.32 (1. 16)	1.65 (0.95)	1.50 (0.80)	1.47 (0.74)	1.70 (1.05)
Controls	1.34 (0.76)	1.21 (0.74)	1.31 (0.59)	1.35 (0.74)	1.91 (0.86)	1.81 (0.74)	1.61 (0.78)	1.75 (0.85)
Parameter 'z'								
Right Prefrontal	0.93 (0.24)	0.85 (0.29)	0.92 (0.19)	0.85 (0.19)	0.71 (0.21)	0.91 (0.32)	0.88 (0.24)	0.80 (0.31)
Left Prefrontal	0.84 (0.24)	0.75 (0.25)	0.77 (0.23)	0.79 (0.23)	0.86 (0.32)	0.76 (0.20)	0.73 (0.16)	0.77 (0.17)
Controls	0.82 (0.23)	0.81 (0.21)	0.88 (0.22)	0.75 (0.22)	0.76 (0.17)	0.82 (0.26)	0.78 (0.19)	0.80 (0.22)
Parameter 't0'								
Right Prefrontal	0.70 (0.21)	0.72 (0.23)						
Left Prefrontal	0.65 (0.08)	0.65 (0.17)						
Controls	0.66 (0.19)	0.64 (0.19)						

when the right prefrontal group is compared to the control group ($p=0.12$) and the left prefrontal group ($p=0.3$), separately. The session by cue interaction [$F_{(1,59)}=20.17$, $p=.00003$, partial eta squared=0.25] showed that the difference between accuracy and speed cues in 'a' values was bigger in the first session than in the second one. Tukey's tests showed that this difference was significant in the first session ($p=0.00016$) and only a non-significant tendency in the second one ($p=0.11$).

Critically, a preceding cue by cue by group interaction was also significant [$F_{(2,59)}=6.18$, $p=0.0037$, partial eta squared=0.17, see Fig. 2]. This 3-way interaction was mainly due to the left prefrontal patients being more dependent on the previous trial cue status in modulating the 'a' parameter than the other two groups in current accuracy trials. In particular, in accuracy trials, they adopted a smaller (i.e., less strict) distance between response criteria ('a') after a preceding speed cue than after a preceding accuracy one (Tukey's $p=0.041$). Importantly, planned comparisons showed that this difference was significantly more pronounced than that observed in controls ($p=0.00017$) and in right prefrontal patients ($p=.00024$). No difference was observed between right prefrontal patients and controls in this contrast ($p=0.42$). These follow-up results show the specificity of the lesion side for this effect. No group difference was observed for the modulation of 'a' during current speed trials according to the previous trial cue for any group pair (for all, $p>0.14$).

To further corroborate these findings, we also performed two follow-up $2\times2\times3$ mixed ANOVAs, separately for each current cue (accuracy and speed), with preceding cue and session as the within-subject factors, and group as the between-subjects factor. The results of these ANOVAs showed a significant interaction between preceding cue and group with current accuracy cues [$F_{(2,59)}=9.85$, $p=0.0002$, partial eta squared=0.25], and no such interaction with current speed cues ($p=0.33$), demonstrating that the critical effect was present in accuracy trials only.

The absence of a 4-way interaction with session ($p=0.59$) indicated that the critical results were not significantly different between sessions. However, given that the deviant sequential effects on accuracy trials in the left prefrontal group were the main finding for our study, we further assessed whether this pattern occurred even in a single (pre- or post-surgery) session. Separate ANOVAs were therefore performed for the 'a' parameter estimated in each session. The critical preceding cue by cue by group interaction reached the significance level in the second session only [$F_{(1,59)}=4.58$, $p=0.014$, partial eta squared=0.13], that is, after the surgical lesion for the patient groups, while it was a non-significant tendency in the first session ($p=0.1$).

3.2.5. Diffusion Model parameter 'v': drift rate

A session main effect [$F_{(2,59)}=5.66$, $p=0.02$, partial eta squared=0.09] indicated that the drift rate ('v') generally increased from the first to the second session. The session by group interaction was nearly significant [$F_{(2,59)}=3.1$, $p=0.052$, partial eta squared=0.09]. The drift rate 'v' parameter increased in the second session with respect to the first one in the control group only (Tukey's $p=0.0004$). Planned comparisons also showed that the 'v' change between the first and the second session was significantly different between the right prefrontal patients and controls ($p=0.025$), but not between left prefrontal patients and controls ($p=0.14$). However, this session differential effect was comparable between the two frontal groups ($p=0.49$).

3.2.6. Diffusion Model parameter 'z': starting point

There was a significant session by cue interaction [$F_{(1,59)}=5.78$, $p=0.019$, partial eta squared=0.09]. Post-hoc tests showed that the starting point 'z' was higher in accuracy trials than in speed ones in the first session (Tukey's $p=0.02$), while this effect disappeared in the second session ($p=0.57$). There was also a non-significant tendency for a preceding cue by cue by group interaction ($p=0.054$), which seemed to be due to left prefrontal patients setting a lower starting point 'z' (i.e., closer to the wrong response threshold) during current accuracy trials after speed trials than after accuracy ones, with opposite tendencies for the other two groups. However, this effect could not be corroborated statistically (i.e., neither the interaction nor post-hoc tests were significant).

3.2.7. Diffusion Model parameter 't0': non-decisional processes

No effect was significant for this analysis (for all, $p>0.56$), indicating that the non-decisional processes (perceptual and response execution processes) did not differ across sessions or across groups.

3.2.8. Voxel Lesion Symptom Mapping (VLSM)

Regardless of any a priori patient grouping, VLSM analysis (see Fig. 3 and Table 5) showed that a large cluster of voxels, with the highest peak *z*-score ($z=3.58$), located in the pars triangularis of the left inferior frontal gyrus (corresponding to BA 45), was significantly associated with a lower 'a' parameter in patients' performance, together with a similar cluster within the pars opercularis (corresponding to BA 44) and pars orbitalis (BA 47). Large significant clusters were also found in the left insula and in the white matter underlying this region.

4. Discussion

Previous neuroimaging evidence showed that the demanding capacity to regulate speed-accuracy response strategies is associated with the functioning of prefrontal regions (e.g., Ivanoff et al., 2008; Van Veen et al., 2008). In particular, switching from a quick to an accurate strategy is associated with the activation of the middle frontal gyrus in the left hemisphere (Vallesi et al., 2012). The present study adds important causal evidence to this finding by showing that, in a selected group of patients with brain tumors (and their subsequent surgical removal) located in the left prefrontal cortex, flexibly selecting an accurate response strategy after a fast one is impaired as compared to keeping the same accurate response strategy across trials. This finding specifically demonstrates higher dependence on sequential carry-over effects in left prefrontal patients when switching their speed-accuracy response strategy, and confirms, at a more general level, their compromised set shifting ability (Milner, 1963; Barceló and Knight, 2002; Shallice et al., 2008).

The impairment observed in left prefrontal patients is process-specific, as demonstrated by a diffusion model analysis, which showed that these patients are less able to adopt a strict response criterion, as captured by the diffusion model parameter 'a', when switching from speed to accuracy strategies than when keeping an accuracy strategy from one trial to the next, while they do not show this deficit in other parameters.

The effect is also lesion-specific within the left prefrontal cortex, since tumors and surgical lesions in right prefrontal regions did not produce this effect. There was no significant modulation of this effect by session (pre-surgery vs. post-surgery) suggesting that the tumor per se may already alter the functionality of the left prefrontal cortex in our specific sample of patients (cf. Vallesi et al., 2007, for an effect of session in a different study). This might be due to the relatively high number of high-grade gliomas included in our left prefrontal sample (8/13; see Table 1), whose disruptive effect on cognition has been demonstrated to be more aggressive than other types of brain tumors in some studies (Kayl and Meyers, 2003; Campanella et al., 2009, 2015). However, follow-up analyses showed that the deviant sequential effects for accuracy

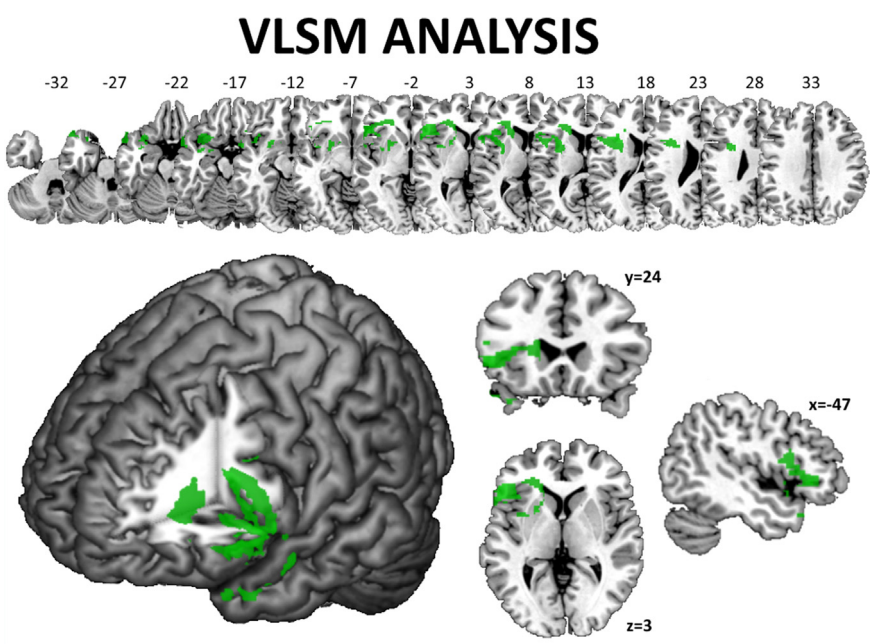

Fig. 3. Voxel Lesion Symptom Mapping (VLSM) analysis. Statistical maps are thresholded at $p < 0.01$, with False Discovery Rate (FDR) correction applied. Only significant voxels are shown ($z > 2.414$). Results show that lesions involving left Brodmann areas 44-45-47 are maximally associated with lower 'a' parameter values (i.e., smaller distance between response criteria) in switch-to-accuracy conditions.

Table 5
Exploratory VLSM results: voxels significant at threshold of $p < 0.01$, using a *t*-test. The table shows the anatomical area involved according to AAL atlas, the number of voxels of the total significant area and the percentage; the percentage of the anatomical region involved in the significant area; the maximum *z*-value registered in that region and the respective MNI coordinates.

Region	Area	N. voxels	% Tot Signif	% of Area	Max *Z*-score	MNI coordinates		
						Max *X*	Max *Y*	Max *Z*
Lateral inferior frontal (5690 voxel)	Left Inferior Frontal Pars Triangularis (BA 45)	2345	20.1	11.7	3.579	−55	18	5
	Left Inferior Frontal Pars Opercularis (BA 44)	2174	18.7	26.3	3.414	−59	16	8
	Left Inferior Frontal Pars Orbitalis (BA 47)	1171	10.1	8.6	3.061	−51	24	−4
Subcortical (5269 voxel)	Subcortical white matter (Left)	5269	45.2	1	3.061	−55	18	1
Insula (2691 voxel)	Left Insula (BA 48)	2691	23.1	17.9	3.213	−43	4	−7
Anterior Temporal (1299 voxel)	Left Superior Temporal Pole (BA 38)	948	8.1	9.3	2.992	−53	16	−4
	Left Middle Temporal Gyrus (BA 21)	176	1.5	4	2.739	−59	10	−23
	Left Middle Temporal Pole (BA 38)	175	1.5	2.9	2.739	−35	16	−31
Basal Ganglia (1924 voxel)	Left Putamen	1464	12.6	18.4	3.061	−23	6	−3
	Left Caudate Nucleus	460	3.9	6	2.523	−17	28	0
Other frontal (151 voxel)	Left Rolandic Operculum (BA 1–4)	151	1.3	1.9	2.560	−51	6	9
	Other (< 100 voxel)	316	2.7	–	–	–	–	–

trials in the left prefrontal group as compared to the two other groups were significantly present after the surgical lesions only, while they showed a non-significant trend in the pre-surgical session, suggesting generally stronger disruptive effects in the post-surgical lesion sub-acute phase.

The described effect cannot be attributed to pre-existing differences in cognitive functioning between left and right prefrontal patients, since the general neuropsychological functioning of the two groups of patients (especially executive functions) was quite comparable, apart from sporadic differences. Moreover, it could not be attributed to differences in language comprehension abilities either. Indeed, although left prefrontal patients had lower naming skills and marginally lower verbal fluency in general, their language comprehension and reading skills (both critical for an adequate comprehension of task instructions) were comparable with those of the right prefrontal patients.

The present study and the neuroimaging work that directly inspired it (Vallesi et al., 2012) highlight the role of left prefrontal regions in setting up strict response criteria in a flexible speed-accuracy manipulation context. Thus, these data show that, at least in humans, a critical way to implement speed-accuracy shifts involves the adjustment of the response criteria by left prefrontal regions, while these shifts may not necessarily be captured by changes in response thresholds in animal models (e.g., Bogacz et al., 2010; Heitz and Schall, 2012).

Previous neuropsychological and neuroimaging evidence suggests that the role of left lateral prefrontal cortex in flexible rule-switching is more general, since this region is involved in setting up the task-criteria during task-switching paradigms (e.g., Brass and von Cramon, 2004; Shallice et al., 2008; De Baene et al., 2015; Ambrosini and Vallesi, 2016). However, various studies differ in the precise localization of the critical area within the left lateral prefrontal cortex commonly involved in task-switching, which may depend on the specific nature of task-rules considered not only in each single task but also in conjunction analyses or meta-analyses (e.g., Kim et al., 2012; Vallesi et al., 2015a, 2015b).

To more precisely characterize the location of the left prefrontal regions managing the particular type of switching involved when changing response criteria from fast to accurate ones, in the present study, we performed an exploratory VLSM analysis, which

suggested critical involvements of the inferior frontal gyrus (pars triangularis and opercularis and, less extensively, pars orbitalis), insula and, at a minor extent, putamen, superior temporal pole and caudate nucleus, all in the left hemisphere. This evidence is therefore in line with more general task-switching literature, since the left inferior frontal cortex (e.g., Brass and von Cramon, 2004) and also the anterior insula (e.g., Dove et al., 2000) have already been shown to be involved in task-switching contexts.

The left lateralization of the effect in the prefrontal cortex seems quite clear even with the present perceptual decision-making task, in which minimal verbalization requirements are present. The results of the VLSM analysis, however, should be treated with caution, given the relatively low degree of lesion overlap among patients in the potentially critical voxels. Future, more extensive neuropsychological or Transcranial Magnetic Stimulation studies with neuro-navigation should provide a more definitive answer to precise localization questions.

The critical involvement of the left putamen during switch-to-accuracy conditions confirms previous fMRI evidence showing the activation of this region in the same type of conditions with this task (Vallesi et al., 2015a, 2015b), and could be interpreted as due to the role of this region of the basal ganglia in inhibiting inappropriate motor programs (e.g., Mink, 1996), a function that is conceivably required when adopting stricter response criteria.

When considering the particular type of switch investigated here, previous fMRI evidence (Vallesi et al., 2012) specifically demonstrated that, in contrast to the left prefrontal cortex, the left superior parietal lobule is activated in the implementation phase of the speed-to-accuracy strategy switch, rather than in the cue-related phase, compatibly with a role of homologous regions in animals in perceptual evidence accumulation (e.g., Hanks et al., 2015). Because of this previous finding, and additionally considering that the left parietal cortex has been shown to be involved in task-switching more generally (Sohn et al., 2000; Gurd et al., 2002; Yeung et al., 2006; Kim et al., 2011; Vallesi et al., 2015a, 2015b), a future extension of the present neuropsychological study should certainly include parietal patients, although the role of parietal regions in adopting different response criteria is probably subordinate to that of left prefrontal region, as also demonstrated for instance by Granger causality (Goebel et al., 2003; but see Bode and Haynes, 2009).

Finally for what concerns the response criterion, it is worth noting that the right prefrontal patients showed the highest values for the 'a' parameter on average, as corroborated by a group main effect. We did not expect this result initially, and its interpretation can only be tentative at this point. Right prefrontal cortex has been shown to be important for monitoring and regulatory processes aimed at endogenously optimizing performance (e.g., Coull et al., 2000; Stuss and Alexander, 2007; Vallesi et al., 2007; Vallesi, 2012). To show a constantly strict response criterion might not be functional to optimize performance, as it is supposedly resource demanding. In line with a regulatory deficit account, only the right prefrontal group was unable to adjust response criteria according to the current instructions (speed vs. accuracy), although a direct comparison with the other groups did not reach significance. Further evidence is therefore needed to appreciate how robust and dysfunctional this effect might be.

Peculiar problems with the speed-to-accuracy sequence seem also to be numerically evident in the left prefrontal group when considering the starting point of the decision process (i.e., the 'z' parameter of the diffusion model). This parameter was closer to the wrong response threshold for preceding speed than for preceding accuracy in the left prefrontal group during current trials with accuracy instructions, a finding that could be indirectly related to the role of lateral prefrontal cortex in adjusting baseline activity in other task-relevant regions (Ivanoff et al., 2008; Van Veen et al., 2008). However, statistical support in this case was not as convincing as for the 'a' parameter and definitive conclusions are not warranted.

The nearly significant session by group interaction in drift rate (parameter 'v') could be tentatively interpreted by assuming that the right prefrontal group was less able than healthy controls to benefit from learning effects in accelerating the accumulation of perceptual evidence for a task that has already been performed in a previous session. Perceptual learning-related changes in higher-order frontal areas, such as the anterior cingulate cortex, have been occasionally reported (Kahnt et al., 2011). Our results are basically compatible with this evidence and may suggest a role of frontal regions in training-related drift rate adjustments. However, given the lack of a significant (right vs. left) laterality effect in our data, and the fact that previous evidence refers to a role of anterior cingulate cortex (Kahnt et al., 2011), further investigation is desirable with higher numbers of patients with not only left and right prefrontal lesions but also purely superior medial frontal ones. Importantly, in order to disentangle the role of the intervening surgical lesions and that of the tumor per se for the lack of learning effects on the drift rate parameter, it would also be advisable, for instance, to test these effects in frontal tumor patients with multiple testing sessions carried out only before or only after surgical operations.

4.1. Conclusions

In conclusion, the present study shows a causal role of left prefrontal cortex in the dynamic regulation of speed–accuracy trade off. Damage to this region and to adjacent ones due to tumor and especially to its subsequent surgical excision interferes with the capacity to adopt appropriately strict response criteria when the patient is required to perform accurate decisions following faster and more liberal responding. More generally, this higher dependence on sequential carry-over effects when adopting response strategies may be at the basis of cognitive inflexibility in left prefrontal patients.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.neuropsychologia.2016.01.008.

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