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Rule perseveration during task-switching in brain tumor: a severe form of task-setting impairment

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Abstract

It has been proposed that at least two distinct processes are engaged during task switching: reconfiguration of the currently relevant task-set and interference resolution arising from the competing task-set. While in healthy individuals the two are difficult to disentangle, their disruption is thought to cause different impairments in brain-damaged patients. Yet, the observed deficits are inconsistent across studies and do not allow drawing conclusions regarding their independence. Forty-one brain tumor patients were tested on a task-switching paradigm. We compared their performance between switch and repeat trials (switch cost) to assess rule reconfiguration, and between trials requiring the same response (congruent) and a different response for the two tasks (incongruent) to assess interference control. In line with previous studies, we found the greatest proportion of errors on incongruent trials, suggesting an interference control impairment. However, a closer look at the distribution of errors between two task rules revealed a rule perseveration impairment: patients with high error rate on incongruent trials often applied only one task rule throughout the task, and less frequently switched to the alternative one. Multivariate lesion-symptom mapping analysis unveiled the relationship between lesions localized in left orbitofrontal and posterior subcortical regions and perseveration scores, measured as absolute difference in accuracy between two task rules. This finding points to a more severe task-setting impairment, not reflected as a mere switching deficit, but instead as a difficulty in creating stable task representations, in line with recent accounts of orbitofrontal cortex functions suggesting its critical role in representing task states.

Keywords: task-switching; perseveration; brain neoplasms; brain injuries; prefrontal cortex; lesion-symptom mapping

"Understanding the functions of the human prefrontal cortex is essential to any understanding of human cognition."

Stuss, Shallice, Alexander, & Picton, 1995

Introduction

One of the core functions of the frontal lobes is to allow flexible behavior in response to the internal and external changes. This ability has long been investigated by means of the task-switching paradigm in which two or more task-sets are presented in an intermixed fashion. By measuring the so-called switching costs (i.e., decrease in performance for switch vs. repeat trials), scientists have gained insight into the cognitive control processes required to shift between different tasks and their neural underpinnings. Different models have been put forward to explain the nature of the switch cost. Some accounts postulated a task reconfiguration process, necessary to activate the currently relevant task-set (Mayr & Kliegl, 2000; Rogers & Monsell, 1995), while others assumed the engagement of an interference resolution process, necessary to overcome the interference arising from the competing task-set (Allport et al., 1994). Although the two processes were originally seen as mutually exclusive, extensive reviews on the task-switching topic have highlighted their interdependence (Kiesel et al., 2010; Vandierendonck et al., 2010), making it hard to disentangle the two accounts. One often-made distinction between the two accounts describes the reconfiguration process as being switch-specific and not required during task repetitions, since the previous task set is still active, whereas the interference resolution is supposed to be more target-related and involved both during switch and repetition trials. Nevertheless, evidence from fMRI studies pointed to the recruitment of the same brain regions when both switching and repeating the task, only to a different degree (e.g., Braver, Reynolds, &

Donaldson, 2003; Crone et al., 2006; Dove et al., 2000), arguing against the reconfiguration process as being switch specific (see Ruge et al., 2013a for a comprehensive review). Similarly, Event-related Potential (ERP) studies showed evidence of common components to both switch and repeat trials (e.g., Jost, Mayr, & Rosler, 2008; Tarantino, Mazzonetto, & Vallesi, 2016; Wylie et al., 2009), even though switch-specific components have also been reported (Karayanidis et al., 2011; Mansfield et al., 2012).

Another complementary and fundamental approach that aimed to dissociate the reconfiguration and interference resolution processes relied on the investigation of the spared abilities in brain-lesioned patients. Based on the aforementioned task-switching models, two distinct impairments could be predicted, one related to the reconfiguration process and the other to the interference resolution process. In terms of behavioral deficits, the former impairment would presumably appear as a switching cost increase, whereas the latter as a greater interference effect during incongruent trials (i.e., when the stimulus affords different responses for the two tasks). However, there are mixing results in the neuropsychological literature. Namely, while some authors report an increased switching cost in both left and right prefrontal patients, with an apparently greater interference effect in the latter group (Aron et al., 2004), others report both an increased switching cost and interference effect only in patients with left prefrontal damage (Mayr et al., 2006; Rogers et al., 1998; Tsuchida & Fellows, 2013). Finally, Shallice and colleagues (2008b) did not replicate this switching cost increase in a study with a large sample of prefrontal patients, although they report a significant accuracy interference effect during the first block of trials in patients with left lateral prefrontal damage.

Taken together, the results from the above reported studies seem to point to left-lateralized prefrontal correlates of the processes underlying task-switching, which is in line with evidence from neuroimaging studies (e.g., Badre & Wagner, 2006; Kim et al., 2012; Vallesi et al., 2015),

but do not add evidence regarding the nature of these processes. In particular, it is not clear whether the two processes can be selectively impaired and, most importantly, whether a reconfiguration disruption should impair the performance during switch trials only, causing a switch cost increase.

In the present neuropsychological study, we approached these unanswered questions by implementing a simple task-switching design which allowed us to minimize the impact of other closely related processes that are frequently impaired in patients with brain damage (e.g., maintenance of stimulus-response associations in memory, processing of verbal vs. spatial material). Moreover, we gave the participants the possibility to fully prepare for the upcoming task (i.e., long cue-target interval), thus reducing the interference from the previous task set during task preparation, while still entailing advance task reconfiguration and target-induced interference control (Kiesel et al., 2010). As a consequence, any switch-specific decrease in performance should be interpreted as evidence supporting a disruption of a task reconfiguration process required only during switch trials. Conversely, if the observed deficit reflects more general interference resolution difficulties, and thus is present on both switch and repeat trials, but only during incongruent trials, as already observed in previous studies (Aron et al., 2004; Mayr et al., 2006; Pohl et al., 2007; Rogers et al., 1998; Shallice et al., 2008b), then a probable underlying cause might not be the disruption of a putative reconfiguration process. Instead, an impaired suppression of information regarding the non-target task would be a more plausible explanation. However, following neuroimaging evidence, a task reconfiguration impairment could emerge on both switch and repetition trials, causing the patients to perseverate on one task rule and rarely switch to the alternative one. Therefore, we took into account a third measure that looked at the absolute difference in accuracy between the two task rules, in order to capture possible

perseverative behavior. Applying more often one task rule would result in a greater difference in accuracy between the two task rules, regardless of the type of trial (i.e., switch, repeat).

Another important aspect of this study is the inclusion of a patient group without lesions in the prefrontal cortex (PFC), which was not done in previous studies investigating the impact of brain damage on task-switching performance (Aron et al., 2004; Mayr et al., 2006; Pohl et al., 2007; Rogers et al., 1998; Shallice et al., 2008b; Tsuchida & Fellows, 2013). Parietal regions are known to have a major role in task-switching performance (Badre & Wagner, 2006; Braver et al., 2003; Sohn et al., 2000; see Jamadar et al., 2015; Kim et al., 2012, for metanalyses) and damage within different non prefrontal areas might induce similar impairments. To this extent, the relationship between damage across multiple areas and the resulting behavioral deficit was investigated by means of multivariate lesion-symptom mapping analysis, which is more appropriate than mass-univariate methods when trying to capture the neural basis of processes known to rely on multiple brain regions (Zhang et al., 2014).

Materials and methods

Participants

Our participant sample was selected from a series of patients that underwent a brain tumor operation at the University Hospital of Padova with age ranging from 18 to 85 years. Patients with previous neurological or psychiatric disorders and recurring brain lesions were excluded a priori. A posteriori, we excluded six patients who did not manage to complete the task because of its difficulty: five with damage in left and one in right prefrontal areas. The remaining forty-one patients were divided in three groups according to the location of the tumor's center of mass and the area with the highest number of damaged voxels: left prefrontal (LPF, n = 12), right prefrontal

(RPF, n = 10) and non-prefrontal (NPF, n = 19). Fisher's exact test revealed a significant difference in the proportion of patients excluded among the three patient groups (p = .02). Lesion overlap maps for each patients' group are shown in Figure 1. The histopathological exam of the lesions revealed 15 high-grade gliomas, 8 low-grade gliomas, 14 meningiomas and 4 metastases. The inclusion of meningioma patients was based on extensive literature research showing pre- and post-operative cognitive deficits in these patients (Arbula et al., 2020; De Baene et al., 2019; Hendrix et al., 2017; Meskal et al., 2016; Rijnen et al., 2019; van Nieuwenhuizen et al., 2007; but see Tucha et al., 2003). Tumor grade distribution was not significantly different across the three groups of patients (Fisher's exact test p = .5). We tested also forty-four healthy participants as a control group; there was no significant difference between the four groups in terms of age (Kruskal-Wallis (K-W) test's p = .82) and years of education (K-W test's p = .5). All but four participants were right-handed (one from the RPF group, one from the NPF group and two from the control group) according to the Edinburgh Handedness Inventory (Oldfield, 1971), (right-handed participants' score range: 40-100).

All participants performed two identical testing sessions, on average 4.3 days before (SD = 7.6) and 5.4 days after (SD = 2.2) the tumor excision surgical operation. One LPF patient did not perform the pre-surgical session due to time constrains, and was included only in the analysis on post-surgical data. In order to control for learning effects, control participants were tested with the same procedure twice, with the second session on average carried out 9 days (SD = 5.6) after the first one. The difference in days between the two sessions was comparable between patients and controls (p = .15). Before each experimental testing session, all participants underwent an extensive neuropsychological assessment that included tests on general cognitive status (Mini Mental State Exam; Measso et al., 1993), premorbid intelligence (Italian version of the National Adult Reading Test – TIB; Sartori et al., 1997), verbal and spatial short-term memory (Digit Span

- Mondini et al., 2011; Corsi - Spinnler & Tognoni, 1987), visuo-spatial abilities (Trail Making Test – A; Mondini et al., 2011), executive functions (Trail Making Test – B; Mondini et al., 2011) and phonemic fluency (letters: C, P, S; Mondini et al., 2011). Neuropsychological data were corrected for age, sex and/or education based on the normative sample data provided in the above referenced test manuals. Data from all tests are reported in Table 1 together with demographic and etiological data. The comparisons between different groups of patients and the control group for each test are reported in Table 2. All participants gave their written informed consent before the experimental testing session. The study was approved by the Bioethical Committee of Azienda Ospedaliera di Padova (Prot. N. 2758P) and was conducted according to the guidelines of the Declaration of Helsinki.

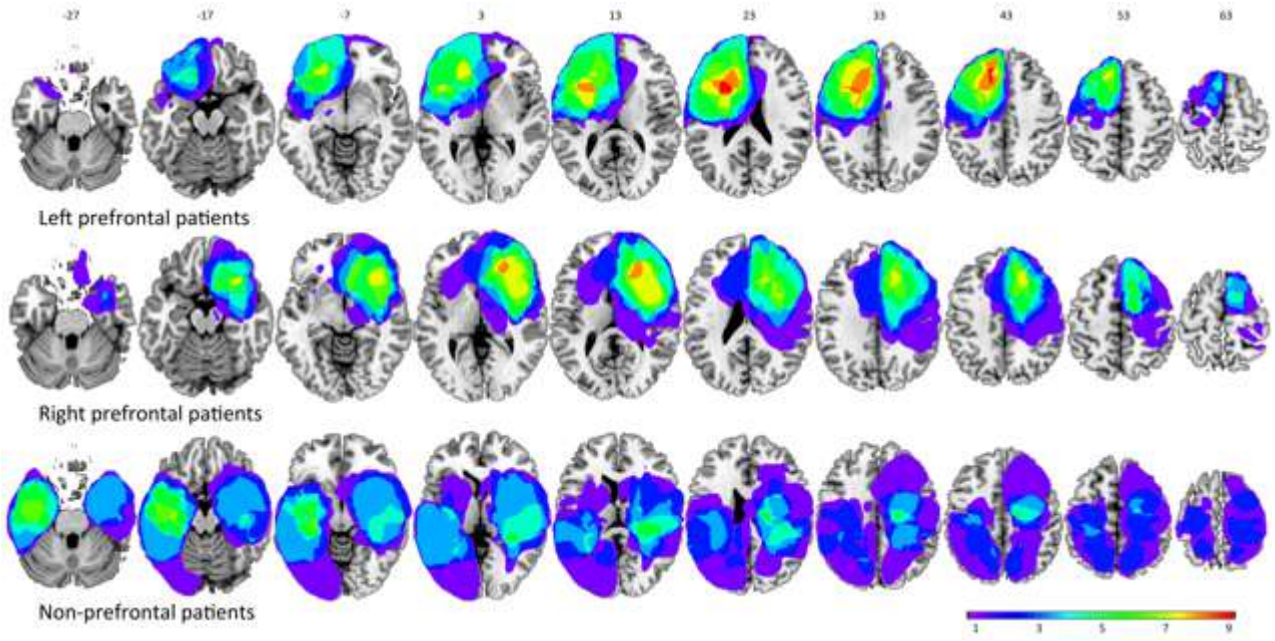

Figure 1. Lesion overlap maps for left prefrontal, right prefrontal and non-prefrontal patient groups. The color bar indicates the number of patients whose lesions overlap on one voxel.

Table 1. Demographical, etiological and neuropsychological data

						MMSE		IQ		Digit span (z-score)		Corsi (z-score)		TMT-A (z-score)		TMT-B (z-score)		Phonemic Fluency (z-score)	
ID	**Sex**	**Edu**	**Age**	**Group**	**Hystol.**	**PRE**	**POST**	**PRE**	**POST**	**PRE**	**POST**	**PRE**	**POST**	**PRE**	**POST**	**PRE**	**POST**	**PRE**	**POST**
PAT_1	F	8	50	LPF	HGG	26.97	29.97	103.38	98.64	n.a.	n.a.	0	-1.02	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
PAT_2	F	18	56	LPF	META	28.31	26.31	119.44	119.44	-0.1	-0.1	-1.02	-1.02	-0.18	-1.92	-1.21	-11.32	-2.11	-3.1
PAT_3	F	23	43	LPF	HGG	28.21	23.21	122.74	104.74	0.07	-0.84	-0.11	-0.11	0.78	0.9	0.77	0.27	-0.46	-2.66
PAT_4	M	18	35	NPF	MEN	27.1	28.1	117.55	117.55	-0.11	-0.11	-0.11	-1.1	0.71	-0.08	0.77	-1.06	-1.44	-1.54
PAT_5	M	13	52	RPF	LGG	27.99	28.99	114.25	115.86	-0.1	-1.97	2.04	0	1.43	1.5	1.55	2.02	0.98	0.7
PAT_6	M	13	70	NPF	HGG	26.86	28.86	n.a.	103.84	0.24	-0.9	-0.42	-0.42	0.58	0.54	-0.28	-0.83	-1.61	-2.19
PAT_7	M	18	52	NPF	META	28.31	28.31	116.6	118.5	-0.1	-0.1	1.02	-2.04	-0.24	0.29	1.44	0.15	-0.21	0.55
PAT_8	F	18	29	LPF	LGG	n.a.	27.07	n.a.	116.31	0.59	-0.33	n.a.	-0.11	0.49	1.05	0.56	1.31	-2.76	-1.51
PAT_9	M	13	37	RPF	LGG	26.75	27.75	111.41	111.41	-0.11	-0.11	-0.11	-1.1	1.11	0.87	0.99	-2.6	-0.22	-0.78
PAT_10	M	13	47	NPF	HGG	27.89	26.89	114.24	116.15	-0.84	-0.84	-0.11	-2.09	0.78	-1.4	0.12	-0.77	n.a.	-1.61
PAT_11	M	11	44	NPF	LGG	28.89	24.89	95.9	93.05	n.a.	-1.76	-1.1	-0.11	n.a.	-0.08	n.a.	-4.3	n.a.	-2.66
PAT_12	F	18	59	LPF	LGG	28.31	22.31	119.4	118.5	n.a.	-2.91	-1.02	-1.02	n.a.	-6.4	n.a.	n.a.	n.a.	-2.53
PAT_13	M	8	54	NPF	HGG	28.97	19.97	81.6	n.a.	-1.35	-1.35	0	-1.02	-1.09	-1.09	-0.18	-1.99	-2.18	-2.35
PAT_14	F	12	46	NPF	MEN	27.89	28.89	n.a.	n.a.	-1.76	-1.76	-0.11	-1.1	0.09	-0.25	-1.24	-7	-2.14	-1.59
PAT_15	M	13	65	NPF	HGG	26.49	27.49	108.57	110.47	-0.9	0.24	-1.86	1.29	0.54	-0.14	-1.66	n.a.	-1.42	-0.85
PAT_16	M	13	59	LPF	HGG	22.99	18.99	106.68	111.41	-1.97	-1.04	-3.06	-2.04	-5.26	-1.72	n.a.	n.a.	-3.02	-3.17
PAT_17	M	5	71	LPF	MEN	29.03	30.03	102.35	n.a.	-1.35	-0.4	-0.42	n.a.	0.9	0.83	n.a.	n.a.	0.55	n.a.
PAT_18	M	20	53	NPF	HGG	28.31	28.31	118.87	118.87	-0.1	-0.1	0	1.02	1.16	1.63	0.76	0.47	-1.33	0.89
PAT_19	M	13	39	RPF	MEN	27.75	28.75	105.73	107.62	-1.86	-0.98	-1.1	-1.1	-0.48	1.03	-1.21	-0.14	-1.44	-0.78
PAT_20	M	5	83	RPF	MEN	29.03	30.03	101.41	107.09	1.95	1.95	-0.51	-1.47	-1.2	n.a.	-1.72	n.a.	-0.61	-1.35
PAT_21	M	13	67	NPF	MEN	27.49	29.49	110.47	111.41	-2.03	-2.03	-1.86	-0.81	0.4	-0.18	0.21	-5.88	-0.93	-1.42
PAT_22	M	18	26	NPF	LGG	28.07	26.07	117.54	118.5	1.52	0.59	0.88	1.87	0.56	0.91	1.06	-0.68	1.95	-0.1
PAT_23	M	13	56	NPF	HGG	26.99	n.a.	n.a.	n.a.	-1.97	-1.97	-1.02	n.a.	0.09	-5.53	-1.64	-4.55	-2.68	-2.53
PAT_24	M	13	33	RPF	LGG	27.75	26.75	101.94	101.94	-0.11	-1.86	-0.11	-0.11	0.32	-1.27	-1.69	-5.75	-1.68	-2.52

PAT_25	M	8	62	NPF	MEN	29.53	30.53	110.01	110.01	-0.62	0.39	-0.77	0.02	-0.12	1.45	-1.23	1.21	-1.9	-0.95
PAT_26	M	11	47	RPF	HGG	27.89	27.89	n.a.	n.a.	-1.76	-1.76	-1.1	-1.1	-1.12	-1.92	-5.02	-5.2	-2.21	-1.95
PAT_27	M	8	46	NPF	HGG	26.62	27.62	103.38	102.4	-0.48	-2.28	-1.1	-2.09	0.57	-0.37	-0.02	-0.25	-1.66	-1.19
PAT_28	F	8	70	RPF	MEN	24.2	26.2	109.06	106.2	-1.63	-1.63	-1.61	-1.61	0.45	0.1	n.a.	n.a.	-1.56	-2.19
PAT_29	F	18	53	RPF	MEN	27.31	27.31	117.5	117.5	-0.1	-0.1	0	-1.02	0.96	1.03	0.58	0.51	0.07	0.49
PAT_30	F	11	53	NPF	HGG	27.99	28.99	113.9	113.9	-1.04	-1.04	0	0	1.23	1.3	1.05	1.59	0	-1.05
PAT_31	M	18	53	RPF	META	27.31	28.31	117.55	116.6	-0.1	-0.1	-1.02	-2.04	-10.68	0.36	n.a.	-9.17	-1.77	-2.19
PAT_32	M	13	20	NPF	HGG	27.59	27.59	101.9	103.8	-0.3	-0.3	-1.1	-0.11	-1.87	-1.87	-1.81	-1.3	-2.09	-1.75
PAT_33	F	8	74	NPF	MEN	31.2	31.2	103.4	107.2	-0.4	0.55	0.77	0.77	0.84	1.08	0.74	1.05	-0.64	-0.46
PAT_34	F	13	48	LPF	LGG	27.89	26.89	112.4	113.3	-1.76	-1.76	-1.1	-1.1	0.44	0.84	1.2	0.23	1	0.66
PAT_35	F	13	47	NPF	MEN	28.89	28.89	106.7	106.7	-0.84	0.07	-0.11	-0.11	0.09	-0.77	0.48	-0.24	-1.61	-1.17
PAT_36	M	8	62	LPF	MEN	30.53	24.53	107.2	106.2	-0.62	-0.62	-0.77	-1.55	0.41	-1.31	-0.51	-3.26	-2.19	-2.88
PAT_37	M	13	62	NPF	HGG	27.49	26.49	104.8	109.5	0.24	1.38	-0.77	0.02	-1.04	-0.18	-4.94	-0.77	-1.85	-1.99
PAT_38	M	13	20	LPF	MEN	27.59	28.59	100.99	105.73	-1.22	-0.3	-0.11	-0.11	-0.4	0.16	-0.74	0.24	-0.87	2.05
PAT_39	F	13	59	LPF	MEN	n.a.	27.99	n.a.	110.4	n.a.	-1.04	n.a.	-1.02	n.a.	-0.44	n.a.	-3.83	n.a.	-2.32
PAT_40	M	11	52	LPF	META	26.99	27.99	113	113.9	0.83	0.83	-1.02	-1.02	-0.11	0.16	1.41	1.44	-0.14	-0.42
PAT_41	M	13	50	RPF	HGG	28.99	28.99	116.5	116.5	0.07	-0.84	0	-1.02	-0.14	-0.66	0.7	-1.28	-1.51	-1.87

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

Table 2. Neuropsychological assessment Task × Group analyses

Test	Session	Group main effect[1]		Average (SD) scores[2]				Correlation with perseveration score[3]	
		H	*p*	NPF	LPF	RPF	CTRL	Spearman's r	*p*
MMSE	pre	**12.768**	**0.005**	**28.03 (1.14)**	27.68 (1.95)	**27.5 (1.36)**	28.64 (0.93)	0.192	0.676
	post	**9.791**	**0.020**	27.7 (2.46)	**26.16 (3.32)**	28.1 (1.15)	28.66 (0.89)	-0.133	0.722
TIB	pre	8.552	0.036	107.84 (9.64)	110.76 (7.83)	110.59 (6.43)	114.2 (4.78)	-0.089	0.820
	post	6.691	0.082	110.11 (7.19)	110.78 (6.42)	111.19 (5.69)	114.15 (5.13)	-0.449	0.084
Digit Span	pre	**10.996**	**0.012**	**-0.77 (0.72)**	-1.02 (1.02)	-0.4 (1.2)	0.09 (1.09)	0.095	0.820
	post	**13.429**	**0.004**	**-0.52 (1.03)**	-0.81 (1.06)	**-0.81 (1.26)**	0.31 (1.05)	-0.330	0.344
Corsi	pre	6.730	0.081	-0.41 (0.83)	-0.86 (0.89)	-0.35 (1.01)	0.03 (1.01)	-0.022	0.893
	post	**14.730**	**0.002**	-0.33 (1.14)	**-0.92 (0.61)**	**-1.06 (0.62)**	0.02 (0.95)	-0.063	0.820
TMT-A	pre	2.267	0.519	0.19 (0.86)	-0.67 (2.3)	-1.16 (3.68)	0.28 (0.72)	-0.076	0.820
	post	5.751	0.124	0.04 (0.98)	-1.09 (2.24)	0.02 (1.21)	0.26 (1.1)	0.144	0.722
TMT-B	pre	**11.071**	**0.011**	-0.55 (1.52)	**0.34 (1.12)**	-0.97 (2.2)	0.52 (0.69)	0.241	0.676
	post	**14.909**	**0.002**	**-1.21 (2.39)**	-2.75 (4.7)	**-2.72 (4.05)**	0.51 (0.98)	0.164	0.722
Phonemic fluency	pre	**18.369**	**0.000**	**-1.57 (0.67)**	-0.78 (1.57)	-1.08 (1.03)	-0.36 (0.87)	0.038	0.893
	post	**18.151**	**0.000**	**-1.19 (0.95)**	**-1.46 (1.98)**	**-1.3 (1.19)**	-0.09 (1.01)	-0.304	0.355

1. In bold significant *p* values (<.029 false discovery rate multiple comparison correction)
2. In bold significant pairwise comparisons with control group (Dunn's test with FDR Benjamini-Hochberg adjustment)
3. In bold significant *p* values (FDR Benjamini-Hochberg adjustment)

Experimental investigation

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

On each trial, one out of two letters (A or E) was presented approximately 2.8° above or below a centrally positioned fixation asterisk that remained constantly on the screen. Each letter subtended a visual angle of approximately 0.8° x 0.8°. During the first two single-task blocks participants performed one task that remained constant throughout the block, in which they were instructed either to identify the letter (A or E) or its position (above or below the fixation point) by pressing the "k" key (marked by the number 1) or the "l" key (marked by the number 2) on the computer keyboard. The order of presentation of the two single-task blocks was counterbalanced between participants.

During the next two blocks of trials both letter identity and letter position tasks were presented together in a pseudo-random order (i.e., task-switching blocks). At the beginning of each trial, a 3000 ms long cue was presented that instructed the participant about which task to carry out. The cue was explicit, as it comprised both the name of the task ("LETTERA" – Italian for letter or "SPAZIO" – Italian for space) and the key association for that task (1: A / 2: E or 1: SOPRA / 2: SOTTO – Italian for above and below). The cue was then substituted by the target stimulus that remained on the screen until a response was detected, which was followed by a 500 ms long response-to-cue interval. During single-task trials a 1000 ms long fixation asterisk was presented instead of the cue.

All four blocks consisted of 40 trials each and had equally distributed letter and position task cues that were presented randomly. During task-switching blocks on average 50% of the trials were "repeat" trials in which the task remained the same as the one performed on the previous trial, and the remaining were "switch" trials in which the task changed with respect to the one in the previous trial. Moreover, each stimulus was categorized as "congruent" if the same response had to be given whichever task had to be performed, or "incongruent" if the response for that stimulus on the current task was different than the response that should have been given under the alternative task rules. The ratio of congruent and incongruent trials was 50:50. Each single-task block was preceded by 4 practice trials, while the task-switching block was preceded by 8 practice trials, that could be repeated if necessary for a maximum of three times. A feedback message, "corretto" in Italian (which means "correct" in English) in blue (for correct responses), "fai più attenzione" ("pay more attention") in red (in case of wrong responses), or "nessuna risposta rilevata" ("no response detected") in red (for null responses), was presented after each response during the practice blocks for a duration of 1500 ms. Participants were instructed to press the keys with their index and middle fingers of their dominant hand, and to respond by equally stressing both speed and accuracy.

Analyses of the behavioral data

Trials with response times (RTs) below 150 ms and above 4 standard deviations from the mean RTs of each participant in each experimental condition were excluded from all analyses, which resulted in 0.99% of excluded trials. Accuracy data were analyzed by means of non-parametric Kruskal-Wallis (K-W) H test if differing significantly from the normal distribution, as assessed by Kolmogorv-Smirnov test. RT data were log-transformed in order to improve normality and reduce skewness. Group differences in accuracy were analyzed within each testing session separately for the two single tasks, congruent and incongruent trials, switching cost (i.e., accuracy difference

between switch and repeat trials) and perseveration. The latter was measured as the absolute difference in accuracy between the two task rules (i.e., letter identity and letter position), which would result higher in patients who applied more often one task rule, regardless of the type of trial (i.e., switch, repeat). Since the accuracy on congruent trials could not reflect possible switching or perseveration errors, the switching cost and perseveration scores were measured on incongruent trials only. Follow up multiple comparisons of mean ranks were used to assess significant group differences. The reported *p*-values refer to two-sided significance levels with a Bonferroni adjustment, as implemented in STATISTICA software (Dell Inc., 2015). The analyses on correct RT data were performed by means of a repeated measures ANOVA separately for single and task-switching blocks. For the single task blocks, Session (pre vs. post surgery) and Type of task (letter identity vs. letter position) were included as the within subject variables, and Group (LPF, RPF, NPF and Controls) as the between subjects variable. For the task-switching blocks, we included Session (pre vs. post surgery), Congruency (congruent vs. incongruent) and Trial type (repeat vs. switch) as the within subject variables, and Group (LPF, RPF, NPF and Controls) as the between subjects variable.

MRI preprocessing and lesion segmentation

For 34 out of 41 patients structural gadolinium-enhanced T1-weighted and FLAIR MR images were acquired as part of the pre-operative protocol and used concurrently to identify the areas affected by the tumor mass. Four patients had only one of these two types of MRI scans available, and three had only CT images available. Tumor lesions were manually drawn on pre-operative structural MRI or CT axial slices with MRIcroN (Rorden & Brett, 2000). The reconstructed lesions included all voxels that showed altered MRI signal. We chose to use the pre-operative scans since the lesion boundaries on post-operative scans are often displaced by the neighboring tissue and are less clearly defined due to the acute effects of surgery on MRI. Moreover, all

surgeries aimed at maximal extent of resection of the tumor mass as possible, some of which were also coupled with awake brain mapping in order to increase the extent of resection.

Both images and lesions were normalized to an age-appropriate template brain using the Clinical Toolbox (Rorden et al., 2012) for SPM12 (Statistical Parametric Mapping; http://www.fil.ion.ucl.ac.uk/spm) with enantiomorphic normalization (Nachev et al., 2008).

Multivariate lesion-symptom mapping analyses

The relationship between lesion maps and behavioral measures was modeled using the support vector regression lesion-symptom mapping toolbox (SVR-LSM; Zhang et al., 2014) with linear kernel. The kernel C parameter was evaluated across the range from $C = 10^{-6}$ to $C = 10^{6}$ by measuring both the prediction accuracy of the behavioral scores and the reproducibility of the SVR-LSM. Following Zhang et al. (2014), the model prediction accuracy was determined by calculating the mean Pearson's correlation coefficient between predicted and actual scores obtained from 40 iterations of a 5-fold cross-validation procedure. Specifically, for each C, the model was trained on lesion data and behavioral scores from 4/5 of all patients and was used to estimate the behavioral score from the left-out 1/5 of patients. To evaluate the reproducibility of the SVR-LSM, the analysis was performed on 40 different subsets of 32 randomly selected patients. The reproducibility index for each C was calculated as the mean Pearson's correlation coefficient between any two pairs of SVR-LSM β-maps from different subsets. The C parameter was selected to have both prediction accuracy and reproducibility as high as possible (see Figure 2 for parameter evaluation results). Once optimally trained, the resulting β-map, representing the predictive weight of each voxel, was compared to a probabilistic β-map obtained by permuting 2000 times the behavioral scores, with a false discovery rate (FDR) of $p < 0.005$ and cluster size > 50 thresholds. Two different approaches were adopted to control for lesion volume effects: the direct total lesion volume control (dTLVC) method, as implemented in the SVR-LSM toolbox

(Zhang et al., 2014) and the regression of lesion volume out of behavioral scores (see DeMarco & Turkeltaub, 2018 for a detailed description and comparison of the two methods). In order to minimize possible outlier effects, only voxels damaged in three or more patients were included in the analysis. Two anatomical templates were used to identify white and gray matter region labels respectively: the "Automated anatomical labelling" (AAL) template (Tzourio-Mazoyer et al., 2002) and the "NatBrainLab" template of the "Tractography based atlas of human brain connections" (Catani & Thiebaut de Schotten, 2008).

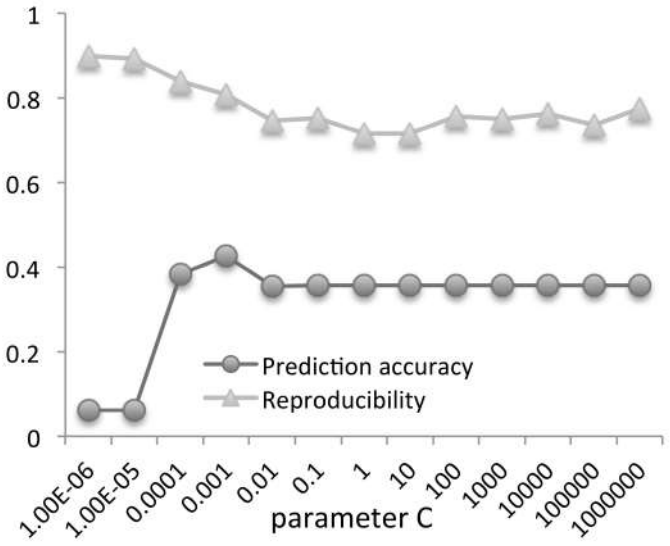

Figure 2. SVR parameter C evaluation results. The graph shows the reproducibility index and the cross-validation prediction accuracy for the perseveration score.

Results

Behavioral results

Group differences on pre-operative accuracy resulted significant only on the single letter position type of task [$H(3) = 7.89$, $p = .048$] and on incongruent trials [$H(3) = 8.57$, $p = .035$], even though post-hoc group contrasts did not yield any significant difference (all corrected ps > .07). Similarly,

post-operative accuracy differed significantly across the four groups only on incongruent trials [$H(3) = 20.42$, $p < .001$]. This time, however, post-hoc tests showed that LPF and NPF patients' accuracy was significantly lower with respect to the control group's performance (both corrected ps < .031; Figure 3A), while RPF patients' performance was comparable to the control group's one ($p = .21$). The perseveration measure differentiated significantly between the four groups both on pre- and post-surgical testing sessions (pre: [$H(3) = 7.87$, $p = .049$], post: [$H(3) = 21.16$, $p < .001$]). However, only for post-operative scores there were significant post-hoc group differences (Figure 3B). In particular LPF and NPF patients' perseveration score was significantly higher than the control group's score (both $ps < .01$). Again, RPF patients did not differ with respect to the controls ($p = .12$).

Additionally, we examined if the patients that had higher perseveration scores perseverated more often on one type of task, to control if higher perseveration could be due to material-specific processing difficulties (e.g., LPF patients could have systematically lower accuracies on the verbal type of task). To identify all patients that had higher perseveration scores, we calculated a cut-off score based on the control population (2 SD above their mean perseveration score). Eighteen patients had scores above this cut-off (> 0.28), and 16 of them belonged to NPF and LPF groups. In particular, 2 out of 6 LPF patients, and 3 out of 10 NPF patients perseverated on the spatial task rule. Their distribution was not significantly different (Fisher's exact test p = 1), suggesting that there was no systematic bias for any type of task. Finally, contrary to our expectations, no significant group differences emerged in terms of switching cost, nor there was any interaction with session. However, to ensure that our task was sensitive enough to detect switching costs also in terms of accuracy, we compared the accuracy on switch and repeat trials for all participants (both patients and controls) and found a significant difference in both sessions (Wilcoxon matched pairs test $ps < .001$).

For the single tasks, the RT analysis showed a main effect of Group [$F(3, 80) = 8.42$, $p < .001$, $\eta^2_p = .24$], Session [$F(3, 80) = 23.99$, $p < .001$, $\eta^2_p = .23$] and Task [$F(3, 80) = 91.74$, $p < .001$, $\eta^2_p = .53$], and an interaction between Group and Session [$F(3, 80) = 4.56$, $p = .005$, $\eta^2_p = .15$] (Table 3). Post-hoc test for the Group main effect showed longer RTs in LPF and RPF groups with respect to the control group (both ps < .025). However, RPF patients were also significantly slower with respect to all the other three groups (all ps < .047). Moreover, the post-hoc test for the Group × Session interaction showed that, while LPF and RPF patients were slower than controls in the second session (for patients: after surgery; both ps < .01), only RPF patients were slower also before surgery when compared to the controls ($p = .001$).

The analysis on RTs from the task-switching block showed a main effect of Group [$F(3, 80) = 6.87$, $p < .001$, $\eta^2_p = .2$] and an interaction between Group and Session [$F(3, 80) = 3.42$, $p = .021$, $\eta^2_p = .11$] (Table 3). While the group main effect was due to a general slowing in all patient groups with respect to the controls (all ps < .044), post-hoc test on the session x group interaction showed that all three patient groups differed significantly from the control group after surgery (all ps < .032), however prior to surgery only RPF patients were significantly slower than the control group ($p = .006$). The main effects of Congruency [$F(3, 80) = 86.26$, $p < .001$, $\eta^2_p = .52$], Trial type [$F(3, 80) = 53.2$, $p < .001$, $\eta^2_p = .4$], and an interaction between the two also emerged [$F(3, 80) = 4$, $p = .049$, $\eta^2_p = .05$] due to a higher switch cost in the incongruent vs. congruent trials (average switch cost: incongruent = 140 ms, congruent = 82 ms). Although the lack of switching cost differences between groups, both in terms of RTs and accuracy, could be due to low demands of the task (e.g., CTI = 3000 ms), the high error rate does not support this suggestion.

To assess whether there was an effect of lateralization also in the NPF group, we separated the NPF group into left and right, and repeated the analyses reported above. All reported results remained unchanged, except for the significant results related to the NPF group, which now

resulted significant only for the left NPF group, confirming the effect of lateralization also in patients with posterior damage.

Additionally, in order to verify whether an increase in perseveration had also consequences in terms of RTs, we correlated the accuracy difference with the RT difference between the two types of tasks. Four patients whose accuracy was null on the alternative task were excluded from the analysis (1 LPF, 1 RPF, 2 NPF). A positive and significant correlation ($r = .53$, $p < .001$; Figure 4) showed that increased perseveration on one task rule was followed by increased RTs when switching to the alternative task rule.

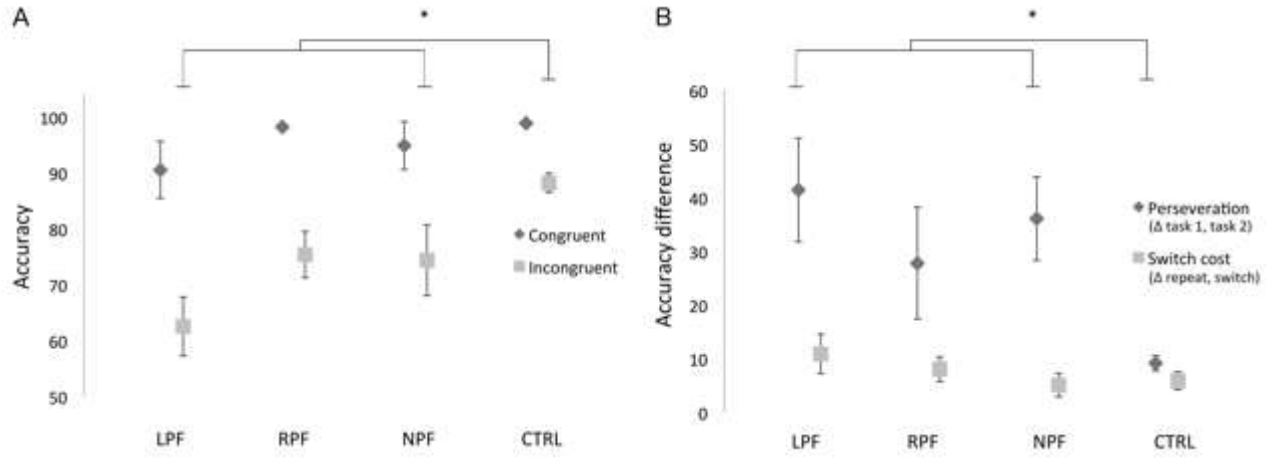

Figure 3. (A) Accuracy (%) on congruent and incongruent trials and (B) absolute accuracy difference between the two types of tasks reflecting perseveration measure, and accuracy difference between switch and repeat trials reflecting the switching cost measure. Both perseveration and switching cost measures were calculated for incongruent trials only. Significant group differences are indicated with an asterisk. The reported data are from the post-surgical session.

Table 3. Average RTs (standard error) for single task and task switching conditions in the pre- and post-operative sessions.

	Single task		Task switching	
Session	Pre	Post	Pre	Post
LPF	683 (72)	970 (165)	1180 (113)	1345 (206)
RPF	1170 (381)	1434 (463)	1712 (476)	1890 (494)

NPF	667 (45)	706 (38)	1128 (77)	1181 (79)
CTRL	539 (21)	541 (19)	955 (61)	850 (45)

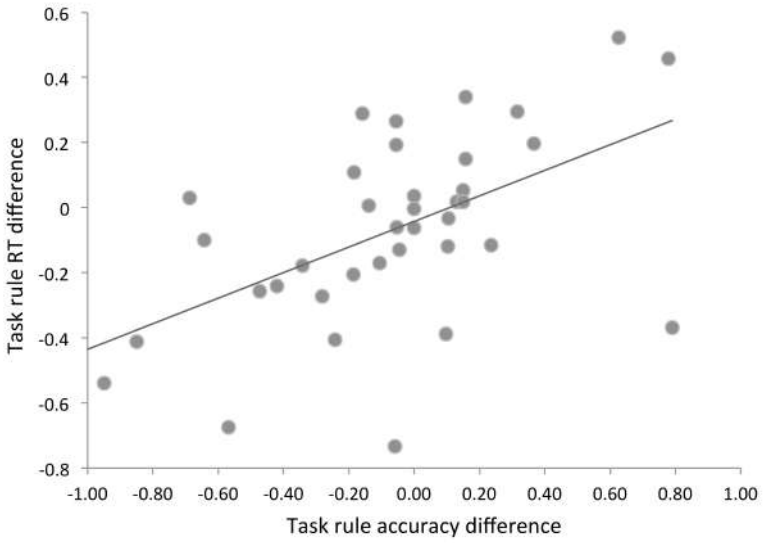

Figure 4. Correlation between the accuracy difference and RT difference for the two task rules. RT difference is measured between the natural log-transformed RTs in the verbal and spatial tasks. Accuracy difference is measured in the opposite direction (spatial – verbal task accuracy).

Multivariate Lesion-Symptom Mapping (MLSM)

The brain-behavior relationship was investigated for measures that were found to significantly differentiate between the three patients' groups and the control group or that were a-priori determined. Thus, the prediction of behavioral measures from lesion data was performed for post-operative switching cost and perseveration measures, and for pre- and post-operative RTs. The correlation between actual scores and those predicted by the linear SVR model was significant only for the perseveration measure (R^2 = .15, p = .013). Lesions that were found to be associated with higher perseveration scores belonged mainly to left white matter pathways, in particular the long segment (fronto-temporal connections) and the anterior segment (fronto-parietal connections)

of the arcuate fasciculus (all peak permutation-based *p*s < .001; MNI coordinates reported in Table 4). Gray matter areas that were associated significantly with perseveration were confined to left orbitofrontal cortex (OFC), left medial PFC and left posterior parietal cortex (all peak permutation-based *p*s < .001; MNI coordinates reported in Table 4). The brain areas that resulted significantly associated with higher perseveration scores, together with the permutation based *p*-values, are visualized in Figure 5; only brain areas with a FDR corrected $p < 0.005$ and cluster size > 50 are shown. The supplemental analysis with lesion size regressed out of perseveration scores confirmed all the above reported results.

Table 4. MLSM results for perseveration scores

Gray matter region	AAL label	N° sign. voxels	% sign. area	MNI coordinates		
				Max X	Max Y	Max Z
Left orbitofrontal cortex	Medial orbitofrontal gyrus	1033	0.18	-9	27	-13
	Middle orbitofrontal gyrus	940	0.13	-32	61	-11
	Superior orbitofrontal gyrus	936	0.12	-9	32	-24
	Inferior orbitofrontal gyrus	162	0.01	-34	35	-11
	Gyrus rectus	635	0.09	-7	32	-24
Left medial prefrontal cortex	Anterior cingulate cortex	569	0.05	-9	30	-9
	Medial superior frontal gyrus	1078	0.05	-2	55	0
Left parietal lobe	Precuneus	508	0.02	-14	-64	33
	Inferior parietal lobule	240	0.01	-40	-39	37
	Rolandic operculum	707	0.09	-45	-19	13
	Postcentral gyrus	411	0.01	-54	-20	16
Left insula	Heschl gyrus	353	0.20	-34	-22	9
	Insula	308	0.02	-33	-23	9
White matter network	NatBrainLab label	N° sign. voxels	% sign. area	MNI coordinates		
				Max X	Max Y	Max Z
Left perisylvian network	Anterior segment (arcuate)	929	0.23	-34	-43	20
	Long segment (arcuate)	927	0.31	-34	-37	14
	Posterior segment (arcuate)	831	0.14	-34	-53	15
Left projection network	Internal capsule	486	0.05	-25	-27	9
	Cortico-spinal tract	2409	0.09	-24	-27	9
Left optic radiations	Optic radiations	342	0.08	-32	-56	12
Left cerebellar network	Cortico-ponto-cerebellar tract	423	0.06	-23	-27	8
Left inferior network	Uncinate	151	0.02	-14	44	-15
Left corpus callosum	Corpus callosum	717	0.02	-12	37	-15
Left fornix	Fornix	145	0.01	-24	-28	9
Left cingulum	Cingulum	487	0.01	-10	28	-15

Voxels significant at threshold of $p < .005$, with false discovery rate correction applied.

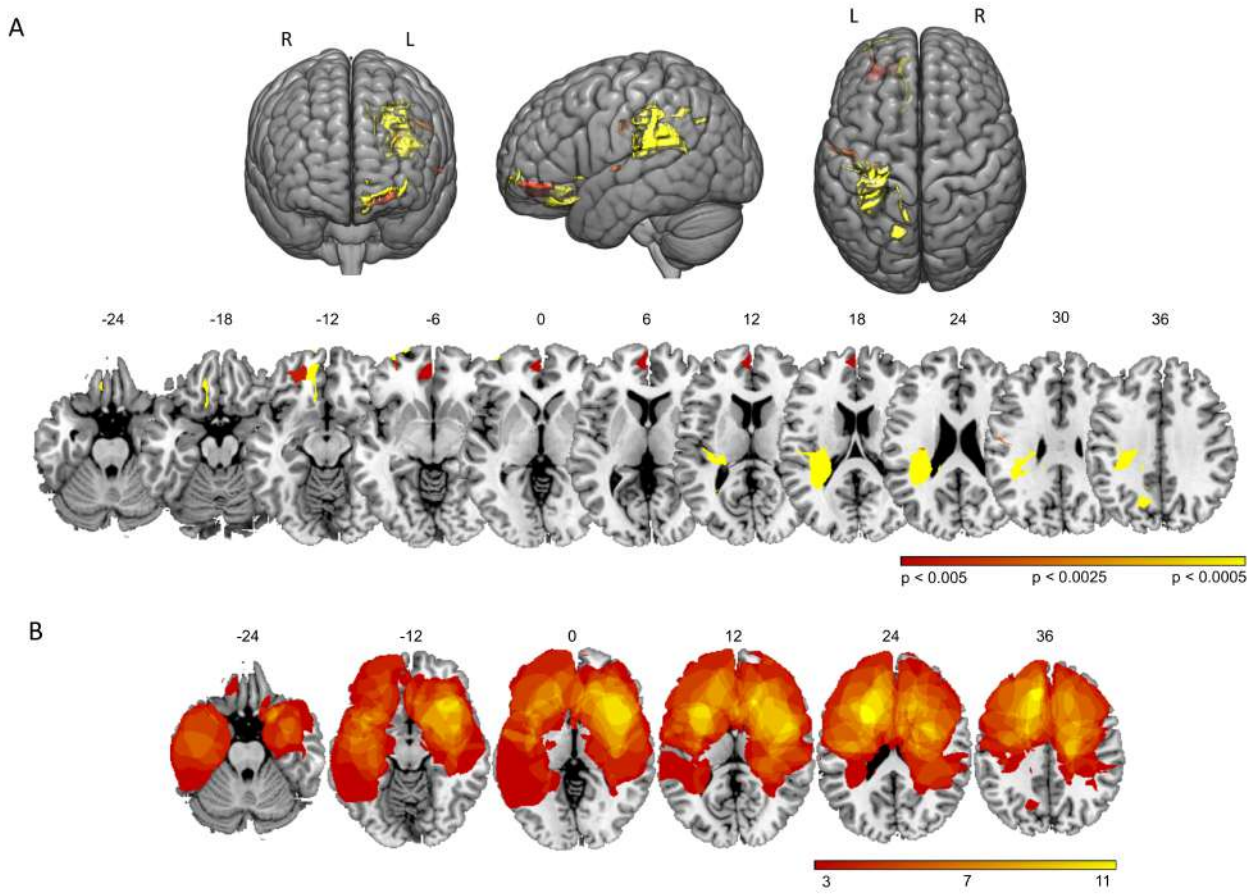

Figure 5. (A) Brain clusters significantly associated with perseveration from the SVR-LSM analysis with dTLVC. Color bar indicates permutation-based *p*-values. The values above the slices indicate the z coordinates in the Montreal Neurological Institute space. In the upper figure L and R indicate left and right, respectively. In the lower figure, left is left. (B) Lesion overlap map showing all voxels included in the SVR-LSM analysis. The color bar indicates the number of patients whose lesions overlap on each voxel.

Discussion

In the present study, our aim was to individuate the cognitive and neural determinants of task-switching impairments in patients with prefrontal and non-prefrontal damage. In particular, by doing so, we were interested in addressing a still open question regarding the processes underlying task-switching and their common vs. distinct engagement in trials that require switching vs.

repeating the previous task, or that require interference control (Jamadar et al., 2015). We hypothesized that a disruption of a hypothetical switch-related process would produce a switch cost increase, probably more evidently during incongruent trials, as typically observed in task-switching paradigms (Wendt & Kiesel, 2008). Alternatively, a larger interference effect during both switch and repeat trials would suggest a disruption of a common process required to overcome conflict, probably not selectively engaged during task-switching performance, but also engaged on other tasks with high demands in terms of interference control (e.g., Stroop, Flanker tasks; see Tsuchida & Fellows, 2012 for a similar result).

Our main finding showed a strong accuracy interference effect in left prefrontal and non-prefrontal groups of patients (Figure 3a), without a significant switch cost increase in any of the three patient groups, neither in terms of RTs nor accuracy. However, a different inspection of the patients' performance pointed to a more severe form of switching impairment: often left prefrontal but also non-prefrontal patients applied only one task rule throughout the task, while less frequently they switched to the alternative one. This resulted in high accuracy on congruent trials, where both task rules required the same response. Conversely, on incongruent trials their performance was significantly reduced, but mostly on trials in which the alternative task rule had to be followed. This difference in accuracy between the two task rules on incongruent trials was captured by a perseveration score, which was significantly higher in the left prefrontal and non-prefrontal patients (Figure 3b). Furthermore, 5 out of 6 patients that did not manage to complete the task because they found it difficult had lesions in left prefrontal areas, which corroborates our main finding of task-setting loss after left prefrontal damage.

Based on previous literature and on evidence provided by the present work on both prefrontal and non-prefrontal involvement in task-switching execution, the brain-behavior relationship was investigated more in detail by means of a multivariate method, which takes into account the

interactions between spatially distributed lesions (Zhang et al., 2014). In this more fine-grain analysis we considered higher switching cost and perseveration as two possible behavioral outcomes of more localized, albeit distributed lesions. A significant prediction of the behavioral scores from the damaged brain areas was obtained only for the perseveration measure. In particular, lesions in left hemispheric fronto-parietal and fronto-temporal white matter tracts, and left OFC and medial PFC were significantly associated with higher perseveration scores.

The association between task perseveration and left prefrontal areas is in line with previous neuropsychological findings, which mainly agree upon the central role of those areas in supporting task-switching execution (Aron et al., 2004; Mayr et al., 2006; Rogers et al., 1998; Tsuchida & Fellows, 2013). However, the type of impairment described in each of these studies is often diverging and not entirely accountable by a pure switching deficit. Indeed, increased switching costs are frequently reported along with reduced interference control. Overall, our results could partially explain these mixed findings by showing that a difficulty in switching between tasks, other than increasing the switch cost, might emerge as a tendency to perseverate on one task and, consequently, reduce performance on incongruent trials. Nevertheless, our results are based only on accuracy and therefore might not resemble the effects found in other studies, which mostly report the interference and switching effects in terms of RTs. Hence, we correlated perseveration and RT difference between the two tasks and observed that patients who often failed to switch to the alternative task showed longer RTs when performing it correctly. This result suggests that patients attempted to switch between tasks, and when succeeded had an increased switching cost in terms of RTs. Moreover, it elucidates how reduced performance on incongruent and switch trials observed in previous studies might have a common underlying impairment.

An important feature of our study is the inclusion of patients with parietal and temporal lesions that allowed us to investigate the causal contribution of those regions in task-switching

performance. In line with evidence from fMRI studies (Jamadar et al., 2015; Kim et al., 2012), we observed severe task-setting impairments also in patients with left parietal lesions, which extended to subcortical regions as well, and compromised fronto-temporal and fronto-parietal white matter tracts. The involvement of subcortical regions in task-switching is supported by multiple white matter connectivity studies (Gold et al., 2010; Jolly et al., 2017; Kucukboyaci et al., 2012; Vallesi et al., 2016). Most pertinent to our finding of decreased accuracy in patients with left fronto-parietal and fronto-temporal damage, Jolly and colleagues (2017) observed similar age-related increase of error rate on incongruent trials that was associated with reduced global white matter integrity. On the other hand, more localized white matter changes in left fronto-parietal tracts were associated with increased RTs during task-switching. As suggested by the authors, diffuse white matter decline may reduce the efficiency of compensatory processes that, when not compromised, trade speed for accuracy. Along this line, we can suggest that our observation of severe task-setting impairment observed in terms of accuracy might be caused by damage in more diffuse left fronto-parietal and fronto-temporal white matter tracts. Likewise, our discrepancy with previous neuropsychological studies observing decreased task-switching performance mainly in terms of RTs (e.g., Aron et al., 2004; Tsuchida & Fellows, 2013) could be accounted for by these more diffuse subcortical lesions in our patients sample.

Our result of left-lateralized lesion involvement in task-setting impairments finds support also in a more general framework of executive function organization within the pFC, initially outlined by Don Stuss and colleagues in their ROtman-Baycrest Battery to Investigate Attention (ROBBIA) model (Stuss et al., 1995), and developed later based on extensive neuropsychological investigations (Picton et al., 2006; Shallice et al., 2008a; Shallice et al., 2008b; Stuss et al., 2005). Two key executive processes that emerged from these studies, criterion-setting and monitoring, were found to rely on distinct and lateralized prefrontal regions. In particular, left-lateralized and

right-lateralized PFC lesions were associated with deficits in setting up and adopting rules to perform a task, and deficits in monitoring and adjusting ongoing performance, respectively. Regardless of their different hemispheric lateralization, these higher-order prefrontal processes are assumed to be domain general because of their interaction with and coordination of domain-specific, lower-level processes, which was confirmed in a series of studies on healthy adults (Ambrosini et al., 2020; Ambrosini & Vallesi, 2016; Capizzi et al., 2016a, 2016b; Vallesi et al., 2015; see Vallesi, in press for a review).

Nevertheless, there are neuropsychological studies reporting contrasting results regarding this domain-general nature of lateralized PFC functions (e.g., Geddes et al., 2014; Tsuchida & Fellows, 2013). In particular, lateralized PFC lesions were found to cause distinct impairments that were, however, strongly related to verbal and spatial characteristics of the tasks. Taking this evidence into account, we adapted our task so as to comprise both verbal and spatial task-rule variations, in order to control for this possible confound. However, we did not observe any systematic difference in performance between the two task rules that could point to different material-related impairments in our patients' groups. On the other hand, we observed a generalized slowing in patients with RPF damage that was present both before and after surgery, and therefore cannot be interpreted as a consequence of surgery, as had been reported in other patient groups. Instead, this slowing could be related to the inability to energize a rapid response after right superior medial lesions, as predicted by the ROBBIA model (Stuss et al., 2005). However, the lesion-symptom mapping analysis did not associate any pattern of lesions to longer RTs either in the pre- or in the post-surgical session. Therefore this result and its interpretation should probably be taken with caution and investigated more carefully with a specific task design and increased sample size.

A somewhat divergent finding that emerged in our study concerns the involvement of the OFC and medial PFC in task switching. Of the aforementioned neuropsychological studies, only

Shallice and colleagues (2008b) observed a similar impairment in their inferior medial group. Their overall increased error rate was ascribed to a reduced subjective cost of committing an error, which, according to the authors, led the patients to care less about the outcome of their responses. There are some similar observations coming from studies assessing reversal learning in patients with orbitofrontal lesions, who show difficulties in learning stimulus-outcome contingencies (Tsuchida et al., 2010) and fail to adjust their behavior after these contingencies have changed (Fellows & Farah, 2003, 2004). All these observations are consistent with a more general role of the OFC in encoding expected outcomes to adjust behavior (Bechara et al., 2000). On the other hand, not considering the outcomes of one's own behavior might reduce the need for control and increase the amount of errors, but it should not induce a more perseverative behavior, at least not in a task-switching setting where neither task was reinforced or overlearned. This sort of impairment could be explained by more comprehensive accounts of the OFC function according to which its fundamental role is to form and maintain neural representations of different task-relevant information (Badre & D'Esposito, 2007; Badre & Nee, 2018; Koechlin, Ody, & Kouneiher, 2003), especially when this information is unobservable and has to be inferred (Schuck et al., 2016; Wilson et al., 2014). Although our task cues were explicit, the bivalence of our stimuli made it hard to distinguish the two task states, which could have led to a greater impairment in patients who were not able to create stable distinct task representations due to OFC disruptions. However, the lack of univalent stimuli in our task does not allow us to assess in depth this consideration and future studies should address this possibility with more appropriate task designs. Alternatively, orbitofrontal and medial prefrontal lesions might have impaired goal-directed behavior (Reber et al., 2017), such that patients have preserved task representations, but fail to use these representations to implement the task. This impairment has been described as "goal neglect" (Duncan et al., 1996), and has been shown to exacerbate with task complexity (Bhandari &

Duncan, 2014). A similar observation comes from a rehabilitation study (Manly et al., 2002) in which the authors observed a significant improvement in performance of dysexecutive patients on a complex goal management task when exposed to brief interruptions which, according to the authors, allow patients to draw their attention from one activity to another. Future studies should explore if this type of approach could alleviate perseverative behavior in patients with orbitofrontal and medial prefrontal lesions.

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

A similar perseveration impairment in task-switching was previously observed in patients with lesions involving the basal ganglia (Yehene et al., 2008), some of whom presented a no-switch behavior by applying only one rule throughout the task, while others made some attempts to

switch between tasks but often failed. Although their performance was compared to that of a group of patients with prefrontal lesions, the authors reported no similar deficit in the latter group. These results are quite in contrast to what we found, but could be partially accounted by a small number of patients with left prefrontal damage (N=2) included in their study, and their different lesion localization (i.e., left inferior frontal gyrus). However, the fact that our lesion-symptom mapping analysis did not show a significant involvement of basal ganglia in perseveration is a bit more concerning. From the MRI scans we identified 30 out of 41 patients whose lesions involved the basal ganglia, suggesting that we had enough power to detect their involvement. Thus, it is more conceivable that rich structural and functional connections between orbitofrontal and posterior parietal regions, and striatal regions (Jarbo & Verstynen, 2015) might have a more critical role in the observed switching impairments. This hypothesis is also supported by recent neuroimaging studies that explored the neural dynamics during acquisition and implementation of novel task rules (Hartstra et al., 2011; Ruge & Wolfensteller, 2010, 2013b). In particular, Ruge and Wolfensteller (2013b) observed an increased functional coupling between lateral prefrontal, orbitofrontal and striatal regions during instruction-based learning of novel stimulus-response rules. According to these findings, damage to both orbitofrontal and striatal regions could disrupt the rule acquisition ability. However, due to a relatively low number of trials in our task design, we were not able to distinguish between learning and implementation stages and future studies should try to dissociate them within patients suffering from different cortical and subcortical lesions.

A further issue worth discussing concerns our choice of testing tumor patients with acute surgical lesions. In their ROBBIA works, Don Stuss and colleagues tested patients in their chronic stage of recovery to exclude confounds due to acute widespread deficits when investigating the effects of focal lesions (e.g., Alexander et al., 2005; Picton et al., 2007; Stuss & Alexander, 2007).

These general deficits, when present, would however be more likely to dilute group differences than to increase false positive rates (Turner et al., 2007), and for this reason do not represent a threat for the internal validity of the effects reported here. We are also aware that brain lesion effects observed in the acute phase could be short-lived (e.g., Campanella et al., 2017, 2018; Kwakkel et al., 2004). Instead of necessarily seeing this only as a methodological limitation, it may rather turn out to be also an advantage with respect to chronic lesions. Stuss and Alexander (2007) indeed notice that "as patients' lesions become more and more chronic, it is possible that brain–behavior relationships are affected by brain plasticity and reorganization". Moreover, it is encouraging that reported acute brain lesion effects may be as focal as those observed in chronic patients and often consistent with them, as also shown by the ROBBIA group (e.g., Alexander et al., 2003; Stuss et al., 1994; Turner et al., 2007).

In summary, the results from this study show that lesions in left orbitofrontal areas and along the left fronto-temporal and fronto-parietal white-matter tracts create a more severe task-setting impairment, which within the task-switching context is not reflected as a mere difficulty in switching between two task rules, but instead as a difficulty in creating stable task rule representations or implementing novel task rules. These results are in line with recent neuroimaging evidence showing that the switching ability requires the creation of different task representations in the brain, and that their distinctiveness predicts the switching performance (Qiao et al., 2017). Future neuropsychological studies should investigate whether damage across different networks involving the prefrontal regions might dissociate the acquisition of rule representations from their implementation.

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