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Research report

Are core component processes of executive function dissociable within the frontal lobes? Evidence from humans with focal prefrontal damage

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ABSTRACT

Executive function encompasses a range of control processes supporting flexible, goal-directed behaviour. Attentional set-shifting, updating of information in working memory, and inhibitory control have been proposed as key components of executive function, but debate continues as to the validity of this conceptual framework, and the neural substrates of these putative components. Here we examined prefrontal structure–function relationships for each of these component processes in a large cohort of patients with focal prefrontal damage. Forty-five patients with focal damage to various sectors of prefrontal cortex (PFC), and 50 demographically matched healthy control subjects performed an attention shifting task, the Stroop colour naming task, and a spatial search task. Voxel-based lesion–symptom mapping revealed that damage to left ventrolateral PFC led to impaired performance on both the Stroop and attention shifting tasks. In contrast, performance of the spatial search task depended on several regions within PFC, but notably not left ventrolateral PFC. These observations were confirmed with direct comparison of performance between patients grouped according to lesion location. This dissociation partly supports the component process view of executive function, distinguishing the goal-directed regulation of attention (perhaps specifically in the verbal domain) from the requirements of the spatial search task, including the updating of information in spatial working memory. These findings are easier to reconcile with modular, material-specific accounts than with more unitary models of executive function.

1. Introduction

Executive function refers to a range of control mechanisms that modulate and organize more basic cognitive operations to allow goal-directed behaviour. Prefrontal cortex (PFC) is thought to make important contributions to executive function, but the precise nature of those contributions remains a matter of debate. Many current theories argue that component processes of executive function rely on specific regions within PFC (e.g, Petrides, 2005; Stuss et al., 1995). This is supported by functional imaging results showing differential haemodynamic responses of specific regions within PFC to

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different executive tasks. On the other hand, unitary accounts propose that at least some regions within PFC carry out general control processes, independent of the type of information being processed and adaptable to changing task demands (Duncan, 2001; Miller and Cohen, 2001). This view accommodates the observation that a large number of seemingly different tasks activate a limited set of regions, consistent with a general-purpose supervisory mechanism central to many cognitive operations (Duncan, 2010; Duncan and Owen, 2000). These regions, which Duncan has termed the 'multiple demand' network, include bilateral ventrolateral PFC (including anterior insula – AI – with its surrounding frontal operculum – FO), dorsolateral PFC, and the pre-supplementary motor area (pSMA) and adjacent dorsal anterior cingulate cortex (dACC) (Duncan, 2006, 2010).

These theoretical issues have important clinical implications for the diagnosis, measurement, and treatment of frontal-executive disorders: is it sufficient to capture executive function as a single construct, or are there key components that must be distinguished? Can we explain the effect of focal prefrontal damage as the disruption of a single, general-purpose control system, or does damage to specific prefrontal sub-regions have distinct effects?

Part of the difficulty in resolving this debate is conceptual ambiguity in the definition of executive function and its putative component processes. The level of explanation in the study of executive function tends to be more abstract than in many other cognitive domains (Burgess et al., 2006). Furthermore, many conventional tests of executive function are complex, plausibly relying on multiple cognitive processes (Jurado and Rosselli, 2007), making it difficult to determine what the basic components of executive function are and how they might be organized within PFC. Nonetheless, certain components recur across a variety of literatures. One reasonable starting point is the work of Miyake and colleagues, which demonstrated the validity of three widely-accepted putative components of executive functioning: mental set-shifting ("Shifting"), inhibition of pre-potent responses ("Inhibition"), and information updating and monitoring ("Updating") using a latent-variable approach in a large sample of young healthy subjects (Miyake et al., 2000).

Whether these component processes rely on distinct neural substrates within PFC remains to be answered definitively. Functional imaging data both support and refute this possibility: meta-analyses using broadly similar conceptual frameworks report both shared and distinct patterns of prefrontal and parietal activations across a range of specific executive tasks (Collette et al., 2005; Wager et al., 2004; Wager and Smith, 2003). In any case, functional imaging findings indicate correlation between brain activity and tasks, and are alone relatively weak tests of functional specialization within PFC.

Studies in patients with focal frontal damage can more directly address whether a given prefrontal region is necessary for performance of a particular task, and the pattern of impairment across tasks can provide evidence regarding the dissociability of these hypothesized component processes. While existing work with this method supports a key role for PFC in all three component processes, the regional specificity of these claims varies, and there has been no strong test of the dissociability of these processes. Here, we used a voxel-based lesion–symptom mapping (VLSM) method as well as region-of-interest group comparisons to test the necessity of specific prefrontal regions for three putative component processes of executive function, and to determine whether these processes can be dissociated.

We focused on three tasks, versions of which are widely used in both research and clinical contexts: an attention shifting task requiring set-shifting, the Stroop colour naming task requiring inhibition of a pre-potent response, and a spatial search task requiring updating. Previous neuropsychological studies have shown all three of these tasks, tested individually, to be sensitive to frontal lobe damage. However, evidence for regional specialization within PFC is either conflicting (Stuss et al., 2001; Vendrell et al., 1995 for Stroop task) or limited, with most studies focussing on the overall effect of frontal damage in patients with relatively large lesions (Owen et al., 1996; Rogers et al., 1998). Further, these studies did not examine the pattern of performance across executive tasks.

Despite the coarse grain of the structure–function evidence base, these tasks are widely used clinically and experimentally to assess the integrity of specific prefrontal sub-regions in various neurological and psychiatric populations. Anatomically specific claims are generally justified by the localized patterns of prefrontal activation observed in functional imaging studies using these tasks (e.g., Stroop task as an index of anterior cingulate cortex; Blair et al., 2006; Orem and Bedwell, 2010).

The aim of this study was to directly test whether distinct prefrontal regions are differentially and critically involved in performance of these tasks, and by extension critical to the three processes proposed as amongst the core elements of executive function. All three tasks were administered to a group of patients with focal lesions affecting various sectors of PFC. If prefrontal sub-regions make distinct contributions to these putative component processes, the effects of lesions to different prefrontal regions should be different for each task, i.e., it should be possible to dissociate performance. On the other hand, if prefrontal regions collectively contribute to a shared underlying mechanism critical for executive function more generally, or if the proposed component processes are not, in fact, distinct, there should be common patterns of widely distributed lesion–symptom associations across all three tasks.

2. Methods

2.1. Participants

Subjects with chronic, focal lesions affecting the frontal lobes (n = 45) were recruited from research databases at the University of Pennsylvania and McGill University. The group consisted of 21 patients with ischaemic or hemorrhagic stroke, 16 with resection of low-grade tumours, and eight with damage resulting from rupture of cerebral aneurysms. Of these, 16 were taking psychoactive medications, most commonly anticonvulsants or antidepressants. The tests were administered at least 6 months after the brain injury (mean 4.5 years, range = 10 months to 16 years). Demographically matched healthy control subjects (n = 50) were

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recruited through local advertisement in Montreal. They had no history of neurological or psychiatric illness, and were not taking psychoactive medications. Control subjects were excluded if they scored less than 28/30 on the Mini–Mental Status Examination (MMSE; Folstein et al., 1975) or less than 26/30 on the Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005). Table 1 provides a summary of demographic information, as well as IQ estimates based on the American version of National Adult Reading Test (ANART) and scores on the Beck Depression Inventory (BDI-II) for all participants. As intended, there was no significant difference between frontal patients (FPs) and control subjects for age or education (unpaired *t*-tests, $p > .05$). The FP group had significantly lower estimated premorbid IQ, and higher BDI scores compared to control subjects ($p < .05$).

All participants also completed a brief neuropsychological screening as summarized in Table 2. Although differences were small, the FP group had significantly lower backward digit span as well as Corsi block span. All participants provided written, informed consent in accordance with the Declaration of Helsinki and were paid a nominal fee for their time. The Institutional Review Boards of both participating centres approved the study protocol.

2.2. *Lesion analysis*

A neurologist (L.K.F) experienced in image analysis and blind to task performance traced individual lesions from the most recent clinical MR or CT images directly onto the standard Montreal Neurological Institute (MNI) brain, using MRIcro software (www.mricro.com; Rorden and Brett, 2000). This standard method combines registration and segmentation into a single step; no additional transformations are required (Kimberg et al., 2007). MRIcro software was used to estimate lesion volumes and to generate lesion overlap images. The estimated lesion size in the FP group ranged from 2.5 to 229.8 cc [mean 37.4 cc (SD 39.7)].

2.3. *Tasks*

All the tasks were computerized, created using E-Prime software (version 1, Psychology Software Tools Inc; www.pstnet.com). For attention shifting and Stroop colour naming tasks, vocal response times were collected with a microphone connected to a Serial Response Box (Psychology Software Tools Inc; www.pstnet.com). Subjects performed all the tasks in one session, with randomized task order.

2.3.1. *Attention shifting task*

Various forms of "attention shifting" or "task switching" tasks exist, with the nature of "shifting" varying across paradigms (Wager et al., 2004, 2005). For example, subjects may be required to shift from one operation to another (e.g., alternate between adding three to or subtracting three from the presented numbers) or to reassign response-mapping rules (e.g., press key X for vowel and Y for consonant in a vowel/consonant judgement but press key X for odd and Y for even numbers in an odd/even judgement on letter-number pairs). However, complex or arbitrary response-mapping rules are likely to tax working memory in addition to the shifting requirement. In order to isolate shifting ability from other potentially PFC-sensitive processes, we chose a task involving shifting between simple, over-learned operations: the letter–number naming task (Rogers et al., 1998). Subjects were presented with a series of letter–number pairs, one at a time on the computer screen. They were required to alternate between letter- and number-reading every two trials (i.e., letter, letter, number, number, letter, letter, and so on) as quickly as possible. A coloured border around the letter–number pair served as a cue indicating the required task (yellow for letter naming and blue for number naming).

Subjects completed a short practice session with letter- and number-only conditions, followed by a short mixed condition similar to the actual task. As a reminder, the colour cue associations were written above the letter–number pairs and remained there throughout the task. The test session consisted of two blocks of 64 trials each. The inter-trial interval was set to 1200 msec to reduce any carryover from the previous trial (Meiran, 1996), and the colour-border cue was presented 150 msec before the target (letter–number pair) stimuli appeared. The main behavioural measure for executive set-shifting ability in this task was the switch cost, expressed as the difference between the mean reaction time (RT) of switch and non-switch trials. The contrast between switch and non-switch trials within a mixed condition is thought to be the most suitable for isolating set-shifting ability from non-specific effects of task difficulty (Rogers and Monsell, 1995; Rogers et al., 1998). The mean RT for non-switch trials was also examined to assess the effect of PFC lesions on baseline speed. We did not focus our analysis on

Table 2 – Summary of performance on selected neuropsychological screening tests for CTL and FP groups [mean (SD)].

Group	Sentence comprehension accuracy	Backward digit span	Backward Corsi span
CTL ($N = 50$)	.97 (.07)	4.9 (1.4)	4.6 (1.1)
FP ($N = 45$)	.96 (.06)	4.2 (1.3)[a]	4.1 (1.3)[a]

a Denotes significant differences (*t*-test, $p < .05$).

Table 1 – Background information for healthy control (CTL) and FP groups [mean (SD)].

Group	Age (years)	Education (years)	Sex (F/M)	BDI	ANART IQ	Lesion volume (cc)
CTL ($N = 50$)	56.8 (11.9)	14.9 (3.0)	32/19	5.2 (4.8)	123.6 (7.3)	—
FP ($N = 45$)	55.4 (12.4)	14.1 (3.4)	28/17	12.7 (9.9)[a]	116.1 (9.5)[a]	37.4 (39.7)

Not all patients completed the ANART.
a Indicates significant differences between CTL and FP (two-tailed *t*-tests, $p < .05$).

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errors, which were highly negatively skewed, indicating a floor effect, and relatively infrequent, with an average of 3.0% and 4.2% in healthy control and FP groups, respectively.

2.3.2. *Stroop colour naming task*

We used a computerized version of the classic Stroop colour naming task, described in detail in (Fellows and Farah, 2005). Briefly, subjects were required to say aloud the ink colour of words that appeared on the computer screen one at a time. These words were five colour names (red, blue, green, brown, and purple), printed in one of the same five colours of ink. Trials were either congruent (e.g., "blue" written in blue ink) or incongruent (e.g., "blue" written in red ink). Stimuli remained on screen until the subject responded. The inter-trial interval was 1000 msec.

Subjects completed a short practice session with equal numbers of congruent and incongruent trials, then 200 trials of the task, in blocks of 50 trials of either 80% incongruent stimuli, or 80% congruent stimuli. The measure of interest here was the ability to inhibit pre-potent responses as reflected in the size of the Stroop effect, i.e., the difference between mean congruent and incongruent RT across all blocks. As in the attention shifting task, the mean RT for congruent trials was also examined to assess the baseline speed, and we focused on RT measures rather than errors, which averaged 2.2% and 4.3% in healthy control and FP groups, respectively.

2.3.3. *Spatial search task*

This task is based on the spatial working memory task described by Owen et al. (1990). Subjects were required to search through a spatially randomized array of boxes presented on a computer screen by touching each one to find yellow tokens hidden inside the boxes. At any time, there was only one token hidden inside one of the boxes, and once a token had been found inside a particular box it would never be hidden in the same box. Subjects were told of this fact and were instructed specifically not to return to the same box once the token was collected. Thus, this task required the subject to maintain and update spatial information in working memory. The search continued until the subject collected the tokens from all of the boxes. After a practice session with three boxes, all subjects completed four test trials each of four-, six-, and eight-box conditions.

Two types of errors are commonly measured in this task: between-search errors, in which the subject returns to a box from which a token had already been collected, and within-search errors, in which the subject returns to a box that has been already opened and found to be empty earlier in the same search sequence. Both reflect a failure to update spatial information in working memory, and it is not clear if the two error types measure distinct processes; within-search errors are generally rare, and subjects with many between-search errors tend to show more within-search errors as well, without any evidence of dissociation (e.g., Owen et al., 1990; van Asselen et al., 2006). Thus, we combined both types of errors, using the total number of errors as the measure of the ability to update information in working memory. Although not directly related to the hypotheses of interest here, for completeness we also examined the strategy index, which has been previously shown to be sensitive to frontal lobe damage (Owen et al., 1990). This index measures the use of one specific strategy that can be applied to improve performance in this task, which is to follow a predetermined search sequence, for example by always starting a search from the leftmost box. The index approximates the use of this strategy by counting the total number of search sequences starting with a different box in most difficult, six- and eight-box conditions (Owen et al., 1990, 1996). Note that, counterintuitively, use of this strategy (i.e., initiating each search from the same box each time) results in a lower strategy index score.

2.4. *VLSM*

VLSM was applied to compare the performance of patients with a lesion affecting a specific voxel against that of those without a lesion involving that voxel, repeated for all eligible voxels. In keeping with standard practice (e.g., Coulthard et al., 2008; Moro et al., 2008), voxels in which fewer than three patients were lesioned were excluded from the analysis. Fig. 1 shows a lesion coverage map, indicating the voxels that were entered in the analysis. This also provides a measure of the power to detect an effect at each voxel, since power generally increases with increasing lesion overlap (Kimberg et al., 2007). The set of prefrontal regions proposed to be part of the general purpose, multiple demand network (Duncan, 2010), is shown in the same figure, illustrating the good coverage of these regions in our sample.

Behavioural measures from the three tasks were first tested for age and lesion size effects. Age was found to influence some measures, and so remaining analyses used age-adjusted z-scores to remove the variance due to age (see Results). The age-adjusted z-scores for each measure did not depart significantly from a normal distribution (Kolmogorov–Sminov tests, all $p > .21$). Thus, *t*-tests were used in the VLSM analysis. The analyses were carried out using the NPM (non-parametric mapping) and MRIcroN (version April 1, 2010) software package (Rorden et al., 2007). All tests were thresholded to control for multiple comparisons by applying Bonferroni correction for distinct lesion patterns, which, in our sample was 2551. This yields a threshold of $z > 4.112$ (for a significance level of $p < .05$ corrected). For illustration purposes, maps were thresholded at $p < .05$ uncorrected, with areas surviving the correction for multiple comparisons highlighted in yellow.

2.5. *Region-of-interest (ROI) group comparison*

The VLSM analyses were supplemented with more conventional group comparisons in the subset of patients ($N = 29$) who had damage largely restricted to one of the following four prefrontal sub-regions of interest: left lateral PFC (LL, $n = 7$); right lateral PFC (RL, $n = 7$); dorsomedial PFC (DM, $n = 7$); orbitofrontal and ventromedial PFC (VM, $n = 7$). Patients were included in the DM group if their lesion involved dACC and surrounding DMPFC, even if this was accompanied by damage extending outside this region, as this area is consistently activated in functional imaging studies that use any cognitively demanding tasks (Duncan and Owen, 2000) and has been proposed to play a prominent role in executive control

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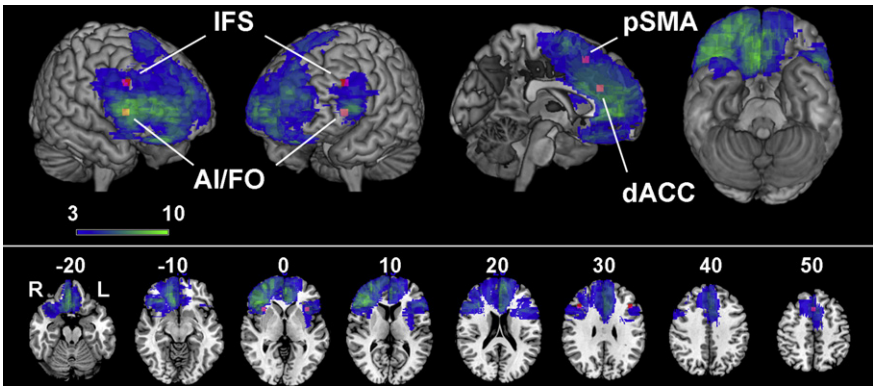

Fig. 1 – Map showing the voxels, in blue, with sufficient lesion coverage to detect an effect in this group of patients, overlaid on the MNI brain in 3D views and in axial slices, with numbers indicating the z-coordinates (MNI) of each slice. The colour bar indicates the degree of overlap across subjects, as shown in the legend. Prefrontal peaks for the 'multiple demand' network are shown in red [taken from Duncan (2010)]. IFS: inferior frontal sulcus, AI/FO: anterior insula and adjacent frontal operculum.

processes (Botvinick et al., 2004; Carter et al., 1998; Ridderinkhof et al., 2004), making it of high *a priori* interest here. As can be seen in Fig. 2, the patients selected for this ROI analysis had very circumscribed lesions, with relatively little overlap between the groups. Although some patients in the DM group had lesions extending to VMPFC, their lesions spared orbitofrontal cortex.

In order to directly test the dissociability of frontal task performance in these four groups, the age-adjusted z-scores of the key measure from each executive task (switch cost from the attention shifting task, total errors from the spatial search task, and Stroop effect from the Stroop colour naming task) were analyzed.

2.6. *Statistical analysis for group comparisons*

To compare performance measures between FPs and control subjects, we used Welch's *t*-tests with Bonferroni correction for multiple comparisons, since the heterogeneity in precise lesion location may result in greater variance in FPs as

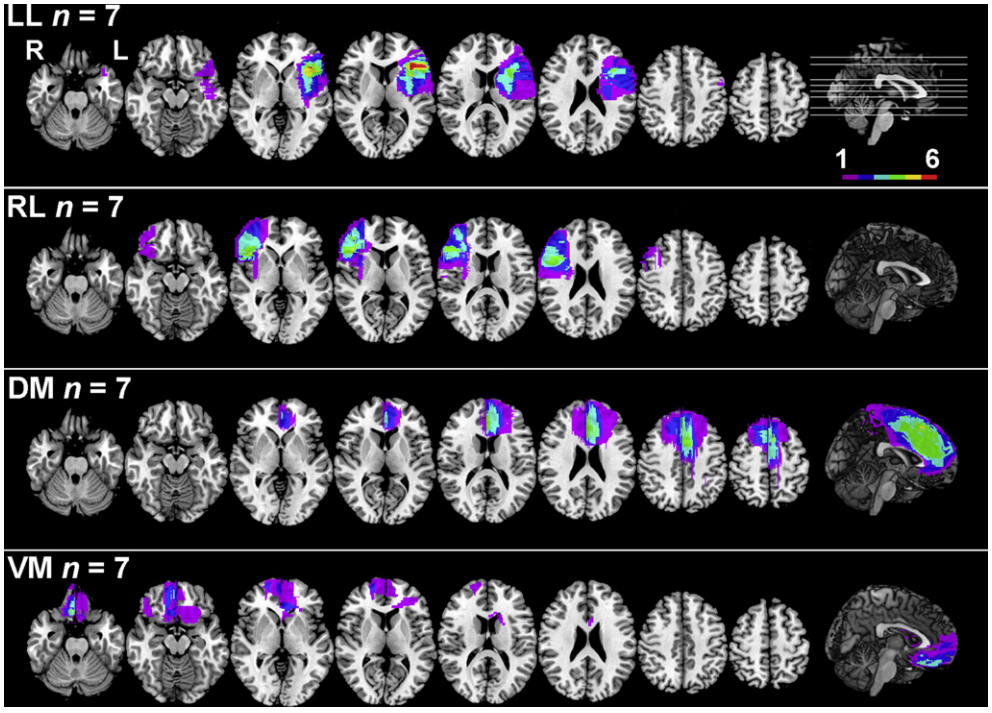

Fig. 2 – Representative axial slices and mid-sagittal views of the MNI brain, showing the degree of lesion overlap for those subjects included in the sub-region group comparisons, with damage affecting LL PFC (LL group, $n = 7$, top row), RL PFC (RL group, $n = 7$, second row), dACC and surrounding DMPFC (DM group, $n = 7$, third row), or orbitofrontal and VMPFC (VM group, $n = 7$, bottom row). Colours indicate the degree of overlap across subjects, as shown in the legend.

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a whole. For comparisons within specific frontal lesion groups, age-adjusted z-scores of the three executive measures from each task were entered in a mixed analysis of variance (ANOVA), with group as a between-subject and executive process as a within-subject factor. For significant interactions, simple main effects tests were performed, followed by Tukey–Kramer pairwise comparisons.

3. Results

3.1. Effect of age on behavioural measures

At least one measure from each task was significantly affected by age in the healthy control group, as summarized in Table 3. In order to obtain individual performance scores adjusted for age for the lesion-mapping analysis, age-adjusted z-scores were calculated based on regression analyses in the healthy control subjects following the method by Altman (1993). We used the same method to calculate z-scores for those measures without strong effects of age for ease of comparison across measures and tasks. This also controlled for any age-related effects on variance.

3.2. Effects of frontal lobe damage

Fig. 3 shows means and standard errors of z-scores for the FPs as well as healthy subjects, overlaid on the distribution of performance for each measure in the three tasks. We used Welch's t-tests to compare the performance between FPs ($n = 45$) and healthy control subjects ($n = 50$), to assess the effects of frontal lobe damage regardless of specific lesion location. The comparisons revealed significant effects of frontal lobe damage on all measures (all $p < .0055$, surviving Bonferroni corrections for multiple comparisons) except the set-shifting measure from the attention shifting task ($p > .05$). As expected, most measures had larger variances in the FP group than in the healthy control group (Fig. 3). Bartlett's test for equal variances revealed significant differences between the control group and the FP group in all but the spatial search strategy score (all $p < .02$). The distribution of performance shows that many with focal frontal lobe lesions perform in the control range on any given task, while others are clearly impaired. Impairment was generally not dependent on lesion volume: only spatial search errors had a weak but significant relationship with lesion volume ($r = .297$, $p = .048$), explaining only 7% of the performance variance. There were no other behavioural measures that correlated with lesion volume (all $r < .18$, $p > .24$). Overall this argues that some frontal lesions affect performance on these tasks more than others, regardless of the overall lesion volume, presumably related to the specific site of damage within the PFC.

Table 3 – Summary of age effects on behavioural measures for each task.

Task	Measure	r	Coefficient	p
Attention shifting	Switch cost	.096	.57 msec/yr	.51
	Baseline RT	.281	3.38 msec/yr	.048[a]
Spatial search	Total errors	.419	.82 errors/yr	.0025[a]
	Strategy score	.023	.01 score/yr	.88
Stroop colour naming	Stroop effect	.335	1.93 msec/yr	.018[a]
	Baseline RT	.165	1.35 msec/yr	.25

a Indicates significant effects.

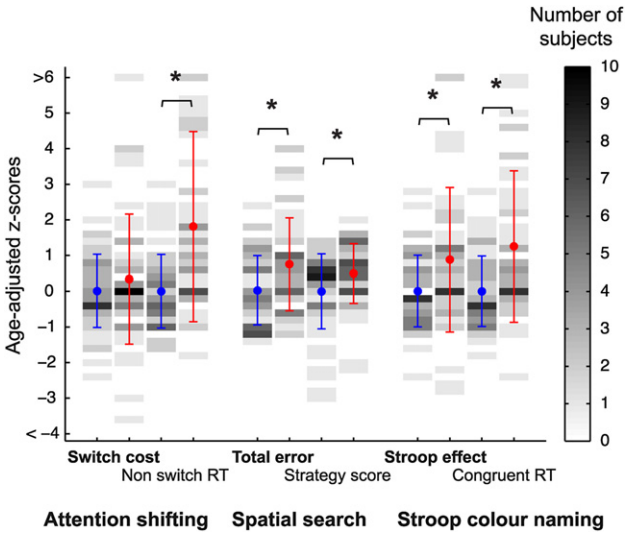

Fig. 3 – Comparison of performance distributions between CTL and FP groups. The grey scale map is a histogram with a bin size of .2 age-adjusted z-score units. The darker the bar, the greater the number of subjects in that z-score bin, as shown in the legend. Mean performance is indicated by overlaid filled circles (blue for CTL, red for FP); whiskers show SD. * indicates significant differences based on Welch's t-tests for comparisons between CTL and FP ($p < .05$ after Bonferroni correction).

3.3. Effects of damage to specific sub-regions within PFC

To examine the contributions of specific regions within PFC, each age-adjusted behavioural measure was analyzed using VLSM. Fig. 4 shows the VLSM results separately for the executive measure from each task. Cold colours indicate areas associated with poor performance at the uncorrected threshold of $p < .05$, and yellow indicates the areas significant after Bonferroni correction (see Methods). Overall, there was a striking similarity between lesion maps for the attention shifting and Stroop tasks: significant and highly clustered voxels were found in the left ventrolateral PFC for both switch cost and Stroop effect. For the attention shifting task, increased switch cost was significantly associated with damage to voxels centred in left AI ($x = -33$, $y = 18$, $z = 12$; 1448 voxels) after controlling for multiple comparisons (Fig. 4A), while a large cluster in left inferior frontal gyrus ($x = -49$, $y = 17$, $z = 25$; 9544 voxels) was significantly related to increased Stroop effect (Fig. 4B). The VLSM results for baseline RT for each task were very similar, with voxels in the left FO (MNI coordinates $x = -53$, $y = 15$, $z = 14$; 1235 voxels) significantly associated with slow non-switch RT for the attention shifting task, and voxels in left FO ($x = -48$, $y = 13$, $z = 11$; 928

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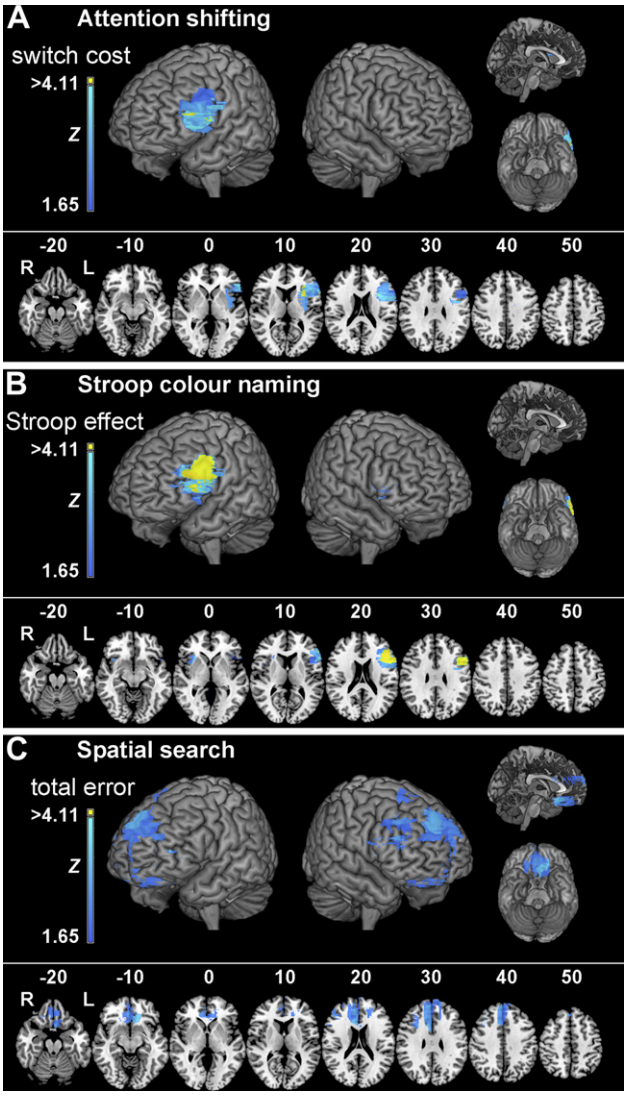

Fig. 4 – VLSM statistical map computed for age-adjusted z-scores shown on the MNI brain in 3D views and in axial slices for (A) attention shifting cost, (B) Stroop colour naming interference effect and (C) spatial search strategy score. The numbers indicate the z-coordinates (MNI) of each axial slice. The blue colour scale indicates t-test results converted into z-scores, thresholded at $p < .05$, uncorrected, with the areas surviving Bonferonni correction for distinct lesion patterns highlighted in yellow.

voxels) and nearby white matter (x = −51, y = 5, z = 20; 1112 voxels) associated with slow congruent RT in the Stroop task (not shown). VLSM analyses with the number of errors as the behavioural measure revealed similar localization, albeit with fewer significant voxels (not shown).

In contrast, no voxels were significantly related to spatial search task performance (Fig. 4C). However, the statistical maps showing the voxels related to poor performance at the more liberal threshold of uncorrected $p < .05$ reveal widely distributed voxels associated with increased errors along the medial wall and superior frontal gyrus in both hemispheres, as well as bilateral VM and right dorsolateral regions. Voxels associated with poorer strategy scores had a similarly distributed pattern, with some overlap between these two performance measures along the medial wall, in particular the VM region (not shown). Notably, damage to the LL frontal region found to be critical for Stroop and attention shifting was not associated with impaired spatial search task performance even at this liberal statistical threshold.

3.4. *ROI-defined group comparison*

The VLSM results show qualitatively different patterns of prefrontal involvement for the attention shifting and Stroop tasks on the one hand and the spatial search task on the other. To directly test for dissociations across tasks within subject, group comparisons were carried out for the subset of patients who had lesions exclusive to one of the four sub-regions of interest within PFC. The key measures from each task in these subjects, all expressed as age-adjusted z-scores relative to healthy control subject performance, were then analyzed with a mixed ANOVA, with the anatomically defined lesion group (LL, $n = 7$; RL, $n = 7$; DM, $n = 7$; VM, $n = 7$) as a between-subject factor and executive task as a within-subject factor (Fig. 5). This analysis revealed a significant interaction between lesion group and task [$F(6, 48) = 3.17$, $p = .01$], while the main effects of group and task did not reach significance [$F(3, 24) = 2.41$, $p = .09$ and $F(2, 48) = .70$, $p = .50$, respectively]. Simple main effects tests revealed that the significant interaction was mainly due to a clear dissociation in the performance pattern of the LL group [$F(2, 48) = 6.29$, $p = .003$], while no other group showed a significant differential pattern of performance across tasks [all $F(2, 48) < 2.5$, $p > .1$]. Corroborating the VLSM results, there were significant effects of group membership on attention shifting and Stroop task performance [$F(3, 67) = 3.98$ and 3.33, $p = .011$ and .025, respectively], with the LL group showing significantly larger switch cost than the VM group and a larger Stroop effect than the RL group (Tukey–Kramer tests, $p < .05$), while there was no effect of lesion group on the spatial search task [$F(3, 68) = .77$, $p = .51$].

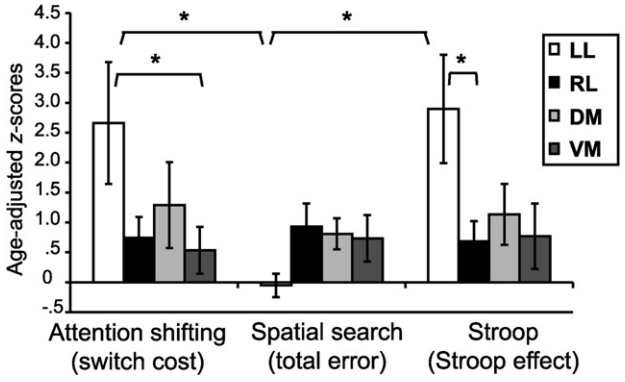

Fig. 5 – Comparison of executive measures between the anatomically defined lesion groups (LL, $n = 7$; RL, $n = 7$; DM, $n = 7$; VM, $n = 7$). Error bars indicate standard error of the mean (SEM). * denotes significant difference for performance on different tasks or between groups (Tukey–Kramer test, $p < .05$).

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4. Discussion

The present study examined three putative component processes of executive function: shifting, updating, and inhibition in a large sample of patients with focal PFC damage. Our aim was to test whether these constructs were dependent on anatomically separable areas within PFC, and by doing so assess the functional dissociability of prefrontal sub-regions. As expected, FPs as a group performed significantly worse than demographically matched healthy subjects on all three executive function tasks. However, the performance distributions indicated increased variability, rather than across-the-board impairment in the FP group, suggesting that lesion location might be a critical factor in impairment. VLSM analyses revealed that performance on both attention shifting and Stroop colour naming tasks relied on the integrity of a similar, relatively circumscribed region within the LL PFC, centred in the inferior frontal gyrus. In contrast, the same analysis failed to identify any strong relationship between specific prefrontal regions and spatial search task performance. Almost any prefrontal lesion, with the notable exception of those affecting LL PFC, was weakly associated with compromised performance on this task. The direct comparison of specific executive measures between patients with lesions restricted to each of four broad sub-divisions within PFC demonstrated a clear dissociation in the performance pattern of the LL group, but not of other lesion groups. Consistent with the VLSM results, there were significant effects of lesion group on attention shifting and Stroop performance, with the LL group performing most poorly, while no significant difference between PFC groups was found for spatial search task performance.

To our knowledge this is the first study to show, within subject, that attention shifting and Stroop tasks have a common requirement for intact LL PFC, and that this is the only PFC region critical for both. This result has converging support: a meta-analysis of imaging studies using various shifting and Stroop paradigms identified a common cluster of activations in left inferior frontal junction (Derrfuss et al., 2005). Another recent meta-analysis that focused on different types of shifting paradigms also identified the same region as being consistently recruited across all switching types examined (perceptual, response, and context; Kim et al., 2012). The spatial extent of our VLSM results should be interpreted with caution, as the spatial resolution of the analysis, which depends on the pattern of lesions across subjects, varies (for example, we did not have enough power to detect effects specific to left dorsolateral PFC). However, the significant cluster identified in the present study overlaps with those identified in these meta-analyses. It is also broadly consistent with existing neuropsychological studies that have reported left-lateralized findings in similar tasks in FPs. For example, despite using very different set-shifting paradigms, several studies have found increased switch costs in left, but not right, frontal (Mayr et al., 2006; Rogers et al., 1998; Shallice et al., 2007) or brain-damaged (Mecklinger et al., 1999) patients (but see Aron et al., 2004a, discussed below). A quantitative meta-analysis of lesion studies also concluded that left FPs performed significantly worse on the Stroop task than right FPs (Demakis, 2004).

An obvious common requirement of both tasks is the need for a verbal response. However, previous lesion studies have reported left-lateralized effects even for shifting tasks with manual responses (e.g., Mayr et al., 2006; Mecklinger et al., 1999), and left FPs are not more impaired than right FPs in word reading or colour naming alone (Demakis, 2004). Previous human lesion work has implicated this area in updating or resolving interference between verbal representations in working memory, regardless of the response modality (Thompson-Schill et al., 2002, 1998; Tsuchida and Fellows, 2009). Further, functional neuroimaging studies report left-lateralized findings for both Stroop and various shifting paradigms even when those tasks require manual responses (Collette et al., 2005; Derrfuss et al., 2005; Laird et al., 2005; Nee et al., 2007). A recent study using complementary functional imaging and transcranial magnetic stimulation methods supports a critical role for LL PFC in directing attention to different categories of stimuli represented in posterior cortical areas (Higo et al., 2011). Together with the results reported here, this argues that this region is essential for maintaining selective attention to task-relevant stimulus features. There may be specific demands shared by these tasks, such as the relevant features being denoted by semantic category, or the need to allocate selective attention under high time pressure, that may be important in understanding the highly left-lateralized contribution of lateral PFC. Further work will be needed to address these possibilities.

Surprisingly, this LL PFC contribution seems to be the only substantial PFC requirement for both Stroop and attention shifting tasks. The sample we studied had good coverage of two other regions often implicated in the inhibitory aspect of cognitive control: right ventrolateral PFC (Aron et al., 2004b) and DMPFC (including dACC) (Botvinick et al., 2004; Ridderinkhof et al., 2004). Damage to these areas was not significantly associated with poor performance on either of these classic tests of cognitive control. The right ventrolateral PFC has been implicated in performance of a more complex task set-shifting paradigm in a previous lesion study focussing on lateral PFC: Aron and colleagues demonstrated that both right and left PFC-damaged patients showed increased switch costs. However, they proposed that right PFC damage led to impairment in reactively suppressing inappropriate responses, and left PFC damage to a general impairment in endogenously imposing the appropriate task set (Aron et al., 2004a; Robbins, 2007). Our attention shifting task deliberately involved two simple tasks with a relatively long preparation time, in an effort to isolate shifting ability from other executive demands. This may explain the disproportionate effect of LL PFC damage in the present study. However, the intact performance of patients with damage to RL (including ventrolateral) PFC in the Stroop task here does not support the view of right ventrolateral PFC as critical for inhibitory control in general.

In contrast to the highly localized effect of LL PFC damage on Stroop and attention shifting performance, likely to be related to disruption of a single underlying process, spatial search task performance (intended to tap updating in working memory) was sensitive to PFC damage rather generally. Other studies have also reported that similar search tasks rely broadly on PFC (with a right hemisphere predominance)

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(Chase et al., 2008; Miotto et al., 1996; Owen et al., 1996; Rogers et al., 1998; van Asselen et al., 2006). At face value, this could indicate that the putative core process of updating in working memory in general, or perhaps in spatial working memory in particular, relies on a single process requiring an extensive network of PFC regions. Alternatively, this rather complex task may be tapping a number of component processes, of which updating in working memory is only one. The present study cannot adjudicate between these explanations, but the literature, on balance, supports the latter.

Comparison with the results of another study in a partly overlapping set of patients argues that updating in working memory in general does not rely on identical PFC regions: updating in working memory as tested by a letter n-back task depended critically on LL and DM PFC (Tsuchida and Fellows, 2009). The distinct, lateralized lateral PFC contributions to these two working memory tasks support material-specific accounts of the role of PFC, consistent with lateralized findings when verbal and spatial working memory are directly contrasted in neuroimaging studies (Fletcher and Henson, 2001; Smith and Jonides, 1999; Wager and Smith, 2003). It is worth noting that this explanation does not account for all neuropsychological results: non-verbal forms of the n-back task can be sensitive to left-sided frontal lobe damage (du Boisgueheneuc et al., 2006; Volle et al., 2008), and frontal damage (in general) disrupted spatial search, but not performance of an analogous non-spatial search task (Owen et al., 1996). While the precise distinctions between the processes involved in these various tasks remain elusive, it seems clear that PFC contributions to "updating in working memory" depend on specific task features to a degree that is challenging for accounts that propose this as a general core process of executive function.

The primary purpose of this study was to test the dissociability of prefrontal contributions to three components of executive function that have been identified as distinct in studies of healthy subjects (Friedman et al., 2006; Huizinga et al., 2006; Miyake et al., 2000). Our findings suggest that there are dissociable components of executive function related to anatomically defined PFC circuits, but the results are only partly aligned with the framework suggested by work in healthy subjects.

These findings highlight the challenges of defining the component processes of executive function. Task features that influence individual differences in healthy subjects seem to be, at least in part, different from those that drive impairment in patients with frontal lobe injury. The former might reflect non-frontal anatomical differences, or differences in the efficiency of distributed but distinct systems engaged in specific executive component processes, perhaps by virtue of different sensitivities to neurochemical modulation (Cools and Robbins, 2004) or different strength or efficiency of distinct networks of prefrontal and other brain regions (Sporns, 2011; Wen et al., 2011).

Nonetheless, it seems clear that there is some degree of functional specialization within the PFC, such that there is a disproportionate effect of damaging a particular sub-region relative to others for any given task. This does not necessarily mean that these sub-regions work in isolation. The unitary model of executive function proposed by Duncan was motivated in part by the consistent patterns of co-activations in the multiple demand network regions associated with a diverse set of cognitive demands (Duncan and Owen, 2000), and similar patterns do recur across a wide range of cognitive operations in functional imaging work. For this reason, the regions overlapping with the multiple demand network have been variously termed as the 'task-positive' (Fox et al., 2005), 'cognitive control' (Cole and Schneider, 2007) or 'task set' (Dosenbach et al., 2006) network. This putative network includes several areas with good lesion coverage in the present study. The lack of significant effects of lesions to some of these areas, including right ventrolateral PFC and dACC, could be explained by reorganization following injury or functional redundancy in networks, although we have identified specific deficits attributable to dACC, for example, in other work (Camille et al., 2011; Modirrousta and Fellows, 2008a, 2008b; Tsuchida and Fellows, 2009). Similarly, we cannot exclude that the effect of LL PFC damage may be due to disruption of normal functions in other regions functionally connected to the site of damage (i.e., diaschisis). However, if disconnection had more substantial impact than the cortical lesion itself, the lesion–symptom relationship should be more diffuse, as damage anywhere along a given critical tract would result in impairment. Instead, that analysis showed detectable effects of white matter injury only adjacent to or underlying the cortical regions of interest. We note that the mechanisms of injury in the patients we studied are such that cortical and adjacent subcortical white matter injury tightly co-varies, making local distinctions at that level of resolution beyond the capabilities of this method.

The existence of dissociations such as those observed here poses a challenge to the concept of a general 'task set' network and what it means to be a component of such a network: Although network redundancy or plasticity might explain how function can be preserved despite damage, it cannot readily account for consistent dissociations of performance across similarly demanding executive tasks following specific focal frontal injury. Our findings argue that specific nodes within these putative networks are functionally specialized, with the effects of disruptions depending on task requirements, consistent with the views of other authors (Knight, 2007; McIntosh, 2000).

The present study focused on the dissociability of anatomically broad sub-regions of PFC, and does not directly inform other models of functional organization along the dorsal-ventral (Petrides, 2005) or rostro-caudal (Badre, 2008; Badre and D'Esposito, 2009; Koechlin and Summerfield, 2007) axis of lateral PFC. Although these models provide interesting perspectives on the organizing principles of the frontal lobe, it is not clear how similarly difficult yet behaviourally dissociable executive tasks should be mapped according to these frameworks. These models also do not address lateralized functional organizations, which our study clearly demonstrates to be relevant.

The tasks used in the present study are widely used in experimental and clinical settings: our results suggest somewhat different structure–function relationships than are commonly inferred from functional imaging findings alone. For example, the Stroop task is not sensitive to dACC damage. Full characterization of PFC function would seem to require

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a component process approach, and details of the tasks used for this purpose may be important in determining how sensitive they are to the integrity of a given region within PFC.

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