Global Increase in Task-related Fronto-parietal Activity after Focal Frontal Lobe Lesion

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Abstract

A critical question for neuropsychology is how complex brain networks react to damage. Here, we address this question for the well-known executive control or multiple-demand (MD) system, a fronto-parietal network showing increased activity with many different kinds of cognitive demand, including standard tests of fluid intelligence. Using fMRI, we ask how focal frontal lobe damage affects MD activity during a standard fluid intelligence task. Despite poor behavioral performance, frontal patients showed increased fronto-parietal activity relative to controls. The activation difference was not accounted for by difference in IQ. Moreover, rather than specific focus on perilesional or contralateral cortex, additional recruitment was distributed throughout the MD regions and surrounding cortex and included parietal MD regions distant from the injury. The data suggest that, following local frontal lobe damage, there is a global compensatory recruitment of an adaptive and integrated fronto-parietal network.

INTRODUCTION

How does the brain react to damage? Traditionally, neuropsychological studies associate cognitive impairments with the function of focal regions of damage, but important changes also occur in brain areas distant from the original injury. Accordingly, it has been suggested that the effects of focal lesions may be best understood in the context of brain-wide functional networks (e.g., Gratton, Nomura, Perez, & D’Esposito, 2012; McIntosh, 2000).

Here, we address the question in patients with focal frontal lesions, examining a distributed fronto-parietal circuit frequently associated with cognitive or executive control (e.g., Cole & Schneider, 2007). Included in this circuit is cortex in and around the inferior frontal sulcus (IFS), anterior insula/frontal operculum (AI/FO), anterior frontal cortex (AFC), dorsal anterior cingulate/presupplementary motor area (ACC/pre-SMA), and intraparietal sulcus (IPS). Because activity is seen in tasks tapping many different kinds of cognitive activity (e.g., Dosenbach et al., 2006; Duncan, 2006; Duncan & Owen, 2000; Nyberg et al., 2003), we have called this the multiple-demand or MD system (Duncan, 2006, 2010). One way to produce strong MD activity is with a standard test of fluid intelligence or novel problem solving (Bishop, Fossella, Croucher, & Duncan, 2008; Lee et al., 2006; Duncan et al., 2000), and damage within this circuit predicts fluid intelligence loss (Woolgar et al., 2010). Loss of fluid intelligence, furthermore, predicts deficits in a number of conventional frontal lobe tests, such as the Wisconsin Card Sorting Task (Roca et al., 2010; Grant & Berg, 1948). Here, accordingly, we used a fluid intelligence test to assess activity across the whole MD system after damage to local frontal lobe regions.

A number of hypotheses were considered. One possibility was that patients would show increased activation of cortex homologous to the area of lesion in the contralateral hemisphere. Contralateral recruitment of this sort, for example, has been seen during performance of motor tasks by patients with focal damage to the motor cortex (for reviews, see Hodics, Cohen, & Gramer, 2006; Ward, 2006). A second possibility was that increased activation would be primarily perilesional, as nearby cortex takes on the function of the damaged region (e.g., Ward et al., 2003). A third possibility was that activation would be widespread and/or of a qualitatively different pattern from normal (Weiller, Chollet, Friston, Wise, & Frackowiak, 1992), perhaps indicating that an alternative strategy was used to solve the task. A fourth possibility was that poorer performance in the patient group would simply be linked to underrecruitment of the MD system.

The data, however, supported none of these possibilities. Instead, we observed a striking additional activation of cortex in and immediately surrounding the MD system, including MD regions distant from the lesion site, without any particular favoring of either perilesional or contrallesional cortex. Differences were not accounted for by difference in fluid intelligence: For the same fluid intelligence score, patients showed increased activation. The results suggest a tightly integrated neural system, which adjusts for damage to one part through a network-wide upregulation of activity.
METHODS

Participants

Five patients were recruited from the Cambridge Cognitive Neuroscience Research Panel. Patients were selected for chronic (minimum time since onset: 3.25 years), focal, adult-onset lesions restricted to the frontal cortex, of varied etiology (Table 1, Figure 1). Exclusion criteria were visual field cut, overt aphasia, preinsult history of epilepsy, or unsuitability for MRI. Mean age was 63.2 years ($SD = 6.3$ years). Following common neuropsychological practice, premorbid IQ was assessed using the revised National Adult Reading Test (NART; Nelson, 1976). Mean NART IQ was $113.0$ ($SD = 13.1$). Control participants ($n = 16$), recruited from the MRC Cognition and Brain Sciences Unit Volunteer Panel, were matched to the patient group for age ($M = 60.3$, $SD = 8.3$) and NART IQ ($M = 116.4$, $SD = 4.7$). Patients and controls had previously been assessed on a standard test of fluid intelligence, the Cattell Culture Fair (Scale 2, Form A; Institute for Personality and Ability Testing, 1973). On this measure, patients were numerically but not significantly impaired compared with controls (patients’ IQ: $M = 95$, $SD = 16.0$; controls’ IQ: $M = 106$, $SD = 12.7$; data missing in one case; $t(18) = 1.62$, $p = .12$). All participants gave written informed consent to take part. The study was approved by the Cambridge Local Research Ethics Committee.

Neurological Assessment

T1-weighted SPGR MRI scans (resolution = $1 \times 1 \times 2$ mm) were acquired for all patients. Lesions were traced by a neurologist who was blind to experimental results, and scans were subsequently normalized using cost-function lesion masking (Brett, Leff, Rorden, & Ashburner, 2001). The derived normalization parameters were used to normalize lesion tracings, which were then used to calculate lesion volume and extent of overlap with MD ROIs.

Experimental Task

Participants were scanned while carrying out a spatial problem-solving task that we had used previously to examine the neural correlates of fluid intelligence (Duncan et al., 2000). On each trial, participants were presented with four display panels (Figure 2), arranged in a horizontal row in the center of the screen and viewed through a head coil mounted mirror in the scanner. Each panel contained one or more line drawings. The task was to identify the panel that differed in some way from the others. Materials for the “fluid intelligence” condition were adapted from the Cattell Culture Fair Scale 2, Form A, and Scale 3 (Institute for Personality and Ability Testing, 1973). The matching panel could differ from the other panels on any figural–spatial, complex, or abstract property; considerable problem solving was required to identify it. In contrast, the “control” condition required minimal problem solving: In each display, the four panels contained a single geometrical shape, three of which were identical, whereas the fourth was markedly different in shape, texture, size, and/or orientation. Performance on the fluid intelligence condition has previously been shown to be highly correlated with standard measures of fluid intelligence ($r = .59$), whereas the control condition was less well correlated ($r = .37$; Duncan et al., 2000).

Before the scanning session, participants carried out an untimed practice on Test 3 (matrices) of the Cattell Culture Fair (Scale 2, Form A; Institute for Personality and Ability Testing, 1973). The purpose of this practice was to give participants an illustration of the range of difficulty of the items they would encounter and to encourage them not to guess answers. They also carried out a block of practice items for both fluid intelligence and control conditions in the scanner before acquisition began. Participants were told that it was essential that they never guessed an answer and were encouraged to puzzle over each item until they were sure.

Acquisition

fMRI data were acquired using a Siemens 3-T TimTrio scanner with a 12-channel head coil. We used a sequential descending T2*-weighted EPI acquisition sequence with the following parameters: acquisition time = 2000 msec, echo time = 30 msec, 32 oblique axial slices with a slice thickness of 3.0 mm and a 0.75-mm interslice gap, in-plane...
resolution = 3.0 × 3.0 mm, matrix = 64 × 64, field of view = 192 mm, and flip angle = 78°. T1-weighted MPRAGE structural images were also acquired for all participants (slice thickness = 1.0 mm, resolution = 1.0 × 1.0 × 1.5 mm, field of view = 256 mm, 160 slices).

Participants carried out alternating blocks of fluid intelligence and control trials lasting 30 sec. On each trial, participants indicated the mismatching display panel by pressing the corresponding one of four buttons on a response box, operated by the index and middle fingers of the two hands. Each display was visible until the participant responded, whereupon the next trial was presented immediately. This design was used to maximize the amount of time spent for the problem solving in each block, so that fluid intelligence and control blocks could be directly compared. Trials were presented in fixed order, drawn from a set of 24 fluid intelligence and 321 control displays. A cue lasting 3000 msec preceded each block indicating whether it was “hard” (fluid intelligence condition) or “easy” (control condition); otherwise, there was no break between blocks. There were eight blocks in all, completed in a single run of scanning lasting 4 min and 24 sec. The remainder of the scanning session (total duration of approximately 40 min) was devoted to other tasks.

Analyses

Preprocessing

Image realignment, slice timing correction, and coregistration of structural images were carried out using Automatic Analysis version 2.0 for SPM5 (imaging.mrc-cbu.cam.ac.uk/AutomaticAnalysisIntroduction). Data were then normalized using a segment and normalize routine (simultaneous gray/white matter segment and normalize) and smoothed (10-mm FWHM Gaussian kernel) using the same software. EPI data were high-pass filtered (128 sec).

ROIs

MD ROIs were defined using data from a prior review of activity associated with a diverse set of cognitive demands (Duncan & Owen, 2000). We used the kernel method described in Cusack, Mitchell, and Duncan (2010). To ensure symmetrical ROIs, all peaks from the original review were first projected onto a single hemisphere. A plane at the local minimum was used to divide lateral prefrontal regions into a more dorsal part, in and around the IPS, and a more ventral part, focused around the AI/FO. The two left and right medial ROIs abutting each other at the midline were unified into a single ACC/pre-SMA region. The procedure yielded nine ROIs (Figure 3): left and right IPS (center of mass: ±35 −58 41, 7 cm³), left and right AI/FO (±35 −58 41, 7 cm³), and ACC/pre-SMA (0 23 39, 21 cm³). All coordinates are given in MNI-152 space (McConnell Brain Imaging Centre, Montreal Neurological Institute, Montreal, QC, Canada).

For patients, we restricted the MD ROIs to include only healthy tissue by masking each patient’s MD ROI with their lesion tracing. We also defined a perilesional non-MD ROI for each patient, which indexed healthy tissue immediately adjacent to the lesion that was not part of the MD network. For this, each patient’s binary tracing lesion was smoothed (20-mm FWHM Gaussian kernel)

Figure 1. Normalized lesion anatomy of patients included in this study. Lesions, traced by a neurologist, are shown in red overlaid on each patient’s normalized structural scan. MD regions are indicated by cyan outlines. Slices correspond to z levels −24, −16, −8, 0, 8, 16, 24, 32, 40, 48, 56, 64.

Figure 2. Adapted Culture Fair task. Participants indicated the mismatching panel from a set of four display elements arranged in a horizontal row. The fluid intelligence condition (top row) required substantial problem solving, whereas the control condition (bottom row) did not. In the fluid intelligence condition, the items could differ on any abstract and/or complex property; in this example, the relevant property is symmetry, and the correct answer is the third item.
and thresholded at an intensity of >0.05 and then masked to exclude voxels from the patient’s original lesion tracing or MD ROIs.

fMRI Analyses

To isolate brain activity associated with the fluid intelligence task, univariate comparisons of BOLD response in fluid intelligence and control conditions were carried out using the multiple regression approach of SPM5 (Wellcome Department of Imaging Neuroscience, London, United Kingdom; www.fil.ion.ucl.ac.uk). At the first level, beta values for the fluid intelligence and control conditions were estimated for each participant. In this general linear model, blocks were modeled as epochs lasting from the presentation of the first stimulus until the end of the block. At the second level, the first-level beta values for the fluid intelligence and control conditions for all participants were entered into a general linear model with four conditions (fluid intelligence/control × two groups) and 21 participant regressors. Three random effects t tests were carried out: (1) fluid intelligence compared with control activation in the control group, (2) fluid intelligence compared with control activation in the patient group, and (3) direct comparison of the two groups (fluid intelligence minus control contrast for patients compared with that for controls). These analyses used a pooled error estimate corrected for nonsphericity using restricted maximum likelihood (Friston et al., 2002). Analyses were carried out on an ROI basis using the MarsBar toolbox for SPM5 (Brett, Anton, Valabregue, & Poline, 2002) and supplemented by a more exploratory whole-brain approach.

For ROI analyses, activity estimates were averaged across voxels in each region. Whole-brain results for fluid intelligence activity in patients and controls separately are reported at \( t < 3.52 \), equivalent to \( p < .05 \), with false discovery rate (FDR) correction for multiple comparisons in the control group fluid intelligence minus control analysis. To visualize regions showing greater fluid intelligence activation in the patient group relative to controls, the whole-brain map for patients (fluid intelligence minus control) minus controls (fluid intelligence minus control) was masked to include only regions showing fluid intelligence > control activation in the patient group, and thresholded at \( p < .05 \) with FDR correction.

To examine the contribution of different regions in different patients, we also report the fluid intelligence minus control contrast for each region in each patient individually, having subtracted the corresponding fluid intelligence minus control contrast value in controls. We also visualize whole-brain results for the fluid intelligence minus control contrast for each patient separately, together with that of the least, median, and most-activating control participants (controls ranked on average MD activation), thresholded at \( p < .001 \) without correction. Finally, we examined whether the group difference in activation for fluid intelligence and control conditions could be accounted for by individual differences on a standard behavioral test of fluid intelligence (Cattell Culture Fair, Scale 2, Form A; data from panel database, missing for one control participant). For this, the number of voxels activated above \( t = 3.52 \) in the first-level fluid intelligence minus control contrast was calculated for each individual. ANCOVA was used to examine the group difference in the number of

Figure 3. Fluid intelligence activity in the MD system in controls and patients. Bars indicate fluid intelligence minus control contrast values for each region for controls (blue) and patients (red). Patients showed greater fluid intelligence activity than controls in the system overall, and the same trend was seen throughout the system when the regions were considered individually. Asterisks above bars indicate significant difference between fluid intelligence and control conditions. Asterisks between bars indicate greater activity difference in patients relative to controls.

\* \( p < .05 \), \** \( p < .01 \).
activated voxels after covarying out individual differences in the fluid intelligence score.

RESULTS

Behavioral Results

Patients and controls answered significantly fewer items correctly in the fluid intelligence condition compared with the control condition (controls: \(t(15) = 17.7, p < .001\); patients: \(t(4) = 5.60, p < .01\)). The two groups were matched in the control condition (controls: mean number of items correct \([M] = 117.0\), patients: \(M = 105.2, t(19) = 0.49, p = .63\)), but controls significantly outperformed patients in the fluid intelligence condition (controls: \(M = 7.9\), patients: \(M = 4.0, t(19) = 2.91, p < .001\)). Both groups achieved a high percentage correct in the control condition (controls: 94.8%, patients: 92.7%). In the fluid intelligence condition, this reduced to 67.4% for controls and 38.7% for patients.

fMRI Results

To isolate brain activity associated with the fluid intelligence task, BOLD response in the fluid intelligence condition was compared with that in the control condition, in the control and patient groups separately. This was carried out on an ROI basis by collapsing activity across voxels in each region. Figure 3 shows the result of this analysis. Considering the MD system as a whole, the control group showed the expected increase in MD activity for the fluid intelligence condition compared with control condition (\(t = 1.73, p < .05\)). Strikingly, the patient group not only showed the expected increase in MD activity for the fluid intelligence condition (\(t = 3.82, p < .001\)), but also, the increase was statistically greater in the patient group than in controls (\(t(19) = 2.07, p < .05\)). Considering each MD region individually, the control group tended to show more activity for the fluid intelligence condition compared with the control condition throughout the MD system, but the difference was only significant in the left IFS (\(t = 2.20, p < .05\)) and right IFS (\(t = 2.02, p < .05\)) ROIs (trend in right IFS: \(t = 1.53, p = .07\); other \(ps > .11\)). The patient group showed significantly more activity in the fluid intelligence condition compared with the control condition in all but the AI/FO ROIs (left IFS: \(t = 3.19, p < .01\); right IFS: \(t = 3.64, p < .001\); left AFC: \(t = 4.10, p < .001\); right AFC: \(t = 3.59, p < .01\); ACC/pre-SMA: \(t = 3.52, p < .01\); left IPS: \(t = 2.80, p < .01\); right IPS: \(t = 3.99, p < .001\); trend in right AI/FO: \(t = 1.42, p = .09\)). Patients showed significantly more fluid intelligence activity than controls in ACC/pre-SMA (\(t = 2.09, p < .05\)), left AFC (\(t = 3.33, p < .01\)), and left IPS (\(t = 2.06, p < .05\)), with trends in three other regions (left IFS: \(t = 1.54, p = .07\); right IFS: \(t = 1.57, p = .07\); right IPS: \(t = 1.72, p = .051\)).

To visualize the activation in the two groups, we carried out the same analyses on a whole-brain (mass univariate) basis. Control group activation for the fluid intelligence minus control contrast is shown in Figure 4A; patient group activation is shown in Figure 4B. Activation peaks are shown in Table 2. The two activation patterns were highly similar, although patient activation was stronger and more extensive. On the left and right lateral frontal surface, activation included the region around the AI/FO (BA 47), IFS (BAs 44, 45, and 47), and FEFs (BA 8). Activation was also seen in the region of ACC/pre-SMA ROI on the superior medial frontal cortex (BAs 8 and 32), around the left and right IPS (BAs 39, 40, and 7), in the left posterior temporal lobe (BA 37), and in the right visual cortex (BA 19).

A further whole-brain analysis compared fluid intelligence activation in patients and controls directly. As shown in Figure 5 and Table 3, patients showed a specific increased recruitment of the MD regions and the brain regions immediately adjacent to them. Increase in activation in both hemispheres was seen anterior to the AI/FO ROI (BA 47), overlapping with and adjacent superiorly and laterally to the IFS ROI (BAs 45 and 46), adjacent to

Figure 4. Fluid intelligence activity in (A) controls and (B) patients. Whole-brain results are thresholded at \(t = 3.52\), equivalent to \(p < .05\), with FDR correction in the control group analysis. The threshold for \(p < .05\) with FDR correction in the patient analysis would have been more lenient (\(t = 2.86\)).
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<tr>
<th>Lobe</th>
<th>Cluster</th>
<th>Hemisphere</th>
<th>Controls</th>
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<th>Patients</th>
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<td>z Score</td>
<td>x</td>
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<td>−46</td>
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<td>46</td>
<td>8/32</td>
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the AFC ROI (BAs 47 and 11), overlapping with and ante-
rior to ACC/pre-SMA ROI (BAs 32 and 8), and adjacent to
and overlapping with the IPS ROI (BA 39). Patients also
showed increased task-related activity in a region of the
posterior temporal lobe (left BA 21), which is associated
with high-level visual activity and often accompanies the
MD pattern in visual tasks, as well as in a small region of
visual cortex in the right hemisphere (BA 19).

Next, we considered whether the pattern of increased
activation differed between individual patients on the
basis of their particular lesion. For example, it was pos-
sible that, given a lesion to a particular MD region, the

Table 3. Representative Peaks in Whole-brain Analysis Showing Significantly Greater Fluid Intelligence Activity in Patients than in Controls

<table>
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<th>Cluster</th>
<th>Hemisphere</th>
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<td>Left</td>
<td>−52 −50 30</td>
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Figure 5. Regions showing greater fluid intelligence activity in patients relative to controls. (A) Surface rendering. (B) Axial slices showing activation (red) and MD regions (cyan outlines) overlaid on the MNI template at z levels −24, −16, −8, 0, 8, 16, 24, 32, 40, 48, 56, 64. $p < .05$, with FDR correction.
homologous region in the opposite hemisphere might show a particularly notable increase in activation. As can be seen in Table 4, there were no patterns to this effect. Similarly, there was nothing in this analysis to suggest a particular role for the perilesional MD ROI. It was also possible that the non-MD perilesional cortex might play a particular role. To address this, for each patient, we extracted an ROI around their lesion, masked to include only healthy non-MD voxels (see Methods). However, in this ROI, patients did not show an increase in activity for the fluid intelligence condition compared with the control condition (contrast value = 0.06, \( t = 0.19, p = .86 \)). Accordingly, whole-brain visualization of fluid intelligence activity in each patient individually (Figure 6) showed a highly consistent pattern across individuals.

Finally, we asked whether the additional activation in frontal patients could be accounted for by difference in fluid intelligence in the two groups. In healthy participants, frontal and/or parietal activity has been reported to vary with IQ (for a review, see Jung & Haier, 2007), so it was possible that individual differences in the current fluid intelligence, rather than frontal brain injury per se, would account for the difference. To assess this, we extracted the total number of brain voxels active above \( t = 3.52 \) in the fluid intelligence minus control comparison for each individual. Patients had a significantly greater number of activated voxels \((t(19) = 2.46, p < .05, \text{two-sample} \ t \text{test})\). This difference remained even if Cattell Culture Fair score was included as a covariate (ANCOVA: main effect of Group, \( F(1, 17) = 7.13, p < .05 \)). The group difference was therefore not accounted for by any difference in IQ.

**DISCUSSION**

The MD regions play a key role in the control of structured, intelligent behavior (Duncan, 2010). In patients with focal brain lesions, they have a causal role in supporting fluid intelligence (Woolgar et al., 2010), which may in turn account for poor frontal patient performance on a range of executive tasks (Roca et al., 2010). Here, we build on this knowledge base by demonstrating the functional response of this system after damage. Our data show that problem solving in the patient brain is supported by increased recruitment of the MD regions and surrounding cortex.

Increased functional activity in patients is in line with hyperactivation seen in a range of disorders including stroke in motor cortex (Carey et al., 2002; Johansen-Berg et al., 2002), schizophrenia (Callicott et al., 2003), and Alzheimer’s Disease (Grady et al., 2003), where an association of increased activity with better performance, within a patient group, suggests that the additional activation may be compensatory. Commonly, compensatory activity includes perilesional cortex and/or cortex in the opposite hemisphere. In the case of damage to the primary motor cortex, for example, increased activation of nearby secondary motor and contralesional motor areas is frequently reported (for reviews, see Hodics et al., 2006; Ward, 2006). Similarly, stroke patients with left inferior frontal gyrus damage have been found to show increased activation of the right inferior frontal gyrus during language comprehension (Thulborn, Carpenter, & Just, 1999) and production (Rosen et al., 2000). However, our data suggest that, in the case of fluid intelligence, damage prompts a specific response from the entire MD system. Increased activity in the MD region close to a patient’s lesion was no greater than such increased activity elsewhere in the MD system. There were also no patterns to suggest that the contralesional MD region in particular showed compensation, and the non-MD region close to each patient’s lesion did not show fluid-intelligence-related activation. Rather, our data suggest that, when part of the MD system is damaged, the system responds with a global increase in activity.

One striking feature of our data is the increased parietal and ventral stream activity in patients with lesions confined to the frontal lobe. Paralleling the frequent coactivation of frontal and parietal brain regions (Duncan, 2006) as

### Table 4. Fluid Intelligence Minus Control Contrast Values for Each Patient and MD ROI, Subtracting Corresponding Mean Value for Controls

<table>
<thead>
<tr>
<th>Patient</th>
<th>Affected MD ROIs</th>
<th>ACC/Pre-SMA</th>
<th>IFS</th>
<th>Left</th>
<th>Right</th>
<th>AL/FO</th>
<th>Left</th>
<th>Right</th>
<th>AFC</th>
<th>Left</th>
<th>Right</th>
<th>IPS</th>
<th>Left</th>
<th>Right</th>
<th>Average MD</th>
</tr>
</thead>
<tbody>
<tr>
<td>PM</td>
<td>L IFS (18%)</td>
<td>0.19</td>
<td></td>
<td>0.18</td>
<td>0.20</td>
<td>0.34</td>
<td>0.31</td>
<td>0.13</td>
<td>−0.08</td>
<td>0.24</td>
<td>0.08</td>
<td>0.20</td>
<td>0.35</td>
<td>0.21</td>
<td></td>
</tr>
<tr>
<td>AD</td>
<td>L AI/FO (61%) and L IFS (75%)</td>
<td>0.45</td>
<td></td>
<td>0.25</td>
<td>0.11</td>
<td>−0.08</td>
<td>0.07</td>
<td>0.24</td>
<td>0.08</td>
<td>0.85</td>
<td>0.50</td>
<td>0.28</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IG</td>
<td>L IFS (10%)</td>
<td>0.12</td>
<td></td>
<td>0.21</td>
<td>0.13</td>
<td>0.03</td>
<td>0.23</td>
<td>0.21</td>
<td>0.17</td>
<td>0.52</td>
<td>0.06</td>
<td>0.19</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MS</td>
<td>−</td>
<td>0.06</td>
<td></td>
<td>−0.13</td>
<td>−0.05</td>
<td>−0.08</td>
<td>0.01</td>
<td>0.12</td>
<td>0.08</td>
<td>0.10</td>
<td>0.17</td>
<td>0.03</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>JM</td>
<td>ACC/pre-SMA (14%)</td>
<td>0.12</td>
<td></td>
<td>0.06</td>
<td>0.23</td>
<td>−0.15</td>
<td>−0.14</td>
<td>0.08</td>
<td>0.10</td>
<td>0.28</td>
<td>0.09</td>
<td>0.07</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table lists affected MD ROIs for each patient; % indicates the percentage of voxels in each ROI that were classified as lesioned. Dark gray shading: perilesional MD ROI; light gray shading: contralesional MD ROI. There were no patterns to indicate that either perilesional or contralesional MD regions were activated differently from other MD regions. L = left.
well as similar single-unit response profiles (e.g., Chafee & Goldman-Rakic, 1998; Quintana & Fuster, 1992), our data suggest a tightly integrated system. Rather than compensating for the loss of a specific function by recruiting more tissue local to the lesion, the system shows a coherent, global upgrade of activity. To this end, our data support previous suggestions that the effect of focal lesions may be best understood in the context of brain-wide networks (e.g., Gratton et al., 2012; McIntosh, 2000).

Individual difference in fluid intelligence has previously been associated with differences in fronto-parietal activation, with individuals with higher fluid intelligence scores tending to show weaker activation (for a review, see Jung & Haier, 2007), although this may only be true for moderately difficult tasks (Perfetti et al., 2009) or after sufficient practice allows high-IQ participants to develop efficient strategies (Neubauer & Fink, 2009). In our data, our patient group showed both reduced behavioral performance and increased activation. This alone, however, does not explain increased MD activity in the patient group, as the difference from controls remained significant after correction for Cattell Culture Fair score.

Our fluid intelligence and control conditions differed in complexity, difficulty, and amount of problem solving required and have different correlations with standard tests of fluid intelligence (Duncan et al., 2000). Further work is needed to understand how these concepts are related to one another. Given that the MD regions are defined as regions that are active for a wide range of cognitive demands (Duncan & Owen, 2000), any of these aspects may contribute to the activation reported here.

One possibility is that the additional activation reflects the use of a different, perhaps less efficient, strategy by the patient group. Alternatively, it may be that, when the MD system is damaged, a greater volume of tissue is recruited to perform the same functions. A growing body of evidence from nonhuman primates (e.g., Freedman & Assad, 2006; Freedman, Riesenhuber, Poggio, & Miller, 2001; Rao, Rainer, & Miller, 1997) and human functional imaging (e.g., Woolgar, Hampshire, Thompson, & Duncan, 2000) supports this view.
2011; Li, Ostwald, Giese, & Kourtzi, 2007) emphasizes that the MD system is highly flexible, adaptively allocating neural activity to the task in hand (Duncan, 2001). As such, a strengthening in the allocation of its resources may be its typical response to any challenge, including that imposed by damage.

Our data emphasize the integration and flexibility of the MD system. Rather than the specific recruitment of perilesional or contralesional cortex, the result after frontal lobe damage is the upregulation of the entire MD system. In line with the arguments of Gratton et al. (2012), McIntosh (2000) and others, the effects of focal brain lesions are seen throughout extensive, distributed, functionally integrated brain networks.

Acknowledgments

This work was funded by the Medical Research Council (United Kingdom) intramural program [MC_US_A060_0001]. A.W. was supported by a Domestic Research Studentship/Millennium Scholarship funded by the University of Cambridge and the Newton Trust, an Australian Research Council (ARC) Discovery Early Career Researcher Award (DECPRA, DEI2100898), and ARC Discovery Project Grant DP12102835. We thank Facundo Manes for tracing the lesions of the patients in this study, and Matthew Brett and Rik Henson for helping with statistical analyses.

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REFERENCES


Journal of Cognitive Neuroscience

Title Details

Basic Description

Title: Journal of Cognitive Neuroscience
ISSN: 0898-929X
Publisher: M I T Press
Country: United States
Status: Ceased
Start Year: 1989
End Year: 2010
Publication History: 1989-2010
Frequency: Monthly
Language of Text: Text in: English
Refereed: Yes
Abstracted / Indexed: Yes
Serial Type: Journal
Content Type: Academic / Scholarly
Format: Print
Description: Provides a forum for research involving the interaction of brain and behavior. Devoted to the field of cognitive neuroscience.

Subject Classifications

Additional Title Details

Publisher & Ordering Details

Online Availability

Abstracting & Indexing

Other Availability

Demographics

Reviews