Topographic Analysis of Individual Activation Patterns in Medial Frontal Cortex in Schizophrenia

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Abstract: Individual variability in the location of neural activations poses a unique problem for neuroimaging studies employing group averaging techniques to investigate the neural bases of cognitive and emotional functions. This may be especially challenging for studies examining patient groups, which often have limited sample sizes and increased intersubject variability. In particular, medial frontal cortex (MFC) dysfunction is thought to underlie performance monitoring dysfunction among patients with schizophrenia, yet previous studies using group averaging to compare schizophrenic patients to controls have yielded conflicting results. To examine individual activations in MFC associated with two aspects of performance monitoring, interference and error processing, functional magnetic resonance imaging data were acquired while 17 patients with schizophrenia and 21 healthy controls (HCs) performed an event-related version of the multisource interference task. Comparisons of averaged data revealed few differences between the groups. By contrast, topographic analysis of individual activations for errors showed that control subjects exhibited activations spanning across both posterior and anterior regions of MFC while patients primarily activated posterior MFC, possibly reflecting an impaired emotional response to errors in schizophrenia. This discrepancy between topographic and group-averaged results may be due to the significant dispersion among individual activations, particularly in HCs, highlighting the importance of considering intersubject variability when interpreting the medial frontal response to error commission. *Hum Brain Mapp 30:2146–2156, 2009.* © 2008 Wiley-Liss, Inc.

Key words: fMRI; anterior cingulate; error; conflict monitoring; interference

INTRODUCTION

One of the goals of functional neuroimaging is to identify neural circuitry underlying basic aspects of human cognition. As the ability to efficiently navigate through the environment requires that actions, thoughts, and emotions be monitored for consistency or errors, it is not surprising that much research has focused on examining neural mechanisms of so-called "normal" performance monitoring. A large body of work now implicates medial frontal cortex (MFC) as a principle node in a performance monitoring network, along with the anterior insula/operculum and various regions of lateral frontal cortex [Botvinick

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et al., 2001; Carter et al., 1998; Ridderinkhof et al., 2004; Taylor et al., 2007]. The majority of existing data employs group averaging techniques that enhance signal-to-noise ratios but confound information about the magnitude and the location of activation foci in individual subjects, posing a challenge for studies aiming for precise localization of function. This may be particularly crucial for investigations of monitoring in MFC, as considerable variability exists across individual subjects [Taylor et al., 2006] and studies [Ridderinkhof et al., 2004] in the spatial location of MFC activations during error processing, one component of monitoring. Given that different functions appear to segregate within MFC, e.g. anterior/rostral areas for emotional processes and posterior/dorsal regions for cognitive processes [Bush et al., 2000; Ridderinkhof et al., 2004; Steele and Lawrie, 2004], group averaging may obscure important functional differences between groups.

The investigation of individual variability within MFC is important for research examining the neural basis of those psychiatric disorders that involve dysfunctional performance monitoring, such as schizophrenia, obsessive-compulsive disorder, and depression [Taylor et al., 2007]. In particular, impaired performance monitoring is suggested to be a core feature of schizophrenia that contributes to the experience of hallucinations, delusions, and disorganization [Frith, 1987; Frith and Done, 1988; Mcguire et al., 1995; Sanders et al., 2002]. Yet, reliable differences in MFC activity between patients with schizophrenia and healthy controls (HCs) have been difficult to identify, possibly due to the fact that significant individual variability in the location of activations may lead to a reduction of the group-averaged signal [Manoach, 2003; Manoach et al., 2000], rendering comparisons between groups difficult. Overall, previous research employing group averaging has found reduced MFC activation in patients compared with controls, although the precise location of these reductions and the conditions under which they are found have been inconsistent [Carter et al., 1997, 2001; Dehaene et al., 2003; Heckers et al., 2004; Kerns et al., 2005; Laurens et al., 2003]. In an investigation of individual activations in patients and HCs during interference (conflict) processing, Heckers et al. [2004] found that the majority of patient clusters were found to be located dorsally to control clusters in posterior medial frontal cortex (pMFC), even though there were no significant differences between group-averaged signals. Although this study represents one of the few attempts to examine task-related activation in schizophrenia at an individual level, the blocked design used by the investigators lead to contamination of the interference signal by errors.

The primary aim of this study was the investigation of the topography of individual neural responses to conflict and errors within MFC. We sought to demonstrate that information about the spatial location of individual activation foci could provide an additional source of information to be considered in conjunction with group-averaged activity. Patients with schizophrenia and HCs performed a version of the multisource interference task (MSIT) that was modified for event-related functional magnetic resonance imaging (fMRI). The MSIT task was developed and validated by Bush et al. [Bush et al., 2003] to produce a robust conflict signal in MFC that is detectable in individual analyses. Importantly, the event-related version of the task employed here permitted the isolation of neural activity related to errors from correctly executed conflict trials, an important distinction given evidence suggesting that schizophrenic patients may be impaired in error, but not conflict, monitoring [Laurens et al., 2003]. We show that, with a two-dimensional topographic analysis of the MFC [Steele and Lawrie, 2004], analysis of the distribution of individual activations can provide a more sensitive assay of group differences than spatial averaging.

MATERIALS AND METHODS

Subjects

From a university-staffed community mental health center, 21 stable outpatients were recruited with DSM-IV schizophrenia/schizoaffective disorder [American Psychiatric Association, 1994] established by a Structured Clinical Interview for Diagnosis [First et al., 1996]. Data from four patients were excluded because of excessive head movement while in the scanner (1), technical errors during the acquisition of behavioral data (2), or failure on the part of the subject to understand the task (1), leaving 17 patients for the current analysis (12 schizophrenia, paranoid; 3 schizoaffective, depressed; 2 schizoaffective, bipolar). All patients were without active depression or alcohol/substance abuse/dependence and were taking antipsychotic medication (four risperidone, three clozapine, two haloperidol, two olanzapine, three quetiapine, one ziprasidone, two aripiprazole). Patients with significant medical illnesses (e.g., diabetes mellitus, hypertension) that could affect cerebral function were excluded. Symptoms of patients were assessed with the Brief Psychiatric Rating Scale [Overall and Gorham, 1962] and the Scale for the Assessment of Negative Symptoms [Andreasen, 1984a]. Levels of premorbid intelligence were assessed with the revised version of the Wide Range Achievement Test, reading subtest [Jastak and Wilkinson, 1984] (Table I).

Twenty-one HC subjects were recruited from community advertisements, selected to match the age range and family education level of the patients (Table I). They were not taking medication, were without any Axis I psychiatric disorders [Structured Clinical Interview for Diagnosis, nonpatient version; First et al., 1996], and had no first-degree relatives with psychosis. The purpose and risks of the study were explained to all subjects, who gave written informed consent to participate, as approved by the institutional review board of the University of Michigan Medical School.

TABLE I. Demographic and clinical characteristics of subjects

	Patients (n = 17)	Healthy controls (n = 21)	Significance
Demographic measures			
Age	39.3 ± 10.2	39.8 ± 9.7	$t = -0.16$, $P = 0.87$
Males/females	10/7	15/6	$\chi^2 = 0.67$, $P > 0.2$
Parental education	16.3 ± 3.6	15.5 ± 3.0	$t = 0.71$, $P = 0.48$
Subject education	14.9 ± 2.5	16.5 ± 3.5	$t = -1.7$, $P = 0.11$
SES	2.5 ± 0.7	2.6 ± 0.7	$t = -0.13$, $P = 0.9$
WRAT-R	51.2 ± 4.4	51.2 ± 4.5	$t = -0.13$, $P = 0.9$
Clinical measures			
Duration of illness	17.4 ± 12.4	—	
No. of Hospitalization	4 ± 2.6	—	
BPRS total	33.1 ± 7.7	—	
BPRS positive	11.5 ± 4.8	—	
BPRS negative	7.6 ± 3.3	—	
SANS global sum	6.2 ± 3.2	—	
HAM-D	4.8 ± 2.5	—	

Abbreviations: SES, socioeconomic status; WRAT-R, Wide Range Achievement Test-Revised; BPRS, Brief Psychiatric Rating Scale; SANS, Scale for the Assessment of Negative Symptoms; HAM-D, Hamilton Scale for Depression.

Task and Procedure

Subjects performed a version of the MSIT, developed and validated by Bush et al. [2003] in order to produce a robust interference signal detectable in the medial prefrontal cortex of individual subjects. On each trial in this task, subjects are presented with a row of three characters, the target number (the "oddball" in the row of characters) and two distractors (see Fig. 1). Subjects press the first, second, or third button on a keypad according to the identity of the target number (1, 2, or 3). On control trials, the identity and spatial location of the target are identical (e.g., the number "1" is the first character), the target is presented in a larger font than the distractors, and the distractors are neutral "x"s. On interference trials, the target number is located in a position different from its identity (e.g., the number "1" is the second or third character), and the distractors are numbers designating a possible but currently incorrect response (e.g., the number "1" surrounded by "3"s). Furthermore, the font size of the target is larger than the distractors on half of the trials and smaller than the distractors on the other half of trials.

Subjects completed 5 runs of 60 trials each, resulting in a total of 300 trials in the experiment. There were 120 control trials, 120 interference trials, and 60 "fixation" trials in which a crosshair was presented for the entire length of the trial for fMRI modeling purposes. To decrease event colinearity, pseudorandom ordering of trials was determined by a design optimization program written in Matlab by RCW. The identity and position of the target were equivalently distributed across the three possible choices. Each trial lasted for 3 s and began directly with the presentation of stimuli. Stimuli were on-screen for 500 ms followed by a black screen for 2.5 s. Subjects were instructed to press the button of the identity of the target number as quickly and accurately as possible. On the day of scanning, practice trials were given to all subjects outside of the scanner in order to familiarize them with the task.

Data Acquisition

MRI scanning occurred on a GE 3T Signa scanner (LX [8.3] release). A T1-weighted image was acquired in the same prescription as the functional images to facilitate cor-

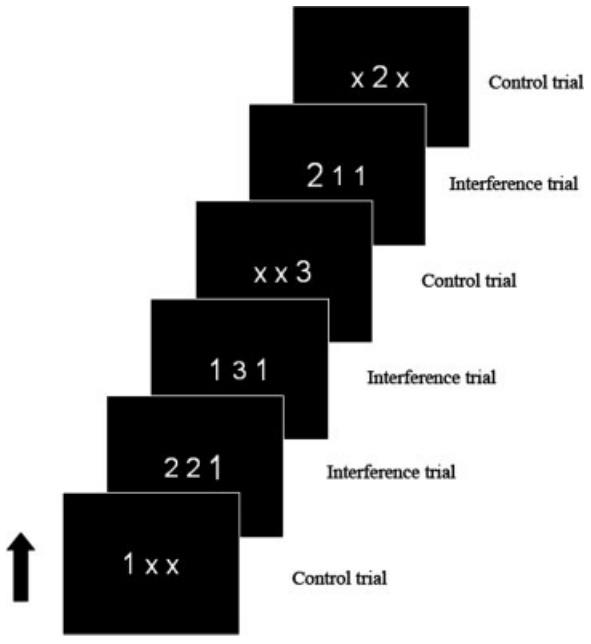

Figure 1.
Examples of trials in the multisource interference task. Subjects are required to press a button according to the identity of the target (oddball) number, ignoring spatial location and distractors.

egistration. Functional images were acquired with a T2*-weighted, reverse spiral acquisition sequence (GRE, TR = 2,000, TE = 30, flip angle = 90, FOV = 20, 40 slices with 3.0 mm thickness, matrix dia. 71 − equivalent to 64 × 64) sensitive to signal in ventral medial frontal regions [Yang et al., 2002]. Subjects underwent 5 runs, each consisting of 90 volumes plus four initial, discarded volumes to allow for thermal equilibration of scanner signal, for a total of 470 volumes. After acquisition of functional volumes, a high resolution T1 SPGR scan was obtained for anatomic normalization. Images were presented to the subjects via MRI-compatible, high-resolution LCD goggles (Resonance Technology, Northridge, CA).

Data Analysis

Behavioral analysis

Behavioral analyses were performed using *t*-tests and analyses of variance with Greenhouse-Geisser corrections where appropriate. All subjects provided data for analysis of RT based on condition and for accuracy data.

Functional analysis

Preprocessing and image analysis of the BOLD signal were performed using statistical parametric mapping SPM2 package (Wellcome Institute of Cognitive Neurology, London), with the exception of realignment, which used MCFLIRT [Jenkinson et al., 2002] and slice-time correction, which was interpolated with an 8-point sinc kernel multiplied by a Hanning window. Realignment parameters were inspected as a proxy for subject movement, in order to ensure that movement did not exceed either 3 mm translation or 1° rotation within each run. Parameters for anatomic normalization to the MNI152 brain, an average of 152 T1 images from the Montreal Neurological Institute, were derived from the high-resolution SPGR T1 image and applied to the time series of coregistered, functional volumes, which were resliced and smoothed with a 5 mm isotropic Gaussian smoothing kernel (voxel size after preprocessing was 3 × 3 × 3). Four regressors of interest for each condition (errors of commission, errors of omission, correct interference trials, and correct control trials) were convolved with the canonical hemodynamic response function (HRF) at the subject level, and estimates were derived for the magnitude (height) of the HRF after high-pass filtering. Contrasts of interest for errors [errors of commission − (correct interference trials + correct control trials)/2] and for interference (correct interference trials − correct control trials) were calculated. Errors of omission were included in the model to reduce noise but were not analyzed further. A large area comprising posterior and anterior regions of medial prefrontal cortex (coordinate bounds: $x = -18$ to $+18$, $y = 1$ to 71, $z = -18$ to 72) was chosen for analyses. Because the intent of the analysis was the delineation of the spatial distribution of individual activation foci, it was important to define a relatively large region to maximize the sensitivity of the analysis. At the same time, the region was limited to the MFC due to previous literature indicating its crucial involvement in error and interference processing [Botvinick et al., 2001; Carter et al., 1998; Ridderinkhof et al., 2004]. Because of our restricted search space, a threshold of $P < 0.005$ uncorrected and an extent ≥10 voxels (volume of 270 mm^3) was used for all analyses. Six controls and three patients had too few errors to reliably analyze the BOLD signal (<3) and were thus excluded from analyses of error contrasts.

For analysis of group data, one-sample *t*-tests on error and interference contrasts were computed separately for patient and control groups, followed by a two-sample *t*-test investigating differences between groups. For topographic analysis of the spatial distribution of individual subject activation, only data obtained from those subjects who exhibited medial frontal activation at the designated threshold was analyzed further (10/14 patients and 11/15 controls for error contrasts, and 10/17 patients and 12/21 controls for interference contrasts). For subjects who exhibited significant MFC activation, the coordinates of the peak cluster (as determined by SPM2) were noted. To account for meaningful differences in the size of clusters, the coordinates of subclusters were noted for all activations that spanned 50 or more voxels. To investigate the spatial distribution of individual activations, a two-dimensional cubic spline (S) was fitted to a series of points located along the border of the corpus callosum [Steele and Lawrie, 2004] of the MNI152 brain. The spline began at $y = 0$ and curved around the genu of the corpus callosum, terminating at $y = 20/z = -4$. For each individual activation cluster, the point P on spline S located closest to the peak of the cluster or subcluster was determined, collapsed across the lateral dimension ($x = -18$ to $+18$), yielding two indices of spatial location (see Fig. 2). First, the radial (*r*) measurement of each cluster was identified as the distance from point P to the cluster. This measure amounted to a dorsal–ventral distinction in posterior regions of MFC. In more anterior regions, this measure reflected the cluster's proximity to the corpus callosum. Second, the longitudinal spline (*ls*) measurement of each cluster was identified as the distance of point P along line S (starting at $y = 0$). This measured the distribution of activations in the anterior–posterior dimension, although it is important to note that subgenual areas of MFC were identified as being located "anterior to" certain voxels having greater *y*-coordinate values. This method is taken directly from that used by Steele and Lawrie [2004] and justified based on anatomic studies indicating that the cingulate cortex wraps around the genu of the corpus callosum [Vogt et al., 1995]. Radial and longitudinal spline measurements were computed for each cluster in both patient and control groups for error and interference contrasts. Comparisons of the distribution of each group's activations were performed using Kolmogorov-Smirnov (KS) tests for both location measures.

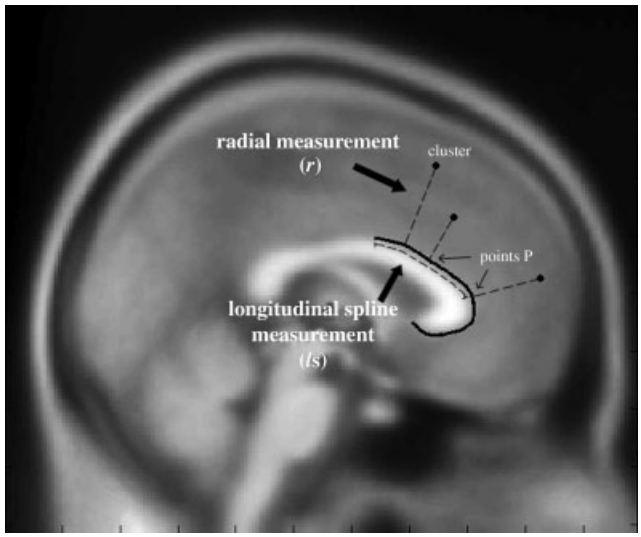

Figure 2.
Measurement of spatial location of individual activation clusters in the radial (*r*) and longitudinal spline (*ls*) dimensions. Distance in millimeters (mm) from point P on spline to cluster is measured as *r*, distance in mm along the spline from $y = 0$ to point P is measured as *ls*.

Structural analysis

Voxel-based morphometry (VBM) was used to investigate whether changes in brain structure may account for group differences identified in the topographic analysis of individual activations. Preprocessing was done with the VBM2 toolbox for SPM2 (http://dbm.neuro.uni-jena.de/vbm/vbm2-for-spm2/), implementing the "optimized" approach with iterative normalization and segmentation [Good et al., 2001]. The VBM2 toolbox employs a Hidden Markov Field model to improve 3-compartment tissue classification [Cuadra et al., 2005]. A 12 mm FWHM Gaussian kernel was used for smoothing, and gray matter (GM) density maps (1 mm^3 voxel size) were used for further statistical analysis. In addition, total intracranial volume (TIV) was computed for each subject and used as a covariate in all analyses.

To allow for appropriate comparisons between VBM and topographic analyses, group-averaged and individual VBM data were analyzed for subjects showing individual activations for error contrasts and using a region of interest (ROI) in anterior medial frontal cortex (aMFC), encompassing the area where group differences emerged in topographic analyses (see Results section). This ROI comprised 19 slices in the lateral dimension ($x = -18$ to $+18$), with y and z coordinates previously used for aMFC by Steele and Lawrie [2004] ($y = +30$ to $+50$ and $z = +15$ to $+41$). Group-averaged GM density maps were compared for HCs and schizophrenic patients, using TIV as a covariate. The same uncorrected *P*-values and volume thresholds were applied to group-averaged VBM results as were used for functional data. To examine the distribution of individual GM density, distributions of individual values were created for each group by extracting each subject's GM density values averaged across the aMFC ROI and creating a ratio of GM density to TIV for each subject. As with topographic analyses of functional data, distributions of individual VBM values for each group were then compared using a KS test.

RESULTS

Behavioral

As shown in Figure 3, patients made significantly more errors of commission than controls [6.8 vs. 2.7%, t (36) = -2.5, $P < 0.05$]. Out of all commission errors, subjects made significantly more on incongruent when compared with control trials [86.2 vs. 13.8%, $F(1, 36) = 132.48$, $P < 0.001$), an effect that not differ between HCs and patients.

For correct trials, patients were significantly slower overall when compared with controls [1063.3 vs. 923.7 ms, $F(1, 36) = 4.135$, $P < 0.05$], and both groups of subjects exhib-

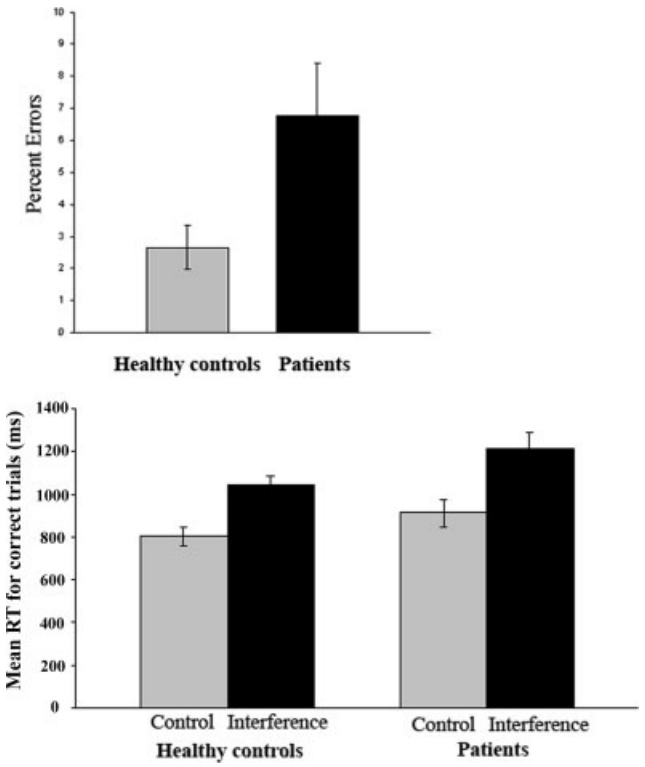

Figure 3.
Accuracy and reaction time (RT). Patients exhibit increased error rates and slower overall RT when compared with healthy controls, with similar amounts of behavioral interference (difference in RT between interference and control trials).

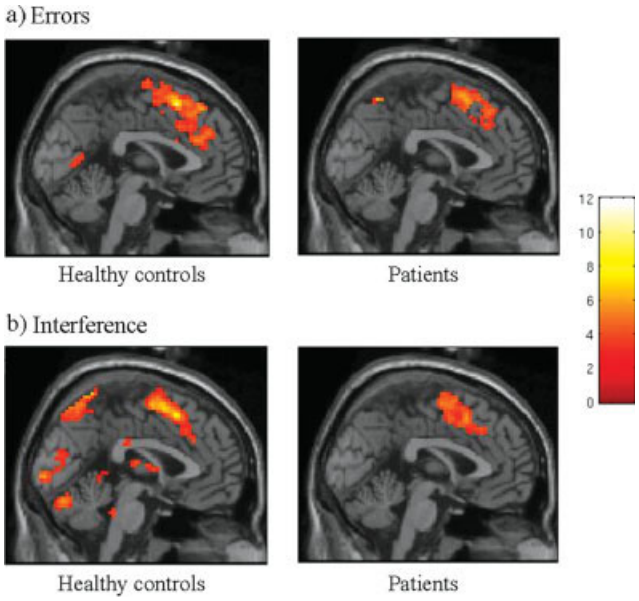

Figure 4.

Group-averaged activations in medial frontal cortex for healthy controls and patients. (**a**) Error and (**b**) interference contrasts. Scale represents *t* values. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

ited slower RT on interference trials when compared with control trials [857.5 vs. 1129.4 ms, $F(1, 36) = 199.36$, $P < 0.001$]. The interaction between trial type (interference vs. control) and group was not significant ($P > 0.1$).

BOLD Signal

Group-averaged analysis

For error contrasts, the control group activated a large area along the medial frontal wall, including dorsal, posterior MFC regions such as presupplementary motor area (pre-SMA), as well as more ventral, anterior regions including the anterior cingulate cortex (ACC). The patient group exhibited activation largely restricted to dorsal regions of pMFC (Fig. 4a and Table II). Of interest, direct comparisons between the groups for error contrasts revealed no significant differences. To confirm that this absence of group differences was not merely the result of overly stringent thresholding, we examined the activation at $P < 0.01$ uncorrected across 10 contiguous voxels. Even at this lenient threshold, no significant group differences were found between patients and controls in MFC.

For interference contrasts, both the HC and patient groups showed significant activation of pMFC (Fig. 4b and Table II). Direct comparisons between the groups for interference contrasts revealed that patients exhibited a small area of greater activity in a posterior region of the cingulate gyrus on the border of Brodmann's areas 24 and 32 (Table II). Inspection of the mean beta values for each subject extracted from this cluster for interference and control trials confirmed that the difference was due to a greater activation on interference trials for patients when compared with control subjects.

Topographic analysis

In the analysis of the spatial distribution of individual foci in the MFC, the *ls* distribution of error-related activations was significantly different between controls and patients (KS $z = 2.04$, $P < 0.001$), with controls activating both posterior and anterior MFC and patients predominantly activating posterior MFC (Fig. 5a). Analysis of the *ls* distribution of interference clusters revealed no significant differences between HCs and patients ($P > 0.7$) (Fig. 5b), and comparisons made within each group revealed significant differences between interference and error contrasts for controls (KS $z = 2.06$, $P < 0.001$) but not for patients ($P > 0.8$). We sought to determine whether this difference between HCs and patients was related to performance differences between the groups. Pearson correlation showed no significant relationship between number of individual clusters derived from error contrasts and percent commission errors in the patient group ($P > 0.7$), confirming that

TABLE II. Group-averaged activations in medial frontal cortex for error and interference contrasts

Errors						Interference					
x[a]	y	z	BA[b]	voxels	z[c]	x	y	z	BA	Voxels	z
Healthy controls											
0	15	54	6, 8, 9, 32	565	5.39	0	15	51	6, 8, 32	271	5.18
Patients											
0	15	57	6, 8, 32	405	4.1	−6	3	54	6, 8, 32	284	4.32
Patients > healthy controls											
		No significant differences				6	9	42	32	12	3.19
Healthy controls > patients											
		No significant differences						No significant differences			

[a] MNI coordinates of peak voxel in cluster.
[b] Predominant Brodmann's areas (BAs).
[c] z score for peak voxel.

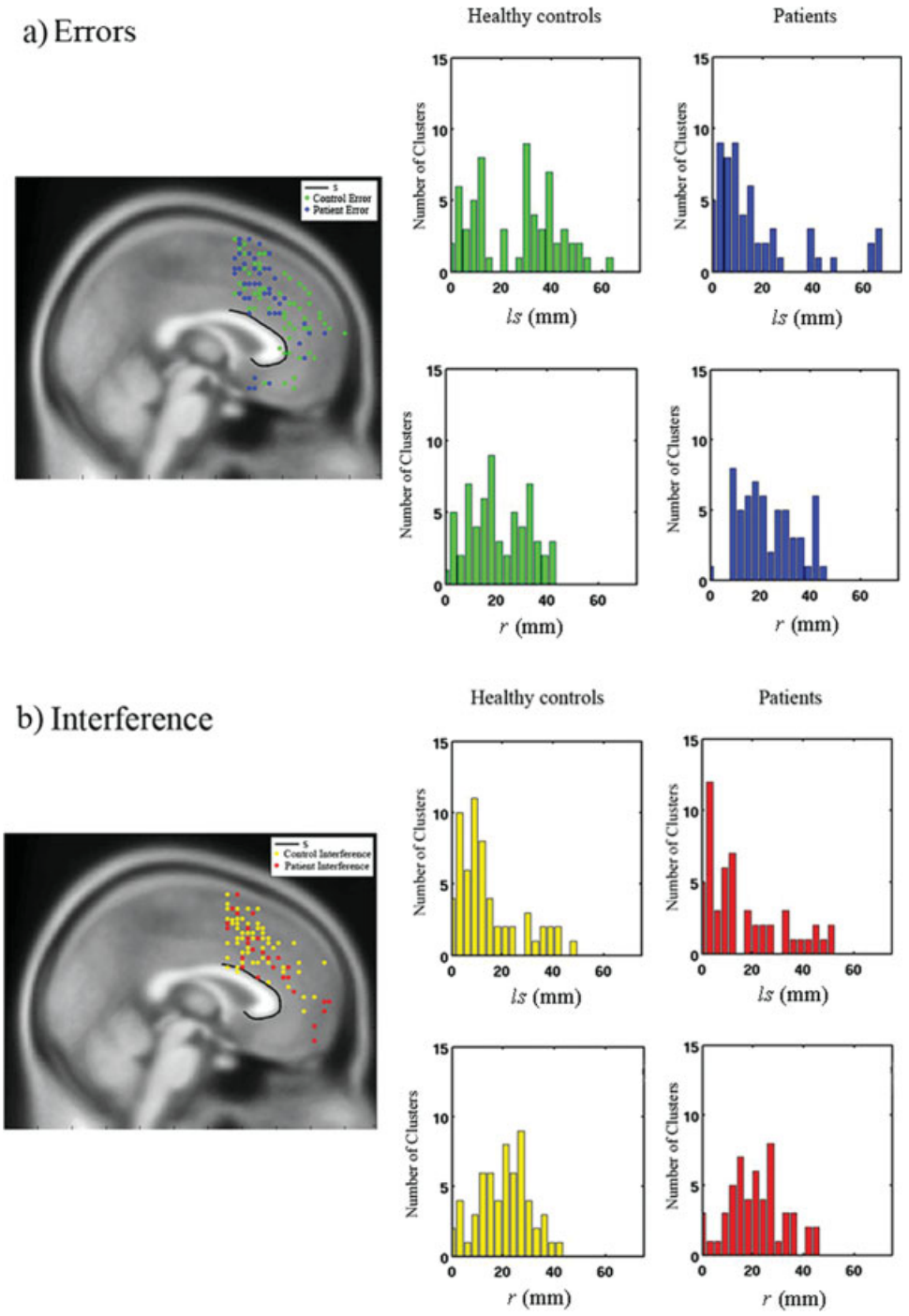

Figure 5.

Distribution of individual activation clusters in medial frontal cortex for healthy controls and patients. (**a**) Error-related clusters for individual healthy controls (green) and patients with schizophrenia (blue), showing different distribution of *ls* but similar distribution of *r* measurements for healthy controls and patients [top panel represents longitudinal spline (*ls*) distribution, bottom panel represents radial (*r*) distribution]. (**b**) Interference-related clusters for individual healthy controls (yellow) and patients with schizophrenia (red), showing no difference between healthy controls and patients on either spatial distribution measurement [top panel represents longitudinal spline distribution, bottom panel represents radial distribution].

the reduced aMFC activation found in patients was not being driven by poorer performance on the task.

Analysis of the radial (r) distribution of clusters revealed no differences between the patients and controls for either interference or error contrasts ($P > 0.5$ for error, $P > 0.9$ for interference) (see Fig. 5). Comparison made within each group showed that error and interference contrasts did not exhibit differing radial distributions (control group, $P > 0.3$; patient group, $P > 0.7$).

There were no group differences in the proportion of subjects showing individual activation clusters for error (10/14 patients and 11/15 controls) and interference (10/17 patients and 12/21 controls) contrasts, although a larger proportion of subjects in both groups showed individual activations surpassing threshold for errors (72.3%) than for interference contrasts (58%). Among those subjects contributing individual activation data, the mean number of clusters contributed by patients (interference: 5.3 ± 4.1, errors: 5.9 ± 5.8) and controls (interference: 5.0 ± 4.3, errors: 5.6 ± 6) was not significantly different for either contrast. Furthermore, even after restricting the groups to those subjects who showed individual activation clusters, behavioral differences between patients and controls in overall RT and accuracy were maintained.

To depict the proportion of subjects who contributed activation peaks across the medial frontal wall, individual activation images were thresholded such that all voxels within a cluster were given equal weight regardless of peak (i.e., a voxel received a value of 1 if activation was present at threshold or a value of 0 if activation was not present at threshold), and the resultant images summed for each group. Figure 6 illustrates the percentage of subjects contributing suprathreshold voxels in MFC. The locations of suprathreshold voxels correspond to the locations of peak activations as depicted in Figure 5, but it can also be seen that in no case did a single voxel reflect contributions from more than 50% of subjects, demonstrating the topographic heterogeneity of activation at the level of the individual subject.

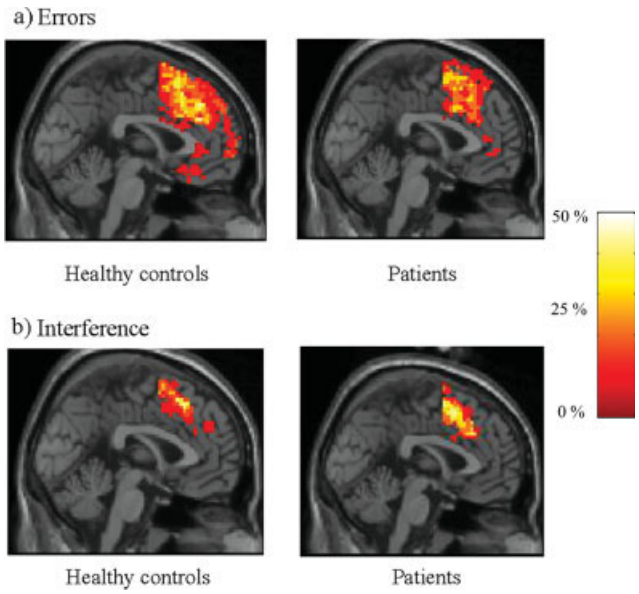

Figure 6.
Percentage of subjects activating individual voxels in medial frontal cortex. (**a**) Error and (**b**) interference contrasts. Unlike Figure 5, which shows activations collapsed in the lateral dimension, data here represent activations present at $x = 0$. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Voxel-Based Morphometry

Analyses of group-averaged and individual distribution of GM density were performed for the aMFC region, where individual activations were exhibited during error processing by HCs but not patients. No significant differences were found in this region for group-averaged or individual distribution VBM analyses (KS $z = 0.728$, $P = 0.66$), suggesting that the group difference identified by the topographic analysis was not due to differences in GM density.

DISCUSSION

In this study, we used a robust interference task in order to investigate the spatial distribution of individual activations in MFC during interference and error processing. Our study employed an event-related design that permitted separation of neural activity related to errors from that associated with cognitive interference, extending previous work examining individual activation in schizophrenia using a blocked design [Heckers et al., 2004]. Topographic analysis of the location of individual activations provided a sensitive measure of group differences, revealing a significantly different anterior–posterior distribution of error-related individual activations in schizophrenics, whereas group-averaged data had inadequate power to detect this difference. These results not only speak to the nature of monitoring deficits in schizophrenia but also provide important methodological implications for analyzing group data in neuroimaging experiments.

When making an error, the HC group showed a pattern of individual activations distributed throughout the entire medial frontal wall, with foci located in pre-SMA, ACC, and anterior medial prefrontal cortex including subgenual cingulate, whereas fewer individual activations were located in anterior regions of MFC/ACC among patients with schizophrenia. For interference contrasts, individual activations in both groups spanned a smaller area of MFC that was largely restricted to (dorsal and ventral) posterior regions. Such findings are consistent with previous studies examining error and interference processing in HCs, additionally providing insight into how psychotic patients differ in error monitoring. Errors and interference have both been found to elicit activity in pMFC [Botvinick et al.,

2001; Ridderinkhof et al., 2004], possibly reflecting the detection of cognitive conflict associated with both conditions. However, error monitoring has been shown to additionally recruit activity in aMFC [Garavan et al., 2003; Kiehl et al., 2000; Taylor et al., 2006], which may be related to emotional processing of an error [Bush et al., 2000; Gehring and Knight, 2000; Luu et al., 2000; Simmons et al., 2006; Steele and Lawrie, 2004]. The altered spatial distribution of individual activations in patients was not related to their decreased overall accuracy and may reflect an impaired emotional response to errors related to reduced motivation [Liddle et al., 2006].

A definitive explanation for altered anterior activity during errors in the patients will require more study, but it is unlikely to reflect a general failure to engage in the task. Error rates were relatively low for both groups, and while the patients were slower to respond, this fits the expected pattern of schizophrenic performance [Nuechterlein, 1977]. Further, during interference, the patient group actually showed a slightly larger BOLD signal in pMFC, a finding that is unlikely to be related to spatial variability considering that the groups did not show differing distributions of individual activations for interference contrasts. This increased pMFC signal for patients was somewhat unexpected, given reports of reduced activation in this area in schizophrenia [Kerns et al., 2005; Morey et al., 2005; Snitz et al., 2005; Yücel et al., 2007]. However, a recent meta-analysis identified MFC hyperactivity in schizophrenia during working memory tasks [Glahn et al., 2005], which may represent a compensatory mechanism resulting from reduced efficiency of cortical processing among patients at relatively low levels of demand. A similar explanation has been put forth to describe DLPFC activation in schizophrenia, where patients show increased activity relative to controls at lower levels of demand but decreased activity at higher levels of demand [Callicott et al., 2003; Manoach, 2003].

Given the degree of dispersion among individual activation foci, especially among HCs, the failure to find error-related group differences in MFC between patients and controls using spatial averaging is not surprising. Both groups exhibited considerable scatter of individual activations in MFC/ACC during errors, perhaps leading to the conclusion that no "true" signal occurs in anterior MFC during error processing. However, as discussed earlier, studies using group-averaged data have found an anterior focus for error processing, and reduced error-related anterior MFC/ACC activity has been identified in schizophrenia [Laurens et al., 2003]. In light of this topographic analysis, we suggest that the lack of MFC/ACC group differences in the spatially averaged data reported here and by others [e.g., Carter et al., 2001; Kerns et al., 2005] may be due to the spatial dispersion of individual activations, especially among HC subjects, and consequent reduction in experimental power to detect differences.

A similar analysis of individual activations in schizophrenia performed by Heckers et al. [2004] found that patients tended to activate locations dorsal to controls in pMFC during interference. Although we did not also find this effect in our radial measurement, these authors employed a blocked version of the MSIT that did not exclude errors from analysis of interference effects. As incongruent blocks had more errors than congruent blocks, it is possible that an anterior/ventral error signal was present in incongruent blocks for HCs. Consistent with the current data, patients with schizophrenia may not have exhibited such an anterior/ventral error signal in incongruent blocks, making them appear to activate dorsally relative to controls for interference contrasts. Thus, even at the level of individual activations, spatially distinct processes that are experimentally confounded may cause apparent shifts in an activation focus.

So, why exactly is there so much dispersion among individual activations in MFC during error processing? There are several possibilities to consider. We believe that it is implausible that the scatter found among individual activations is a methodological artifact arising from differences in head movement or preprocessing parameters between subjects, as realignment of no more than a few millimeters (see Methods section) is not likely to give rise to a difference of several centimeters in the location of activation foci. However, individual differences in the anatomical structure of multiple cortical regions, including MFC, have been noted [Devlin and Poldrack, 2007; Paus et al., 1996; Uylings et al., 2005; Yücel et al., 2001], and interindividual variability in MFC folding patterns are related to differences in the location of functional activations [Crosson et al., 1999]. Although our study was not able to assess the contribution of morphological or cytoarchitechtonic variability to functional activations, VBM analysis indicated that density of GM in anterior regions of MFC was not different between HCs and patients, either in variability of individual GM density values or group-averaged data. Even assuming similar anatomical structure, is it possible that dispersion of activations could be due to individual differences in the distribution of functional networks, with the same cognitive or emotional processes accomplished by different regions of cortex across subjects. Alternatively, variability in the location of activations may have a more functional significance, such that the processing elicited by a given task varies between subjects due to differences in individual strategies or personality characteristics (e.g., subjects who feel greater negative affect when making a mistake may show individual activations that are located anterior to those exhibited by subjects unconcerned about errors). Although this study was not able to directly address the causes of individual activation variability, we probed for correlations between location of activations and number of errors, and, in the patient group, between location of activations and positive and negative symptomotology but did not find any significant relationships. However, more comprehensive personality measures were not examined and may indeed be related to individual differences in the neural response to errors.

Several caveats should be noted for these data. All patient subjects were taking antipsychotics (the majority of which were atypical) and adjunctive psychotropic medications, making it difficult to disentangle the effects of the disorder from those of chronic medication. However, the fact that we found slightly increased activation for the interference condition in the schizophrenic subjects suggests that a general impairment of activation due to medication is not likely. Moreover, antipsychotics tend to normalize activity in MFC/ACC [Honey et al., 1999; Lahti et al., 2004; Ngan et al., 2002; Snitz et al., 2005], and it is possible that our findings represent an underestimation of the true impact of the disorder on neural activity in MFC/ACC. Clearly, however, future research would benefit from obtaining data from patients before and after antipsychotic treatment.

It is also important to note that the current methodology employing a nonparametric analysis of the distribution of clusters in a group allowed for variability in an individual's contribution within each group (i.e., not all subjects contributed an equal amount of activations). However, this within-group variability was the same for both patients and controls, as evidenced by very similar standard deviation values (reported in results), and the groups were equated on total number of clusters contributed to the analysis. Furthermore, a larger sample size would have increased statistical power, possibly revealing differences in our group-averaged data. Nevertheless, the fact remains that, for the majority of researchers, the time and expense of neuroimaging experiments limit the ability to test the large number of subjects that would needed in order to eliminate this problem.

CONCLUSIONS

Illustrating the limitations of spatial averaging, it has been noted that if one averaged all the cars in London and Paris, an illinformed observer would conclude that the typical European car had its steering wheel in the middle of the dashboard. Nevertheless, averaging of noisy functional imaging data sets was one of the key innovations that ushered in the modern era of brain mapping. Although the limitations and advantages of statistical averages have been widely acknowledged for many decades, the actual implications of averaging for functional imaging, which occurs for both spatial information and magnitude of signal, has drawn surprisingly little attention. The analysis presented here demonstrates that topographic information about the spatial distribution of individual activations can serve to guide and strengthen interpretations of fMRI data. The two-dimensional spline analysis employed here is a simple technique that demonstrates the possibilities inherent in this approach. More sophisticated topographic analyses could, in theory, be adopted in future studies to develop this method. Whatever the cause of this variability—anatomical structure or functional differences among neural networks or, most likely, a combination of all of these—the importance of individual differences for interpretations of structure-function mapping deserves attention.

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