Physiological Dysfunction of the Dorsolateral Prefrontal Cortex in Schizophrenia Revisited

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Evidence implicates subtle neuronal pathology of the prefrontal cortex (PFC) in schizophrenia, but how this pathology is reflected in physiological neuroimaging experiments remains controversial. We investigated PFC function in schizophrenia using functional magnetic resonance imaging (fMRI) and a parametric version of the *n*-back working memory (WM) task. In a group of patients who performed relatively well on this task, there were three fundamental deviations from the 'healthy' pattern of PFC fMRI activation to varying WM difficulty. The first characteristic was a greater magnitude of PFC fMRI activation in the context of slightly impaired WM performance (i.e. physiological inefficiency). The second was that the significant correlations between behavioral WM performance and dorsal PFC fMRI activation were in opposite directions in the two groups. Third, the magnitude of the abnormal dorsal PFC fMRI response was predicted by an assay of *N*-acetylaspartate concentrations (NAA) in dorsal PFC, a measure of neuronal pathology obtained using proton magnetic resonance spectroscopy. Patients had significantly lower dorsal PFC NAA than controls and dorsal PFC NAA inversely predicted the fMRI response in dorsal PFC (areas 9, 46) to varying WM difficulty — supporting the assumption that abnormal PFC responses arose from abnormal PFC neurons. These data suggest that under certain conditions the physiological ramifications of dorsal PFC neuronal pathology in schizophrenia includes exaggerated and inefficient cortical activity, especially of dorsal PFC.

Introduction

Attempts to map the physiological signature of putative prefrontal cortex (PFC) neuronal pathology in schizophrenia have been numerous, but the results have been inconsistent and controversial. Of the various functional neuroimaging findings in schizophrenia, reduced function of PFC, so-called 'hypofrontality', has been both the most prominent and most controversial (Ingvar and Franzen, 1974; Weinberger *et al.*, 1986; Andreasen *et al.*, 1992; Frith *et al.*, 1995). According to its proponents, hypofrontality is a marker of PFC dysfunction in schizophrenia that most reliably arises during demanding cognitive tasks that tax PFC function (Weinberger *et al.*, 1986; Carter *et al.*, 1998a). A corollary of this explanation is that cortical activation is relatively 'normal' during cognitive tasks that are less taxing on PFC (Berman *et al.*, 1988; Weinberger and Berman, 1996).

On the other hand, critics have raised a number of objections regarding the relationship between hypofrontality and schizophrenia, invoking issues of experimental design and related inconsistencies. For example, an alternative interpretation of hypofrontality is that it arises as an epiphenomenon of patient behavior, specifically task performance, that is typically abnormal in schizophrenic patients (Frith *et al.*, 1995; Gur and Gur, 1995; Price and Friston, 1999). Thus, while many studies of PFC function in schizophrenia have reported reduced PFC activation when patients perform poorly (Franzen and Ingvar, 1975; Weinberger *et al.*, 1988, 1992; Callicott *et al.*, 1998a; Carter *et al.*, 1998a; Fletcher *et al.*, 1998; Stevens *et al.*, 1998), others have observed normal (Frith *et al.*, 1995; Mellers *et al.*, 1998; Curtis *et al.*, 1999), reduced (Yurgelun-Todd *et al.*, 1996; Curtis *et al.*, 1998) and even increased PFC activation (Stevens *et al.*, 1998; Manoach *et al.*, 1999) when patients' performance is near normal. Indeed, Ragland *et al.* reported both reduced and intact PFC regional cerebral blood flow (rCBF) in a cohort of schizophrenic patients given both an executive (i.e. Wisconsin Card Sorting Test) and a declarative (i.e. paired associate recognition test) memory task respectively (Ragland *et al.*, 1998). Similarly, Bullmore *et al.* recently reported both attenuated and normal PFC activation in a group of schizophrenic patients during a single scanning session given both a covert verbal fluency task (attenuated PFC activation) and covert semantic decision task (normal PFC activation) respectively (Bullmore *et al.*, 1999). Understandably, cohort differences in measures like clinical presentation and medication status could be expected to generate inconsistencies, as could the small numbers of subjects and varying cognitive challenges used in such studies. It is also possible that these studies have been inconclusive because PFC function has not been examined across a wide enough dynamic range of cognitive demand and because PFC function has not been examined at the sub-regional level. Until recently (Bertolino *et al.*, 2000a,b), there have not been independent *in vivo* measurements of PFC neuronal pathology to substantiate the assumption that abnormal functional imaging findings arise from abnormal PFC neurons.

Regardless of these uncertainties, most authors agree that the physiological responses of the schizophrenic brain are abnormal when cognitive challenges are beyond these patients' behavioral capacity (Weinberger and Berman, 1988). Working memory (WM) is a well-documented cognitive challenge that has been examined in many studies of patients with schizophrenia (Goldberg *et al.*, 1987, 1998b; Park and Holzman, 1992; Fleming *et al.*, 1995, 1997; Goldberg and Weinberger, 1995; Keefe *et al.*, 1995; Carter *et al.*, 1996; Stone *et al.*, 1998; Wexler *et al.*, 1998). WM is a construct meant to encompass the storage of information and various associated 'executive' processes (e.g. attention, inhibition, planning, updating and spatial/temporal encoding) that occur over a relatively brief period of time (Baddeley, 1981, 1986; Hitch, 1984; Goldman-Rakic, 1990, 1996; Smith and Jonides, 1998, 1999). While WM is thought to be capacity-limited in all subjects (Miller, 1956; Just and Carpenter, 1992), schizophrenic patients appear to have additional capacity limitations presumed to arise from dorsal PFC dysfunction (Goldberg and Weinberger, 1988; Goldman-Rakic, 1991, 1994).

The interpretation of hypofrontality in the context of capacity limitations is further complicated by recent studies in healthy subjects. For example, Goldberg *et al.* found that healthy subjects performing a dual task paradigm became relatively hypofrontal when pushed beyond their capacity to maintain

accuracy (Goldberg *et al.*, 1998a). Grasby *et al.* found this 'healthy' hypofrontal response by using a word-recall task of increasing word-list length (Grasby *et al.*, 1994). Similarly, Callicott *et al.* found evidence of an inverted-U shaped PFC response to parametrically increasing WM difficulty in healthy subjects who became relatively hypofrontal as they were pushed beyond their WM capacity (Callicott *et al.*, 1999). In addition, diminished PFC activity coincident with diminished behavioral capacity has been found in single-unit recording studies in non-human primates during WM tasks (Funahashi *et al.*, 1989, 1991) and in electrophysiological studies in humans attempting complex motor tasks (Gevins *et al.*, 1987). Thus, under certain circumstances, hypofrontality can be a normal physiological response to excessive load. Collectively, these data make it difficult to resolve whether hypofrontality as a 'finding' in schizophrenic patients is a direct (i.e. disease dependent) manifestation of PFC pathology or whether hypofrontality simply reflects diminished behavioral capacity as might occur for any subject pushed beyond capacity (i.e. disease independent). A further illustration of this latter possibility is a study by Fletcher and colleagues (Fletcher *et al.*, 1998), who gave a parametric word-list recall task to schizophrenic patients and found that hypofrontality occurred only in the context of list lengths beyond the patients' memory capacity. Thus, schizophrenic patients with limited WM capacity, based on these preceding data, might be expected to become hypofrontal when studied beyond their WM capacity.

To complicate matters further, there is also evidence that the 'healthy' relationship between reduced WM capacity and PFC neuronal function could be over-activation of PFC (i.e. relative hyperfrontality). Rypma and D'Esposito recently demonstrated that healthy controls who have longer reaction times during a WM task respond by increasing activation in dorsal but not ventral PFC (Rypma and D'Esposito, 1999). They interpreted these results as a reflection of reduced efficiency of WM information manipulation within dorsal PFC. Further, they interpreted the failure of reaction time to correlate with fMRI activation in ventral PFC as a reflection of the putative link between ventral PFC and WM maintenance functions (Owen *et al.*, 1996; D'Esposito *et al.*, 1998; Smith and Jonides, 1998, 1999; Wagner, 1999). Thus, it is conceivable that under certain circumstances schizophrenic patients might evidence over-activation especially in dorsal PFC given their poor performance.

While hypofrontality as a finding generates continued debate, there is less debate that PFC neuronal pathology exists in schizophrenia and that this pathology may be more prominent in dorsal PFC (areas 9, 46). Similarities between some of the clinical symptoms of schizophrenia – particularly between the negative or deficit symptoms in schizophrenics and those of patients with frontal lobe lesions – have long implicated PFC in schizophrenia (Kraepelin, 1919; Piercy, 1964). Even though the heterogeneity of clinical symptomatology implicates multiple brain regions, evidence that schizophrenia fundamentally involves dorsal PFC neuronal pathology continues to accumulate from many directions (Lewis, 1997; Selemon and Goldman-Rakic, 1999). Postmortem neuropathological studies have reported dorsal PFC gray matter abnormalities, including reductions in the abundance and metabolic activity of dorsal PFC interneurons (Benes *et al.*, 1991; Akbarian *et al.*, 1996). Other dorsal PFC abnormalities include diminished inhibitory inputs from prefrontal chandelier cells onto the axonal processes of dorsal PFC pyramidal neurons (Woo *et al.*, 1998) and reduced neuropil without neuronal loss in dorsal PFC (areas 9, 46) (Selemon *et al.*, 1995; Selemon and Goldman-Rakic, 1998). Along similar lines, proton magnetic resonance spectroscopy (^{1}H-MRS) studies have repeatedly found reduced concentrations of the intraneuronal chemical *N*-acetylaspartate (NAA) in PFC (Bertolino *et al.*, 1996, 1998a,b; Thomas *et al.*, 1998; Cecil *et al.*, 1999). Furthermore, those studies that have examined sub-regions within PFC have found NAA reductions in dorsal but not ventral PFC (Bertolino *et al.*, 1996, 1998a,b). In addition, we have demonstrated dorsal but not ventral PFC NAA reductions specifically predicted the extent of negative symptoms in schizophrenic patients (Callicott *et al.*, 2000). Neurophysiological experiments in schizophrenic patients have noted abnormal eye tracking function referable to dorsal PFC (Holzman *et al.*, 1973) and altered PFC electroencephalographic patterns (Abrams and Taylor, 1979), particularly a disruption of normal coherence between PFC and other brain regions (Tauscher *et al.*, 1998). These data provide a strong basis for the assumption that specific neurocognitive abnormalities in schizophrenia (particularly WM) result from physiological dysfunction of PFC neurons. Given the preponderance of evidence for PFC pathology in schizophrenia, it seems surprising that the physiological data regarding WM in schizophrenia are not more conclusive.

The present study was undertaken to address the question of prefrontal dysfunction in schizophrenia from another perspective. Using fMRI, we mapped the response to varying WM difficulty in schizophrenic patients and healthy comparison subjects using a parametric version of the '*n*-back' WM task (Gevins and Cutillo, 1993; Cohen *et al.*, 1994). We hypothesized that if PFC neuronal pathology exists in schizophrenia, its physiological characteristics should have three fundamental features, regardless of whether there is hypofrontality or hyperfrontality. First, an *abnormal* physiological response should be present at every level of WM difficulty in which patients show a behavioral deficit. Second, given the neuropathological and ^{1}H-MRS (i.e. NAA) evidence suggesting pathology within dorsal PFC (areas 9, 46), we predicted that there would be greater abnormalities in dorsal as opposed to ventral PFC in response to varying memory difficulty in schizophrenic patients. At the very least, since some WM studies in healthy controls suggest a functional distinction between dorsal and ventral PFC, we predicted that these regions might not show the same abnormal response. Finally, a disease-dependent pathophysiological profile should be related to an independent *in vivo* measure of neuronal integrity (i.e. ^{1}H-MRS-derived NAA measures) (Bertolino *et al.*, 2000a). We assumed that while there may be many cortical regions within the cortical network subserving WM evidencing an abnormal response to varying WM difficulty in schizophrenic patients, the regional physiological response(s) arising directly from underlying neuronal pathology would correlate strongest with NAA measures of neuronal pathology.

Material and Methods

Subjects and Task

We studied 37 schizophrenic patients and 32 healthy controls using a parametric version of the *n*-back task. As reported previously (Callicott *et al.*, 1998a, 1999), we used a no back (0B) condition pseudo-randomly interspersed with one back (1B) and two back (2B) conditions (hereafter referred to as 0B–1B–2B). Patients were recruited from the inpatient wards of the Neuropsychiatric Research Hospital of the Intramural Research Program, National Institutes of Mental Health at St Elizabeths, Washington, DC. Healthy volunteers were recruited from National Institutes of Health staff and through the Normal Volunteer Office of the National Institute of Mental Health. The fMRI and ^{1}H-MRS examinations

were conducted under a protocol (91-M-0124) that was approved by the Institutional Review Board of the National Institute of Mental Health, Intramural Research Program. All subjects gave written informed consent prior to participation in this protocol.

Prior to the scanning session, all healthy subjects completed a screening questionnaire (medical, psychiatric and neurological history) and a screening magnetic resonance imaging (MRI) exam. Additionally, these subjects were given instruction and practice with the *n*-back task. As inpatients, all schizophrenic subjects underwent formal and detailed psychiatric and neurological examinations, a screening MRI exam, and the same instruction and practice with the *n*-back task. All subjects were screened for a history of concomitant neurological illness, active substance abuse or dependence, and significant abnormalities on the screening MRI examination. Handedness was assessed using the Edinburgh Handedness Survey (Oldfield, 1971).

Based on the markedly impaired performance of patients in our prior cohort (Callicott *et al.*, 1998a), we sought a group of patients who would perform closer to controls. Therefore, in addition to exclusion criteria detailed below, schizophrenic subjects were not included in this study if they were unable to reach minimal proficiency (≥90% accurate) on the control version of our *n*-back working memory task and are not included in the cohort numbers noted. One schizophrenic patient who surpassed minimal proficiency was unable to complete the scan session due to claustrophobia. From the remaining cohort of 36 patients and 32 controls, we excluded 23 schizophrenic patients and 14 healthy subjects for the following reasons: excessive inter- or intra-scan motion (see below) (22 patients, 11 controls), fMRI data lost due to computer malfunction (1 patient, 1 control), and failure to comply with task instructions (i.e. placing thumb over answer button during the delay period of the 1B or 2B) (2 controls). Those patients excluded did not differ significantly from those included in terms of age, gender, handedness, duration of illness or psychiatric symptomatology (Psychiatric Symptom Assessment Scale (PSAS) (Bigelow and Berthot, 1989).

The final cohort for the 0B–1B–2B comparison consisted of 13 patients with schizophrenia and 18 healthy volunteers. Twelve patients met criteria for schizophrenia and one patient met criteria for schizoaffective disorder according to the Diagnostic and Statistical Manual of Mental Disorders–IV (First *et al.*, 1995). Patients were rated at the time of scanning using the PSAS and were mildly to moderately ill (15.4 ± 14.3). In addition, patients had been ill for an average of 10 (± 6) years. Data from seven controls have appeared previously (Callicott *et al.*, 1999). Patients and healthy volunteers were demographically similar (Table 1). The groups did not differ in age, handedness or the ratio of women to men. Our patients had significantly fewer years of education (patients 14.5 ± 2.3 versus controls 16.4 ± 2.0, $t = 2.6$, $P = 0.02$) (Table 1). This educational difference typically arises in schizophrenia cohorts because patients become ill during late high school or early college years. To ensure that our data were not driven by general intellectual differences, we compared Hollingshead parental socio-economic status (SES) — a measure that is generally felt to represent a more realistic appraisal of intellectual potential were schizophrenia not present (Table 1) (Hollingshead and Redlich, 1958). We were unable to obtain these data for two controls and two patients. Three subjects (two controls and one patient) were lost to follow-up and one patient was adopted and had no information on their birth parents. The groups were not different in this measure (patients 57.3 ±10.1 versus controls 53.3 ± 8.6, $t = 1.09$, $P = 0.3$).

As previously described (Callicott *et al.*, 1998a, 1999), our version of the *n*-back task differs from the standard letter or number recall *n*-back tasks that use infrequent targets (Cohen *et al.*, 1994; Smith and Jonides, 1999). Instructions appearing on screen above the stimuli told subjects to recall the stimulus seen '*n*' previously. Stimuli were presented for 1800 ms with a 2000 ms break at the start of each new task epoch. In addition, the stimuli were limited to the same four numbers throughout (i.e. 1–4) in order to simplify the instruction and learning process for the schizophrenic patients. Designed to force subjects to constantly update their mental set while minimizing interference from incoming stimuli, our version of the *n*-back task emphasizes the 'executive' aspects of WM with continual presentation of incoming stimuli and continual WM response (i.e. 100% target). However, both 'executive' and maintenance requirements likely increased parametrically with *n*-back level (i.e. 0B–1B–2B). As in past reports (Callicott *et al.*, 1998a, 1999), we attempted to control for learning effects by starting the fMRI session only after each subject had achieved the same accuracy level on at least three successive trials at each WM difficulty immediately prior to scanning. In the past, we have found no evidence for a significant change in patient or control accuracy over a scanning session (Callicott *et al.*, 1998a, 1999).

Table 1
Demographics

Diagnosis	*n*	Age (years)	Gender	Handedness	Education (years)	SES
Patients	13	33.9 (9) [17–44]	3 F 10 M	12 R 1 L	14.5 (2) [10–18]*	57.3 (10) [38–64.5]
Controls	18	29.6 (7) [18–42]	7 F 11 M	16 R 2 L	16.4 (2) [11–20]	53.3 (9) [37–66]

Data are mean ± SD [range].

The stimuli were generated by a standard desktop computer running in-house software (R. Coppola) and presented via a fiber-optic goggle system (Resonance Technology, Van Nuys, CA). Responses were recorded via a specially designed fiber-optic response box (D.W. Jones) with buttons arrayed in the same configuration as the stimuli presented on screen and relayed back to the computer for tabulation of performance accuracy. We did not record reaction time. Performance was recorded as the percentage correct for 0B, 1B and 2B. Between-group comparisons performed using a repeated-measures analysis of variance (ANOVA) with diagnosis as the between-group and time and WM difficulty as the within-group factors followed by *post hoc* planned comparisons within Statistica (Statsoft, Inc., Tulsa, OK).

fMRI Data Acquisition and Analysis

All MRI studies were performed on a standard 1.5 T General Electric Signa Scanner (Milwaukee, WI) outfitted with a combined radiofrequency (RF) and gradient insert coil (Medical Advances, Milwaukee, WI). High-resolution T_1-weighted spin echo whole-brain anatomical images [echo time (T_E) = 10 ms, repetition time (T_R) = 500 ms, field of view (FOV) = 240 mm, 256 × 256 matrix, flip angle = 90°, voxel dimensions = 3.75 mm isotropic] were acquired to orient the fMRI data acquisition. Blood oxygenation level dependent (BOLD) fMRI data (Ogawa *et al.*, 1992) were acquired as previously described (interleaved, T_E = 60 ms, 'whole-brain T_R' = 4000 ms, flip angle = 90°, FOV = 24, 64 × 64 matrix, voxel dimensions = 3.75 mm isotropic) (Mattay *et al.*, 1996; Callicott *et al.*, 1999). We minimized head movement by placing additional padding around each subject's head inside the gradient insert coil. Between fMRI runs, we communicated with all subjects to assure that the visual stimuli were in view and monitored performance throughout to ensure consistent performance. During scanning, task epochs lasted 20 s and were performed in nine runs of 4 min each with pseudo-randomization of task order (e.g. rest–0B–1B–2B–rest–2B–1B–0B, rest–1B–0B–2B–rest–2B–0B–1B). We obtained 90 whole-brain fMRI volumes for each level of WM difficulty [5 whole brain volumes × (2 task epochs/run) × 9 runs].

Data processing began with registration of whole-brain fMRI volumes using a sinc interpolation to the initial timepoint of the experiment (Ostuni *et al.*, 1997). Prior to this analysis, registered fMRI were examined via cine loop to detect gross uncorrected inter-scan movement. This procedure did not result in the exclusion of subjects. fMRI data sets were then interrogated in three ways for high data quality (scan stability) prior to inclusion in further statistical analyses. First, the registration parameters derived by the interpolation were extracted and used to exclude subjects with excessive inter-scan motion (>2 voxels translation, >1° rotation) (Callicott *et al.*, 1999). Second, we used evidence of motor cortex activation as an 'internal' activation standard for both intra- and inter-scan stability (Weinberger *et al.*, 1996; Callicott *et al.*, 1998a). Since subjects responded using their right thumb, subjects had to demonstrate activation of contralateral (left) primary motor cortex in a comparison of each task to rest ($P < 0.001$). As described previously (Weinberger *et al.*, 1996), our version of the *n*-back task was designed to require a continuous thumb press (~0.6 Hz) throughout. This motor response fails to produce activation of contralateral sensorimotor cortex when voxel-wise signal stability has been compromised (Mattay *et al.*, 1996; Callicott *et al.*, 1998a). Subjects without such activation would be excluded based

on the assumption that MRI artifact of some kind remained in the data after reconstruction and registration. Third, a measure of voxel variance was used to match groups for other undetected sources of fMRI artifact (inclusive of intra-scan subject motion, but also of any scanner-related artifacts). This involved a review of plotted histograms of normalized standard error of the mean difference between all cognitive tasks versus rest at each voxel (Mattay *et al.*, 1996). Groups were then matched in a subject-wise fashion by visual inspection of these curves – a sharp peak centered over low variance values for high-quality studies and a broad peak spanning higher variance in low-quality studies. Our approach is more conservative than alternative approaches that include derived measures of movement or global variance as confounds within the statistical analyses themselves (Curtis *et al.*, 1998). However, we have argued that any differences in voxel variance at this early stage of analysis might unduly bias further statistical comparisons of fMRI signal magnitude given the low inherent physiological signal-to-noise ratio in fMRI data – particularly worrisome in schizophrenic cohorts where under-activation might be an expected result (Weinberger *et al.*, 1996).

Voxel-wise signal intensities were ratio normalized to the whole-brain mean and then detrended using a third-order polynomial procedure with the baseline at each voxel arbitrarily set to 1000 prior to statistical analysis (Ostuni *et al.*, 1997). This procedure was also assumed to remove any remaining signal drift. Whole-brain fMRI volumes were transformed to the International Consortium for Human Brain Mapping project (ICBM) template (Mazziotta *et al.*, 1995) using Automated Image Registration 3.0 (AIR 3.0) (Woods *et al.*, 1998a,b). Because this template closely, but not exactly, approximates the space described by Talairach and Tournoux (Talairach and Tournoux, 1993), we have reported activation in both ICBM space and Talairach space (see Table 2). The formula to convert the ICBM template locations to the standard space of Talairach and Tournoux was kindly provided by Mathew Brett (Cambridge University; http://www.mrc-cbu.cam.ac.uk/Imaging/mnispace.html). To control for inter-individual variance in regional activation and increase the signal to noise ratio, data were smoothed using a 10 mm full width at half maximum (FWHM) isotropic Gaussian kernel.

These data were then analyzed with Statistical Parametric Mapping (SPM96) (Wellcome Department of Cognitive Neurology, London, UK) (Friston *et al.*, 1995). Data were analyzed using the SPM96 random effects kit (SPM96_RFX). Effects of varying WM difficulty were estimated according to the General Linear Model. Since the first two whole-brain collections per 20 s epoch are contaminated by BOLD signal bleed-over from the prior epoch, we collapsed fMRI data from the final three whole-brain volumes into one adjusted mean per task condition. We used a set of linear contrasts to define regions exhibiting significant group differences in the response to varying WM difficulty. Linear contrasts were weighted to identify condition effects that were stronger in one diagnostic group against the other group (e.g. positive linear increase in response to WM difficulty in patients compared to the opposite for controls). Within SPM96, *t* scores were converted to *Z*-scores (Table 2). We chose a threshold of $P \leq 0.001$ (uncorrected). We also indicated those locales that reached significance within SPM96 after correction at both the voxel-level and the cluster-level (Table 2). For ease of interpretation, standard space coordinates noted within the text conform to ICBM standard space (*x*,*y*,*z*).

To test the relationship between PFC fMRI activation and both performance and ^{1}H-MRSI measures (see below), we performed linear correlations within ICBM standard image space using MEDx (Sensor Systems, Sterling, VA) (Callicott *et al.*, 1999). MEDx adopts the conventions of the General Linear Model for these linear correlations. Specifically, we calculated linear correlations between averaged fMRI signal (as the response variable) and both performance and NAA measures (as indicator variables) in two separate correlation analyses. Within these MEDx correlation analyses, the significance of the linear correlation was expressed as both a product moment correlation coefficient (*r*) and a two-tailed probability (*Z*). Linear correlation maps (Fig. 5) were generated in MEDx as thresholded probability maps ($Z \geq 3.0$, uncorrected $P \leq 0.001$) that were converted to product–moment correlation coefficients thresholds based on the number of subjects in each group (see below) as described previously (Callicott *et al.*, 1999). All correlations were performed for each group separately and for 1B and 2B separately. Correlations maps were displayed on a co-registered template (ICBM). Significant positive linear correlations are highlighted in red, while significant negative linear correlations are highlighted in blue (see Fig. 5). Since we used averaged fMRI volumes, a correction for temporal autocorrelation was not chosen within MEDx. Since this analysis was directed specifically at finding relationships within PFC, a correction for multiple statistical tests was not applied.

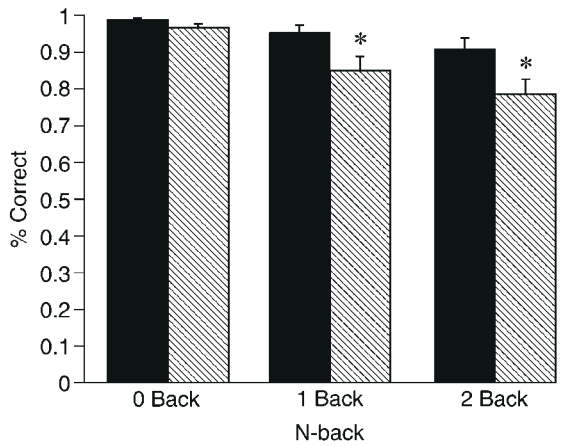

Figure 1. Performance results for *n*-back task. Performance is represented as the percentage correct (accuracy, *y* axis) across WM load (*x* axis). The *n*-back task was parametrically varied between no-back condition (*A*), one-back (*B*) and two-back (*C*) conditions. Dark bars indicate control performance (± SEM), while light bars indicate patient performance. Significant *post hoc* differences ($P < 0.05$) are indicated by an asterisk (*).

^{1}*H-MRSI Data Acquisition and Analysis*

^{1}H-MRSI data were collected as described previously (Duyn *et al.*, 1993; Bertolino *et al.*, 1996). The ^{1}H-MRSI sequence used spin-echo slice selection (T_E = 272 ms; T_R = 2200 ms; voxel dimensions 7.5 × 7.5 × 15 mm) to acquire four oblique 15 mm thick spectroscopic volumes following suppression of lipid signal from the skull and surrounding tissue. Data analysis proceeded as described previously (Bertolino *et al.*, 1996). Relative concentrations of NAA, choline (CHO) and creatine + phosphocreatine (CRE) were obtained and statistically analyzed as ratios: NAA/CRE, NAA/CHO and CHO/CRE. This convention reduces errors arising from variations in magnetic field homogeneity, coil loading and partial volume effects from cerebrospinal fluid (Bertolino *et al.*, 1998b). NAA, an exclusively intraneuronal amino acid, is interpreted to reflect neuronal pathology (Tsai and Coyle, 1995). Just as with the fMRI data, ^{1}H-MRSI data were discarded on a subject-wise basis to remove those studies contaminated by excessive ^{1}H-MRSI artifact (Bertolino *et al.*, 1996). Following exclusion, we had NAA/CRE data for 13/18 healthy controls and 11/13 schizophrenic patients. These subgroups did not differ significantly from the larger schizophrenic and control samples in demographics, task performance or fMRI activation. We compared NAA/CRE, NAA/CHO and CHO/CRE values between groups in multiple regions of interest (ROIs) that included both a dorsal PFC and ventral PFC ROI (Bertolino *et al.*, 1996, 1998a,b) using a repeated-measures ANOVA followed by Mann–Whitney *U*-tests *post hoc* in Statistica (Statsoft, Inc., Tulsa, OK).

Results

Working Memory Performance

Consistent with previous reports (Goldberg and Weinberger, 1995; Fleming *et al.*, 1995; Carter *et al.*, 1996, 1998a; Callicott *et al.*, 1998a; Goldberg *et al.*, 1998b; Stevens et al., 1998; Stone *et al.*, 1998; Wexler *et al.*, 1998), patients with schizophrenia performed worse at higher levels of WM difficulty implicating an overall limited WM capacity. The patients performed similar to controls at the lowest level of difficulty (0B), while performing

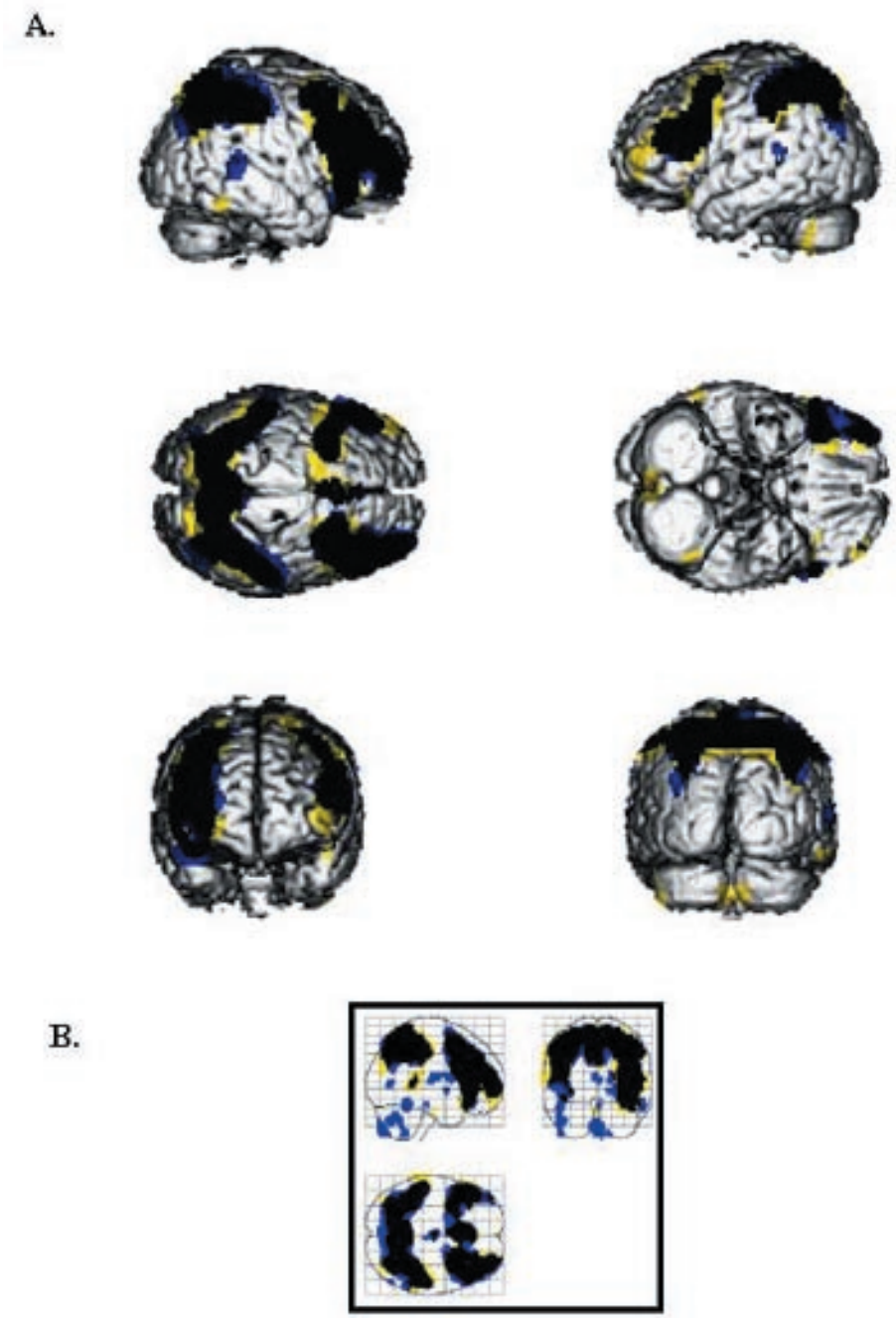

Figure 2. Dynamic fMRI response to increasing working memory difficulty: similarities between patients and controls. Dynamic fMRI response maps (SPM96) during varying WM difficulty in schizophrenic patients and controls rendered onto three dimensional brains (right = right). To demonstrate the spatial overlap between patients and controls, the groups maps showing the effect of varying WM difficulty across 0B–1B–2B were superimposed. The patient map was highlighted in blue, while the control map was highlighted in yellow. Areas of overlap are black. (*A*) Overlap presented in the following order: right and left lateral views, top and bottom views, and anterior and posterior views respectively. In those areas thought to be critical for working memory including bilateral PFC, parietal and cingulate cortices, there was almost complete overlap in brain activation. (*B*) The same overlapping maps presented in traditional SPM 'look-through' views in the sagittal, coronal and oblique views respectively.

worse at 1B and 2B [diagnosis by WM difficulty: $F(2,58) = 4.4$, $P = 0.02$] (Fig. 1). *Post hoc* testing revealed that group performance differences were significant at 1B ($P = 0.01$) and 2B ($P = 0.01$). Nonetheless, patients performed well above chance indicating their engagement in the task (~86% at 1B and ~80% at 2B).

fMRI Across a Dynamic Range of Working Memory Difficulty

Both schizophrenic patients and healthy controls showed a regionally similar pattern in the response to varying working memory difficulty across the range from 0B–1B–2B. Figure 2

presents the overlap in regional activation for the main effect of increasing memory difficulty in schizophrenic patients and controls. Regions showing a similar response to varying WM difficulty between groups included bilateral PFC, bilateral parietal cortex, the anterior cingulate, various subcortical regions and bilateral cerebellum (Fig. 2), as has been found previously in fMRI studies of WM in healthy controls (Cohen *et al.*, 1994, 1997; McCarthy *et al.*, 1996; D'Esposito *et al.*, 1998; Smith and Jonides, 1998; Callicott *et al.*, 1999). However, while qualitative patterns of activation were similar, the dynamic fMRI responses to increasing WM difficulty were distinct between patients and controls (Fig. 3).

Across the 0B–1B–2B range, schizophrenic patients had a greater dynamic response in most of the major 'nodes' of the putative WM network typically activated by the *n*-back task in healthy controls (see above). These regions included right dorsal PFC [Brodmann areas (BA) 9–10, 46], medial prefrontal gyrus (BA 9–10), right inferior parietal lobule (BA 40), and the anterior cingulate (BA 32) (Table 2, Fig. 3*A*). These differences are illustrated in Figure 4. Additionally, we compared the proportion of individuals in each group who evidenced a fMRI signal increase from 1B to 2B, assuming that this *post hoc* measure should not differ if the diagnosis by WM difficulty interaction was driven by a linear increase in fMRI signal as WM increased. This proportion did not differ between groups in those PFC locales identified as hyper-responsive to varying WM load in patients (see Table 2) [e.g. right dorsal PFC (30,46,12), Fisher exact two-tailed $P = 0.96$; right dorsal PFC (34,26,28), $P = 0.99$].

Healthy controls showed a greater dynamic response across the 0B–1B–2B range in ventral PFC and in regions outside of PFC (Table 2, Fig. 3*B*). Often related to storage or phonological processing in WM (Baddely, 1986; Cohen *et al.*, 1997; Chafee and Goldman-Rakic, 1998; Smith and Jonides 1998), some locales within the parietal lobes, namely right temporo-parietal cortex (BA 39) and left precuneus (BA 7), were more responsive to varying WM difficulty in controls. However, as noted above, there was also a region within parietal cortex in which patients showed a greater dynamic response than controls. Controls showed a greater response within the cerebellum, left superior temporal gyrus and posterior cingulate. The anterior cingulate yielded somewhat ambiguous results. There were locales within the right anterior cingulate (BA 24) that were more active in controls, perhaps as a result of increased error detection demands (Pardo *et al.*, 1990, 1991; Carter *et al.*, 1998b). However, as noted above, there was also a locale within anterior cingulate that showed a greater dynamic response in patients. The hippocampal area is often thought abnormal in schizophrenia (Weinberger, 1999), but not typically reported in WM functional neuroimaging studies as an area of increased blood flow (activation) for healthy controls during the *n*-back task [reviewed elsewhere (Smith and Jonides, 1999)]. Nonetheless, in the right hippocampus, healthy controls did not show differential activation, but rather patients showed a linear deactivation with increasing WM difficulty (Fig. 4).

Distinct Relationships Between fMRI Activation and Working Memory Accuracy

Performance on the *n*-back task was significantly correlated with fMRI activation in dorsal PFC (areas 9, 46) for both subject groups. Consistent with our earlier data for healthy controls (Callicott *et al.*, 1999), right dorsal PFC (areas 9–10, 46) activation was positively correlated with performance. In other words, better performers utilized greater right dorsal PFC activation to tackle increasing memory difficulty at least as long as it is within their capacity to do so (Fig. 5) [r threshold ≥ 0.7 (95% confidence intervals 0.53–0.87), $n = 18$ controls]. Patterns of correlation were similar between 1B and 2B in healthy controls. In contrast, schizophrenic patients evinced a qualitative disruption in the relationship between performance and activation in right dorsal PFC (Figure 6) [r threshold ≥ -0.7 (–0.49 to – 0.91), $n = 13$ patients]. In essence, greater dorsal PFC fMRI activation predicted lesser performance (i.e. inefficiency). The correlations in the two groups are not exactly overlapping, but are part of larger clusters that are contiguous in right dorsal PFC. However, both regions fall within clusters of activation in which patients showed an exaggerated response to varying WM difficulty (Table 2). There was also a dissociation within the PFC of schizophrenic patients in the relationship between fMRI activation and performance. Interestingly, left ventral PFC (BA 45), showed a positive correlation between fMRI activation and performance, similar to that found in controls, e.g. (–36,56,–12). This might suggest that ventral PFC activation is necessary, but not sufficient, for WM accuracy. However, just as there were no areas of negative correlation within dorsal PFC in controls, there were no areas of positive correlation within dorsal PFC in patients supporting the fundamental difference between dorsal PFC activation in these groups. In general, there was a more diffuse pattern of both positive and negative correlations in regions outside of dorsal and ventral PFC (data not shown) in the patients. For example, performance was positively correlated with fMRI activation in left premotor (BA 6) and parietal cortices for the schizophrenic patients, suggesting that the more successful patients recruited additional resources outside of dorsal PFC or may have had a less organized and more diffuse response to varying WM difficulty – regardless, several clear departures from the 'normal' pattern.

As a *post hoc* exploration of the hyper-frontal response of dorsal PFC in schizophrenics, we performed an additional analysis by scanning a subset ($n = 9$) of our healthy controls using a more difficult range of memory difficulty (0B–2B–3B) in a separate scanning session. In this comparison, accuracy was more comparable between groups [patient 0B (96 ± 2 %) versus control 0B (98 ± 1%); patient 1B (86 ± 3%) versus control 2B (93 ± 5%); patient 2B (80 ± 10%) versus control 3B (90 ± 8%)], although patients were still slightly more impaired than controls even though this difference did not reach statistical significance in this smaller sample [diagnosis by WM difficulty $F(2,40) = 2.0$, $P = 0.1$]. However, the addition of 3B should have increased both the maintenance and manipulation difficulty in WM for controls. We found in this new comparison that dorsal PFC was still hyper-responsive in the patients [right BA 9/46 (30,36,17); (50,36,13); (32,27,28), $P = 0.001$, uncorrected]. Thus, the continued increased activation of dorsal PFC, even as controls experience greater manipulation demands, suggests that this sub-regional response was particularly inappropriate in schizophrenic patients.

NAA Measures and the Physiological Response

As a specific test of the hypothesis that our fMRI data could be interpreted as reflecting neuronal pathology of the PFC, we compared the ^{1}H-MRSI data for healthy controls and schizophrenic patients. Right dorsal PFC NAA/CRE values were significantly lower in these schizophrenic patients, with a trend in left dorsal PFC (right $U = 26.0$, $P = 0.008$; left $U = 45.0$, $P = 0.12$). There were no significant differences between groups in

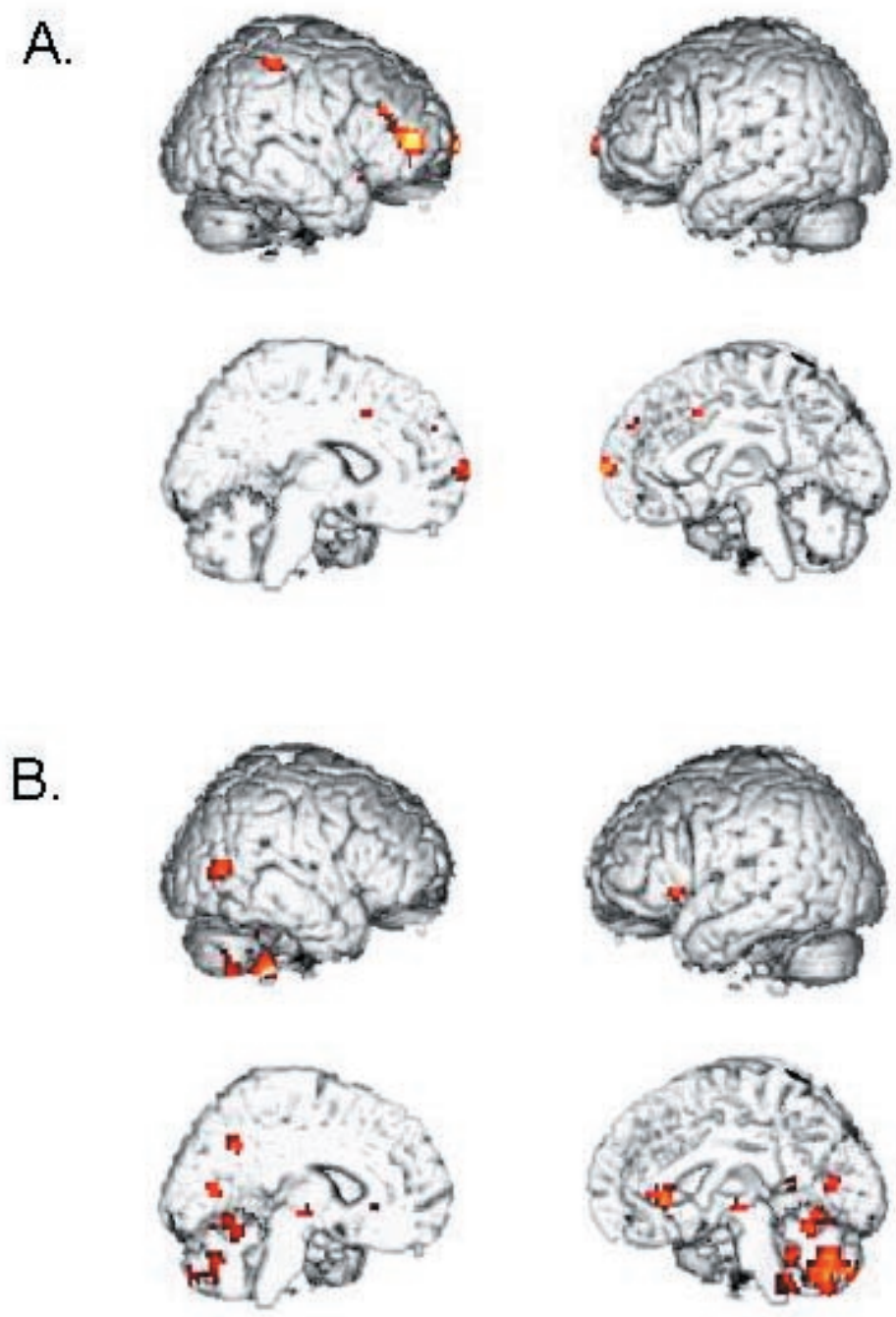

Figure 3. Exaggerated response to varying working memory difficulty in schizophrenic patients (I). Dynamic fMRI response maps during varying WM difficulty rendered onto three-dimensional standard brains in SPM96 displayed in the right lateral, left lateral, right medial and left medial views respectively (right = right). (*A*) Regions in which patients showed a greater dynamic response to varying WM difficulty than controls across the range 0B–1B–2B (see Table 2). (*B*) Regions in which controls showed a greater dynamic response to varying WM difficulty than patients across the range 0B–1B–2B.

right or left ventral PFC NAA measures. As in prior reports (Bertolino *et al.*, 1996; Callicott *et al.*, 1998b), right and left hippocampal area NAA/CRE were also significantly reduced (right $U = 33.0$, $P = 0.03$; left U = 34.0, $P = 0.03$). Patients were also not significantly different from controls in the superior temporal gyrus, thalamus, putamen, anterior or posterior cingulate, frontal white matter or centrum semiovale, consistent with earlier reports (Bertolino *et al.*, 1996, 1998a,b).

Based on our prior hypothesis regarding the relationship of PFC dysfunction to PFC neuronal pathology (Bertolino *et al.*, 2000a), we correlated dorsal and ventral PFC NAA measures and BOLD fMRI signal change (see above) (Fig. 6). Correlations were performed also between other regional NAA measures and fMRI activation at each level of memory difficulty (i.e. 1B and 2B). In schizophrenic patients alone, right dorsal PFC NAA measures were negatively correlated with right dorsal PFC fMRI activation

Table 2
Regions in which groups had differing dynamic responses to varying working memory difficulty

Comparison	Area (BA)	Anatomy	*Z* score	Talairach			MNI		
Patients > controls	right dorsal PFC (10)	middle frontal gyrus	4.32	30	46	12	30	45	9
	left PFC (10)	medial frontal gyrus	4.30	–2	72	8	–2	70	4
	right PAR (40)	inferior parietal lobule	3.75	36	–36	56	36	–32	53
	right dorsal PFC (9)	middle frontal gyrus	3.73	34	26	28	33	26	24
	right dorsal PFC (46)	middle frontal gyrus	3.65	32	34	20	32	34	17
	right PFC (9)	medial frontal gyrus	3.44	2	54	32	2	54	27
	left ACING (32)	anterior cingulate	3.35	–2	14	40	–2	15	36
Controls > patients	right cerebellum	cerebellum	4.50	20	–40	–48	20	–41	–38
	cerebellum	cerebellum	4.23	0	–68	–32	0	–67	–24
	right PAR (39)	medial occipital gyrus	4.21	54	–68	8	53	–66	11
	left PAR (7)	precuneus	4.14	–18	–58	36	–18	–55	36
	right ACING (24/32)	anterior cingulate	4.05	4	28	0	4	27	–1
	right Hippocampus	hippocampus	4.01	32	–50	4	32	–48	6
	left ventral PFC (47)	inferior frontal gyrus	3.96	–60	20	0	–59	19	–1
	right cerebellum	cerebellum	3.92	6	–78	–40	6	–77	–30
	right basal ganglia	caudate	3.84	14	32	4	14	31	2
	right ACING (24/32)	anterior cingulate	3.71	0	–18	–4	0	–17	–2
	left brainstem	red nucleus	3.70	–4	–68	8	–4	–66	11
	right ACING (24/32)	anterior cingulate	3.58	20	38	4	20	37	2
	right PCING	posterior cingulate	3.58	22	–46	12	22	–44	13
	left STG (22)	superior temporal gyrus	3.29	–34	–38	20	–34	–36	20

Significant foci of activation showing a differential response to varying memory difficulty between patients ($n = 13$) and controls ($n = 18$). Abbreviations: Talairach = standard brain space as defined by Talairach and Tournoux (x, y, z) (Talairach and Tournoux, 1993); ICBM = standard brain space as defined by the International Consortium for Human Brain Mapping (x, y, z) (Mazziotta *et al.*, 1995); PFC, prefrontal cortex; STG, superior temporal gyrus; PAR, parietal cortex; CING, cingulate; HIPPO, hippocampal area; EX, extrastriate cortex; CER, cerebellum.

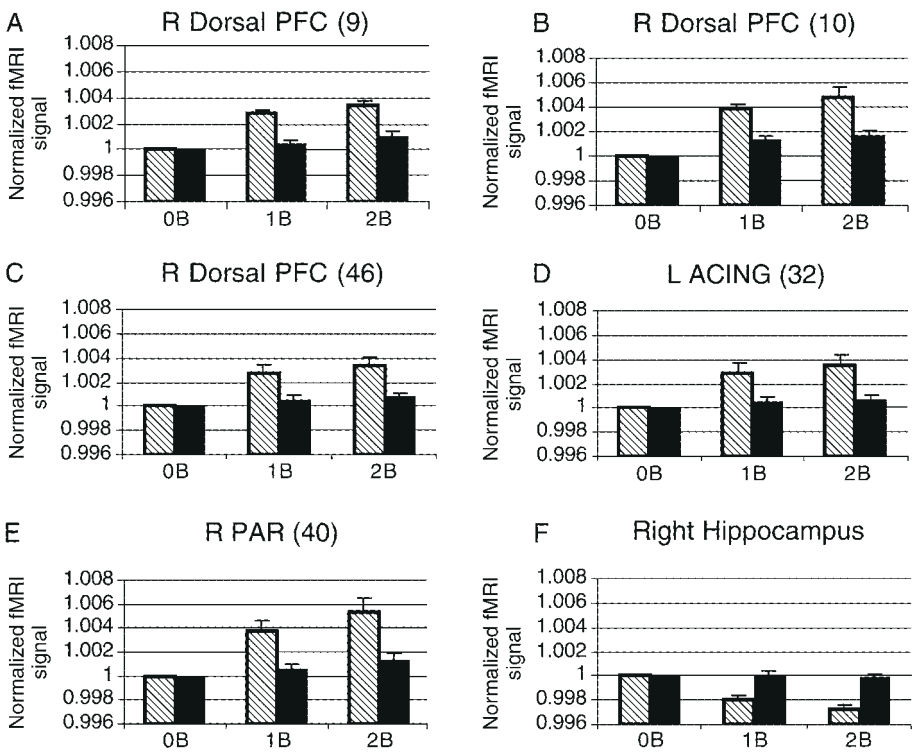

Figure 4. Exaggerated response to varying working memory difficulty in schizophrenic patients (II) Legend: The mean fMRI response for each group at five local maxima in which patients showed an exaggerated response to varying WM difficulty (*A–E*). Mean normalized fMRI signal (normalized to 0B signal) (±SEM) are presented for the 1B and 2B tasks for schizophrenic patients (light bars) and healthy comparison subjects (dark bars). (*F*) The mean response in right hippocampus wherein patients showed a decreased fMRI response to increasing WM difficulty.

at 1B and at 2B (Fig. 6) [r threshold ≥ –0.7 (–0.47 to –0.93), n = 11 patients]. In other words, lesser neuronal integrity meant greater fMRI activation, and by inference greater dorsal PFC inefficiency. This relationship was not found in controls at any level of memory difficulty (data not shown). Furthermore, we found a distinction between the relationship of dorsal and

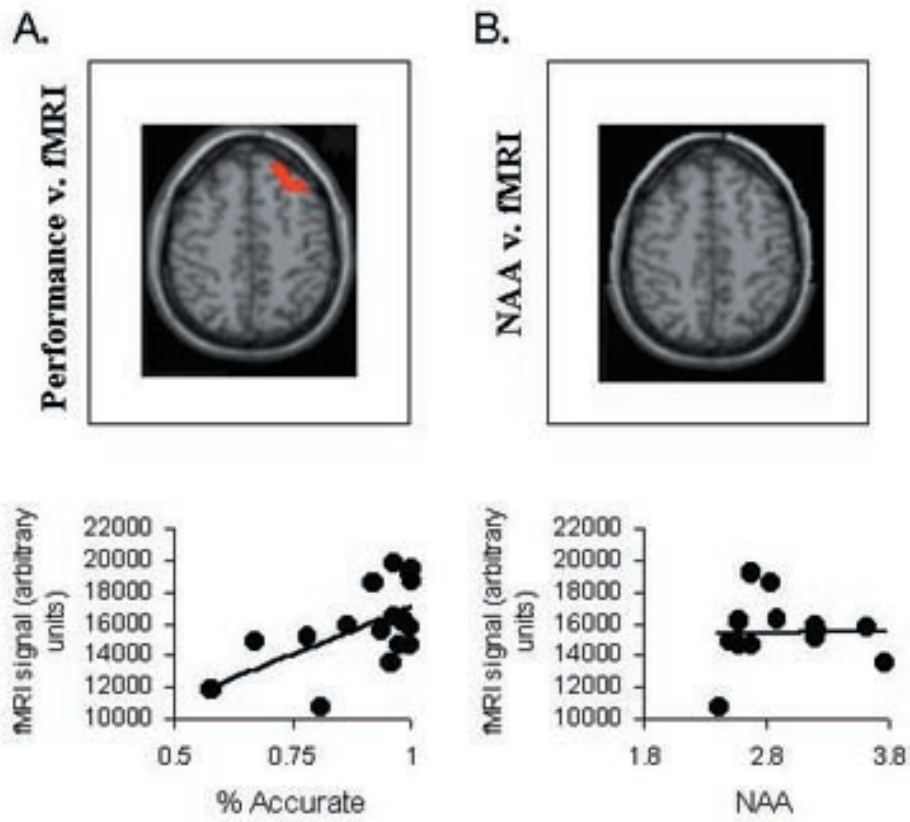

Figure 5. Performance, but not NAA, correlates with fMRI signal in dorsal PFC for controls. Correlation maps between mean fMRI signal and performance (% correct) (*A*) and right dorsal PFC NAA (*B*) at 2B for controls (right = right). Positive linear correlations are highlighted in red, while negative linear correlations are highlighted in blue. (*A*) In dorsal PFC, greater BOLD fMRI activation correlated with greater accuracy in controls [*r* threshold ≥0.7 (95% confidence intervals 0.53–0.87), $n = 18$ controls] ($z = +28$). This relationship is illustrated graphically below image. (*B*) In right dorsal PFC, we found no correlation between fMRI signal and right dorsal PFC NAA/CRE at 2B for controls (presented graphically below image).

ventral PFC NAA measures to fMRI activation. Ventral PFC NAA measures were not predictive of BOLD fMRI activation in either group. Additionally, NAA measures in the other regions did not predict the fMRI response in either group (data not shown). That the relationship between measures of neuronal integrity and the fMRI response to WM difficulty is particular to dorsal PFC NAA further suggests that dorsal PFC neuronal pathology may be the origin of the abnormal activation in these patients.

Discussion

Consistent with earlier neuropsychological studies, we found that schizophrenic patients had limited WM capacity compared to healthy subjects. Although patients activated the same distributed WM network, the schizophrenic response to increasing working memory difficulty was abnormal in dorsal PFC, even when compared to healthy controls experiencing a more difficult version of the WM task. The salient characteristic of PFC dysfunction in schizophrenia in our paradigm was not that the PFC was relatively 'up' or 'down' in terms of activation when compared to healthy subjects — a theme that has dominated this literature for more than a decade (Ingvar and Franzen, 1974; Weinberger *et al.*, 1986, 1988; Williamson, 1987; Andreasen *et al.*, 1992; Berman *et al.*, 1993; Frith *et al.*, 1995; Gur and Gur, 1995; Callicott *et al.*, 1998a; Carter *et al.*, 1998a; Gracia Marco *et al.*, 1997; Spence *et al.*, 1998; Manoach *et al.*, 1999). Rather, the salient characteristic was an inefficient dynamic modulation of dorsal PFC neuronal activity. While several regions within a larger cortical network also showed abnormal dynamic responses to varying WM difficulty, the fMRI response in dorsal PFC (areas 9–10, 46) met additional criteria for a disease-dependent signature of PFC neuronal pathology.

First, at higher memory difficulties (1B and 2B) wherein patients showed diminished WM capacity, dorsal PFC was consistently hyper-responsive (Table 2). These results are similar to those of Manoach *et al.* who have reported hyper-frontality in left dorsal PFC for a group of schizophrenic subjects performing two levels of WM difficulty during the Sternberg task (Manoach *et al.*, 1999). While finding ventral PFC hypofrontality during a word serial position task, Stevens *et al.* found greater activation of ventral PFC during a tone serial position task (Stevens *et al.*, 1998). In addition, Curtis *et al.* found a greater power of response in the dorsal PFC of schizophrenic patients performing a covert semantic decision task (Curtis *et al.*, 1999). While this group interpreted their findings to reflect the fact that this task may not have been sufficiently difficult to generate hypofrontality (Bullmore *et al.*, 1999), their unexpected finding may have arisen because semantic decision involved greater involvement of dorsal 'executive' PFC and thus may be in accord with our findings in patients and the findings of Rypma and D'Esposito in healthy controls (Rypma and D'Esposito, 1999). Furthermore, while other putative WM nodes, such as locales within parietal cortex and anterior cingulate, showed a greater

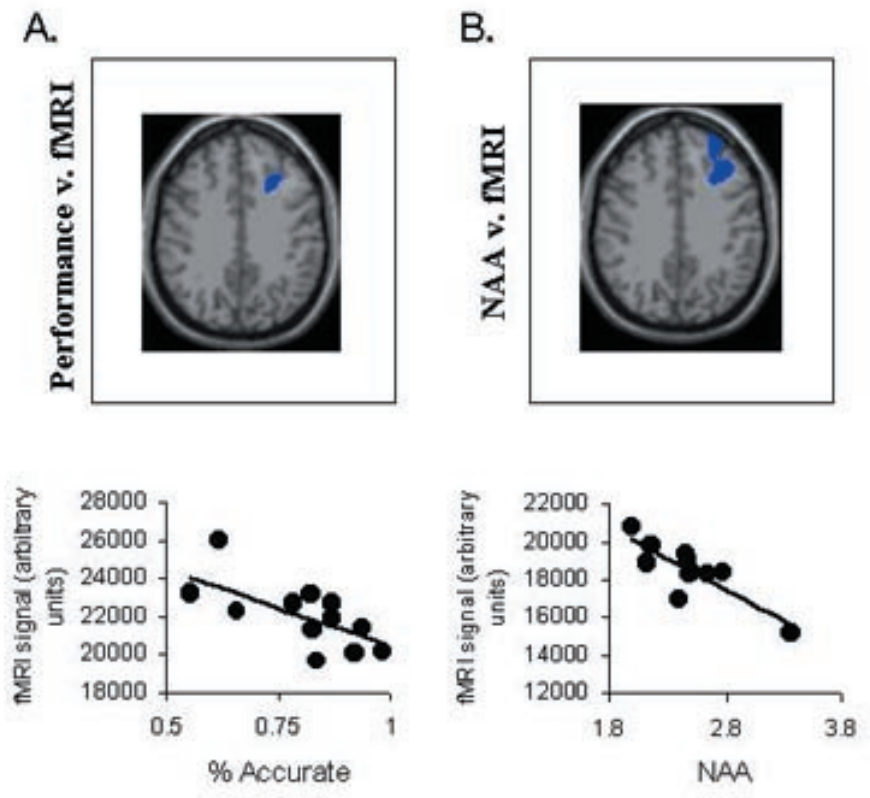

Figure 6. Performance and NAA correlate with fMRI signal in right dorsal PFC for patients Correlation maps between mean fMRI signal and performance (% correct) (*A*) and right dorsal PFC NAA (*B*) at 2B for patients (right = right). Positive linear correlations are highlighted in red, while negative linear correlations are highlighted in blue. (*A*) In dorsal PFC, greater BOLD fMRI activation correlated with lesser accuracy in patients [*r* threshold ≥–0.7 (–0.49 to –0.91), $n = 13$ patients] ($z = +16$). This relationship is illustrated graphically below image. Thus, patients who performed the worst showed the greatest exaggerated fMRI response in right dorsal PFC response. (*B*) In right dorsal PFC, fMRI signal was inversely correlated with right dorsal PFC NAA/CRE at 2B for patients [*r* threshold ≥–0.7 (–0.47 to –0.9), $n = 11$patients] (presented graphically below image). Those patients with the greatest PFC neuronal pathology (i.e. lowest NAA) showed the greatest exaggerated fMRI response in right dorsal PFC.

dynamic response to varying WM difficulty in our schizophrenic patients, we found additional locales within the same regions evincing a decreased dynamic response compared to controls – thus clouding their interpretation (Table 2).

Second, we found a functional distinction between the response of ventral and dorsal PFC, even though both were abnormal to some extent. In contrast to dorsal PFC, ventral PFC (BA 47) was hypo-responsive to varying memory difficulty. Furthermore, the linear correlation between WM accuracy and ventral PFC BOLD response was similar between patients and controls (i.e. both positive), whereas the correlation in dorsal PFC was opposite (i.e. negative in patients, positive in controls) (Figure 4). While dorsal PFC 'dysmodulation' correlated with WM performance (i.e. reaction time) in healthy controls (Rypma and D'Esposito, 1999), this relationship in healthy subjects may only hold true when accuracy is preserved. When accuracy was forced to decay (Goldberg *et al.*, 1998a; Callicott *et al.*, 1999), healthy controls no longer continued to invoke dorsal PFC resources and dorsal PFC activation fell. Thus, continued activation of dorsal PFC in the face of failing performance is probably another aberration of PFC function observed in our patients.

Still, if dorsal PFC inefficiency, like hypo-frontality in general, was merely a predictable and non-disease-dependent manifestation, dorsal PFC dysmodulation still met other criteria,

Table 3
Summary of distinctions between the fMRI response of ventral and dorsal PFC to varying WM difficulty in schizophrenic patients

fMRI response magnitude in patients	Greater than controls in 0B–1B–2B comparison	Greater than controls in 0B–2B–3B comparison	Predicted by ventral PFC neuronal pathology (NAA)	Predicted by dorsal PFC neuronal pathology (NAA)
Ventral PFC	–	–	no	no
Dorsal PFC	+	+	no	yes

This table summarizes the distinctions between the fMRI activation of ventral PFC and dorsal PFC in schizophrenic patients. +, increased dynamic response; ++, increased dynamic response meeting corrected significance in SPM96; –, decreased dynamic response (see Table 2, Fig. 4).

particularly the third and last. To wit, only the abnormal dynamic response of dorsal PFC (and not ventral PFC) was predicted by an independent measure of *in vivo* neuronal pathology (i.e. NAA measures) (Fig. 4). Thus, while one could argue other interpretations (e.g. differential engagement of the groups in our WM task) of the qualitatively different relationship between fMRI response and poor performance, we have concomitant and neurobiologically independent *in vivo* evidence (NAA data) that this inefficiency was predicted by the extent of PFC neuronal pathology in schizophrenia patients. Those with the greatest neuronal pathology (i.e. lowest NAA) generated the least efficient dorsal PFC response. The various differences in our data

between dorsal and ventral PFC are summarized in Table 3. That NAA measures did not predict the response in controls was presumably because it reflected a pathological condition of neuronal function that was qualitatively distinct in patients (Bertolino *et al.*, 2000 a,b).

Other brain regions within the larger cortical network responded abnormally to varying memory difficulty and may represent important responses for understanding WM dysfunction in schizophrenia (see below). However, as we set our standard for disease dependence on the ability of any given abnormal finding to correlate with other measures of pathology (e.g. NAA measures), we are cautious in describing these findings as disease-dependent manifestations of neuronal pathology in schizophrenia. For example, we found that the hippocampus was abnormally responsive to varying memory difficulty in these schizophrenic patients (Table 2). However, while this finding is in line with neuropathological, ^{1}H-MRS and fMRI data, suggesting that the hippocampus is also abnormal in schizophrenia (Weinberger, 1999), it was not predicted by hippocampal area NAA measures in these patients even though hippocampal NAA measures were abnormal. Thus, we are cautious in describing such responses as disease dependent based on a failure to meet other criteria. One noteworthy point of similarity between these findings and those in previous studies is the reciprocal but inverse relationship between dorsal PFC activation (here, greater activation) and hippocampal activation (here, decreased activation) (Heckers *et al.*, 1998). Again, both regions showed significant neuronal pathology as measured by ^{1}H-MRSI as compared to healthy subjects. A relationship between hippocampal pathology and abnormal dorsal PFC blood flow measures has been reported previously (Weinberger *et al.*, 1992). Collectively, this reciprocal relationship may suggest important interconnection between these regions that is highlighted in the schizophrenic brain under demanding task designs.

Thus, while both groups engaged a common WM network, abnormal physiological responses of dorsal PFC may be most germane to an understanding of limited WM capacity in schizophrenia. As alluded to above, a functional abnormality relatively particular to dorsal PFC concurs well with postmortem neuropathological (Selemon and Goldman-Rakic, 1999) and *in vivo* ^{1}H-MRS/^{1}H-MRSI data (Bertolino and Weinberger, 1999), implicating dorsal PFC neuronal pathology in this illness. Although various populations of neurons within and outside of frontal cortex are active during WM, a recent study of visuospatial short-term memory in the non-human primate suggests a critical role of dorsal PFC neurons in maintaining visuospatial accuracy within a wider memory network of regions (e.g. premotor frontal cortex and parietal cortex). By dissociating those neurons responding during the delay period in the service of maintaining accuracy from those apparently devoted to preparing the motor response associated with a spatial delayed matching-to-sample task, Sawaguchi and Yamane concluded that dorsal PFC neurons were critical for tuning visuospatial accuracy (Sawaguchi and Yamane, 1999). In a larger sense, greater dysfunction within the more dorsal executive areas of PFC (areas 9–10, 46) resonates with clinical experience and neuropsychological evidence implicating a general loss of executive functions in schizophrenia (Goldberg *et al.*, 1990; Seidman *et al.*, 1994; Fleming *et al.*, 1997; Nestor *et al.*, 1998; Mahurin *et al.*, 1998) and other conditions involving damage to dorsal PFC (McDowell *et al.*, 1998).

It is conceivable that conflicting findings in the schizophrenia literature may have been driven by variations in the experimental context, accounting for both hypo- and hyperfrontality. The brain lesion tradition in clinical neurology makes it conceptually appealing that hypofrontality would underlie decreased WM capacity and poor performance and reflect PFC neuronal dysfunction and pathology. However, hypofrontality, as a phenomenon in schizophrenia, is inexorably conflated with performance. Hyperfrontality, on the other hand, while less intuitively attributable to a 'lesion', is difficult to attribute to non-specific features of patient performance or engagement. For example, it would be difficult to argue that decreased engagement in our WM task would lead to greater PFC neuronal activity. Overall, both hypo- and hyperfunction of PFC may be different aspects or manifestations of the same underlying PFC neuronal pathology engaged in varying fashions.

A note of caution is in order when attempting to attribute to one primary node of dysfunction (here, dorsal PFC) behavioral or physiological abnormalities arising during the use of a task that evokes a wide cortical network. It remains uncertain as to whether these problems arise from inherent neuronal abnormalities primarily in dorsal PFC or as a result of abnormal feedforward or feedback input to PFC from neuronal pathology in other brain areas. Because WM relies on an integrated network, it is likely that there are significant interactions between PFC and other nodes within this network, including parietal cortex, anterior cingulate and the hippocampal area, all of which were found herein to have different responses to WM difficulty in patients as compared to healthy subjects. While these patients were not hypofrontal, they were less active than controls in other areas thought to have underlying neuronal pathology, such as the hippocampus and cerebellum (Weinberger *et al.*, 1980; Andreasen *et al.*, 1996). One could argue that these non-PFC regions may play important modulatory roles in WM either directly or indirectly via their reciprocal connectivity with PFC. Thus, it is conceivable that limited WM capacity in these patients arose as a result of neural pathology in these non-PFC regions that further interacted in some fashion with PFC to produce abnormal hyperresponsiveness to varying WM difficulty. For example, in a study reporting hypofrontality, under-activation of PFC was predicted by apparent pathology in the hippocampal formation (Weinberger *et al.*, 1992). However, that reduced NAA predicted physiological abnormalities only in dorsal PFC supports the contention that dorsal PFC neuronal pathology is a necessary, but perhaps not a sufficient, factor in WM dysfunction in schizophrenia.

Given the dynamic nature of the dysfunctional response to increasing WM difficulty, one of the major limitations of this study was that we have probably covered too small a portion of the difficulty–response curve. While we have previously demonstrated hypofrontality in schizophrenic patients well beyond capacity (Callicott *et al.*, 1998a), this study did not measure patient performance at this level (probably 3B in this sample). Performance accuracy was clearly the most important behavioral variable in our design. A long-running criticism of this approach to studying schizophrenia is that such fundamental differences in group performance may not arise simply from diagnosis, but may also arise from differences in attention, motivation or cooperation. The relatively high degree of accuracy exhibited by these patients in some ways mitigates the idea of reduced engagement in the task. Further, the idea of increased responsiveness to varying memory difficulty is counterintuitive to the idea that these patients were less attentive or motivated.

This experiment, like its forebears using positron emission tomography (PET), relied on a traditional block design. However, whereas PET measures brain activation over a few long temporal epochs (e.g. 60–90 s), fMRI relies on repeated and brief temporal collections (e.g. 20–30 s). This systematic difference in temporal 'windows' with which to capture differences in brain activation may also underlie conflicting reports of hypofrontality during PFC-demanding tasks in PET versus reports of hyperfrontality in similar conditions using fMRI. Because fMRI relies on repeated short imaging windows, it may be easier to capture consistent PFC activity than in the longer PET acquisition during which PFC activity would be relatively less uniform or more diluted by other processes, such as attending to the environment during PET scanning. Alternately, it may be the case that one finds PFC hyper-responsiveness at this early stage of task performance using fMRI (i.e. ≤20 seconds), and hypo-responsiveness at later stages of performance (i.e. ≥20–60 seconds of task performance) using PET. Thus, time on task may be a factor in determining relative hypo- or hyperfrontality. Such distinctions should be easy to test and remain to be explored in future experiments designed to elucidate the temporal determinants of these responses.

An important group difference was the presence of antipsychotic medication in the majority of our patient sample. In our earlier fMRI sample (Callicott *et al.*, 1998a), individual maps of medication-free patients were not distinct from patients receiving medication. While it is likely that past findings of hypofrontality could not solely be attributed to medication effects (Weinberger and Berman, 1996), the precise interaction between antipsychotics and evoked cortical activation remains unclear. However, the observation that these medicines often do not correct behavioral cognitive deficits, like WM, in schizophrenic patients should mitigate concerns that all functional findings are medication artifacts (Gur and Gur, 1995). Moreover, the correlation with NAA argues for a neuronal origin to these findings; as NAA concentrations do not appear to be reduced by neuroleptic medication (Bertolino *et al.*, 1998a). However, antipsychotic medications could have more subtle effects, such as altering the global blood flow, baseline blood flow or magnitude of any evoked brain activation responses measured indirectly via regional cerebral blood flow. More definitive answers to these specific concerns will have to wait for future samples, particularly those incorporating within-subject comparisons of medication-free to medicated states. Finally, our rigorous approach to data analysis entailed the exclusion of a number of schizophrenic subjects. This sample bias is unavoidable and may mean that our results apply to a select subgroup of patients, namely those able to remain motionless during a scanning session.

In conclusion, we found that schizophrenic patients had a combination of reduced cortical physiological efficiency and behavioral capacity. Dorsal PFC neuronal responses – putatively linked to more executive WM functions like information manipulation – may be relatively more impaired in schizophrenia than ventral PFC regions associated with maintenance of WM content. A non-behavioral, biological measure of PFC neuronal pathology revealed that these schizophrenic patients had specific reductions in dorsal PFC NAA measures that specifically predicted functional abnormalities in dorsal PFC. Thus, we infer that dorsal PFC neuronal pathology is a plausible cause of cortex-wide abnormal physiological responses in WM.

Notes

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