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ScienceDirect
Schizophrenia Research 89 (2007) 191–197
SCHIZOPHRENIA RESEARCH
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The relationship between performance and fMRI signal during working memory in patients with schizophrenia, unaffected co-twins, and control subjects

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Received 29 May 2006; received in revised form 9 August 2006; accepted 11 August 2006
Available online 5 October 2006

Abstract

While behavioral research shows working memory impairments in schizophrenics and their relatives, functional neuroimaging studies of patients and healthy controls show conflicting findings of hypo- and hyperactivation, possibly indicating different relationships between physiological activity and performance. In a between-subjects regression analysis of fMRI activation and performance, low performance was associated with relatively lower activation in patients than controls, while higher performance was associated with higher activation in patients than controls in DLPFC and parietal cortex, but not occipital cortex, with unaffected twins of schizophrenics being intermediate between the groups. Accordingly, this supports the idea that both hyper and hypoactivation may be possible along a continuum of behavioral performance in a way consistent with a neural inefficiency model. Further, this study offers preliminary evidence that the relationship between behavior and physiology in schizophrenia may be heritable.

Keywords: Schizophrenia; Working memory; fMRI; Twin; Genetic; Inefficiency

1. Introduction

Functional magnetic resonance imaging (fMRI) of working memory (WM) in schizophrenia has generated conflicting findings of hypofrontality (Barch et al., 2003; Cannon et al., 2005; Ragland et al., 1998; Stevens et al., 1998) and hyperfrontality (Callicott et al., 2000;

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doi:10.1016/j.schres.2006.08.016

Manoach et al., 2000, 1999). It has been proposed that patients' and controls' relationships between task difficulty and brain activation differ. Specifically, while both groups express an inverted-U shaped function relating fMRI signal to WM load, the patient curve is shifted, reflecting lower WM capacity. This difference may reconcile these discrepant findings (Callicott et al., 2003a; Manoach, 2003) and indicates that inefficiency may be characteristic of brain function in schizophrenia.

This model supports previous findings that fMRI activation in dorsolateral prefrontal cortex (DLPFC) increases with WM load in controls (Rypma et al., 1999) but is less consistent in schizophrenics (Callicott et al., 2000; Perlstein et al., 2001). However, assessing load interactions with brain activation has garnered mixed results (Callicott et al., 2000; Manoach et al., 2000, 1999), as has matching for performance (Cannon et al., 2005; Manoach et al., 2000, 1999; Perlstein et al., 2001; Thermenos et al., 2005). We posit that behavioral performance may more sensitively relate to variations in fMRI signal than load or task difficulty, as variance in behavior is lost when difficulty is categorized by load. We further propose that overall behavioral performance may be reflected in the degree of functional activation, and that relationships between these factors may differ between patients and controls.

Our goal was to investigate performance/activation interactions in chronic schizophrenic patients, unaffected co-twins of schizophrenics, and healthy twins during verbal WM. In particular, we assessed the DLPFC and posterior parietal cortex (PPC), with the occipital lobe (OCC) as a control region. We hypothesized that in a between-subjects analysis, patients would be relatively hyperactive at high performance levels (needing greater activation to perform easy task) and hypoactive with lower performance (demonstrating an inability to activate WM circuitry sufficiently for a difficult task). Because WM deficits (Cannon et al., 2000; Conklin et al., 2005; Shaw et al., 2002) and frontal lobe changes (Cannon et al., 2002) may be heritable, and fMRI findings in siblings of patients with schizophrenia are also inconsistent (Callicott et al., 2003b; Keshavan et al., 2002; Thermenos et al., 2004) we predicted that unaffected co-twins would show a similar physiologic-performance pattern to probands.

2. Methods and materials

2.1. Participants

Institutional review boards of the University of California, Los Angeles and the National Public Health Institute of Finland approved this study. Eight schizophrenic patients with an unaffected co-twin, 10 unaffected co-twins of schizophrenics [4 monozygotic (MZ), 6 dizygotic (DZ)], and 13 healthy twins participated (Table 1). This group included 7 intact pairs [4 discordant (2MZ/2DZ); 3 healthy (2MZ/1DZ)] and 17 subjects without their matched co-twin [4 schizophrenic, 6 co-twins (2MZ/4DZ), and 8 controls]. Participants were drawn from a cohort of Finnish twins born between 1940–1957 and gave informed consent. All subjects were assessed using standardized clinical and medical history measures (Cannon et al., 1998) including Structured Clinical Interview for DSM-IV (Spitzer et al., 1979) Patient or Non-Patient edition, Scale for Assessment of Positive Symptoms (SAPS; (Andreasen et al., 1990)) and Scale for Assessment of Negative Symptoms (SANS; (Andreasen, 1982)) which were given to any subjects with psychotic conditions, the Personality Disorders Examination (Loranger et al., 1985), and a medical-record coding form (Cannon et al., 1998). No unaffected co-twins or control subjects had any psychotic disorder or any cluster A personality disorder. However, two controls had histories of anxiety disorders (lifetime but not current social phobia and panic disorder, respectively), and one control and one proband had alcohol abuse. Subjects were excluded for poor or missing behavioral data, scanner artifacts, or excessive motion.

2.2. Behavioral task

We employed a modified Sternberg item recognition task (Sternberg, 1966). A target set of 3, 5, 7, or 9 yellow uppercase consonants was displayed for 2 s, followed by a 3-s fixation. A green uppercase probe then appeared for 3 s, followed by 1 s of fixation before the next trial.

Table 1
Subject demographics

	Probands	Unaffected co-twins	Healthy controls
n	8	10	13
Age (mean±SD)	50.5±5.1	51.9±5.1	50.3±4.4
Gender (males/females)[a]	5/3	7/3	6/7
Handedness (R/L)[b]	6/2	10/0	12/1
Socio-economic status[c]	6.66±1.15	7±1.73	6.7±.948
Age of onset (yrs)	26.9±6.3	–	–
Duration of Illness (yrs)	23.3±6.4	–	–

[a] Gender does not significantly differ across groups $c^2(2, n=31)=1.41, p>.05$.
[b] Handedness does not significantly differ across groups $c^2(2, n=31)=3.27, p>.05$.
[c] Rauhala scale, range 1–9 (Rauhala, 1970).

Subjects indicated whether the probe matched the target set. The task included 12 trials per load, which were clustered by load into two-trial long blocks; presentation order of the blocks was counterbalanced, but remained the same for all subjects.

2.3. Scanning parameters

Imaging was performed on a Siemens (Erlagen, Germany) 1.5-T Vision scanner in the University of Helsinki. A high-resolution T1 image for anatomical reference (TR/TE=720/14 ms, 24 axial slices, 256×256 matrix) and twenty-four contiguous AC-PC aligned 4 mm gradient echo EPI slices were acquired (TR/TE=3 s/64 ms, flip angle 90°, 64×64 matrix, FOV 256 mm). Stimuli were projected onto a screen and viewed through a head-coil mounted mirror. Accuracy and response time were recorded via button-box. The scanning battery included two other WM paradigms and one hemodynamic response task, which were counterbalanced across subjects; this task's functional run lasted 7 min and 12 s.

2.4. Image processing

Since the brains of the patients with schizophrenia are expected to be morphologically different from those of the control subjects, as well as from subjects who's brains have been used to create traditional standard space templates, rather than using a pre-existing standard space a group-average template brain was created out of the subjects included in the analysis using the Automated Image Registration (AIR) package (Woods et al., 1998). The purpose of using a study specific standard brain is to minimize the distortion of the functional data during spatial normalization and, in particular, to avoid creating group differences by causing relatively greater distortion in the patient group than in the control group. EPI Data were motion corrected, registered to the individual's T1, and then to the study specific standard brain using FSL (FMRIB's Software Library, (Jenkinson et al., 2002; Smith et al., 2004)).

Individual subject analyses were performed using FEAT (FMRI Expert Analysis Tool v5.4). Data were spatially smoothed (8 mm FWHM Gaussian Kernel) and high-pass filtered. In the individual first-level analyses, loads 5, 7 and 9 were modeled with load 3 as baseline. Results were fed into a second-level group analysis in which probands, co-twins, and controls were separately modeled so that variance was calculated for each group individually. The second-level design matrix was applied to all contrasts from the first-level analysis. Motion parameters were analyzed and found to not differ between groups.

Functional regions of interest (ROI's) were created in the space of the study-specific standard brain. Active regions were defined using activations from the all subjects all loads contrast to allow both groups to contribute to definition of the ROI. The *t*-statistic map for this contrast was thresholded at $T_{30}>2.042$(2 tailed, $p<.05$). From this thresholded map, clusters in the DLPFC, PPC, and OCC were identified using Brodmann's and anatomical landmarks. In each of these regions all contiguous voxels above the threshold were included in the ROI (see Fig. 1). The Featquery (fmrib.ox.ac.uk/fsl/feat5/featquery.html) program applied the inverse of the transformation matrix from individual to standard space that was generated during the initial registration to warp the ROI's back into each subject's individual space where the statistics were performed. The motion corrected, smoothed, and filtered data across each entire ROI were probed for their percent signal change from baseline (load 3). ROIs were moved into MNI space for regional localization (see Fig. 2 for coordinates).

2.5. Function-behavior analysis

To assess the relationship of performance and fMRI signal between subjects, ROI activation and performance data (percent correct) for each subject were collapsed across load. We performed a robust linear regression, predicting fMRI signal with performance as a factor using Stata (v8.1, Stata Corporation). Group differences (proband vs. co-twin vs. control) were examined using the interaction between the slopes of the relationship of performance and BOLD signal for the groups and tested for significance using a Wald test. To account for relatedness between co-twins, the pair IDs were clustered to adjust standard errors for intragroup correlation of twin pairs.

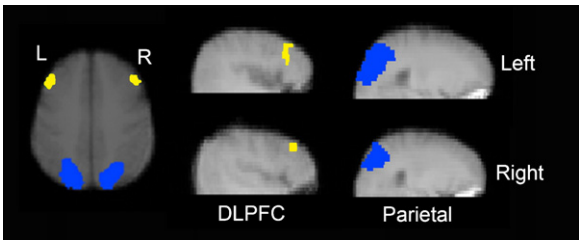

Fig. 1. Regions of interest.

3. Results

3.1. Behavioral data

All groups showed a decrease in accuracy and increase in reaction time as load increased, there were no group differences in the analysis by load. When performance data was collapsed across load a pattern in which probands had lower performance than cotwins who had lower performance than controls was observed (see Fig. 3). This pattern is generally consistent with previous work in which co-twins have shown intermediate performance

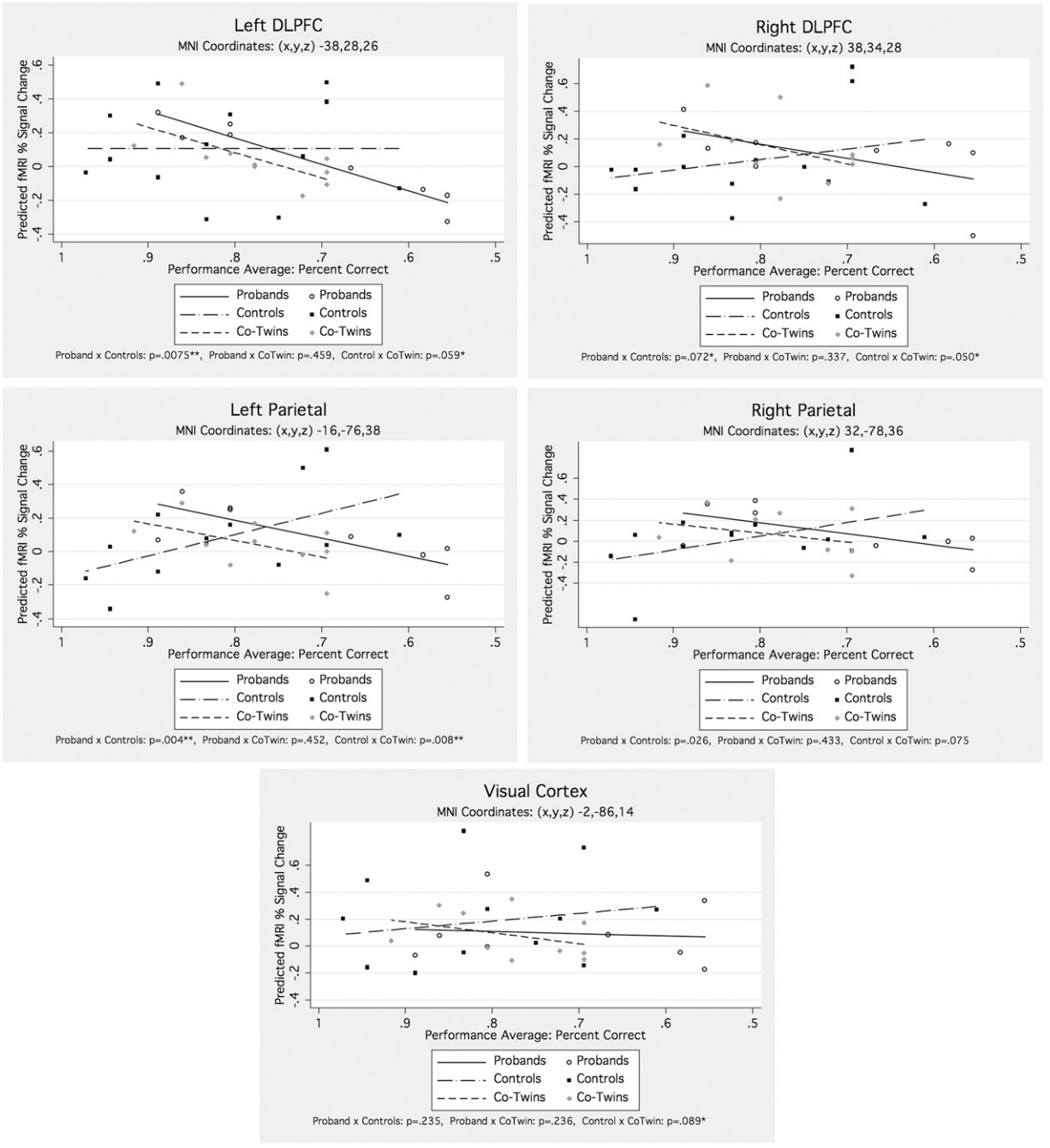

Fig. 2. Regression analysis predicting percent signal change with behavioral performance, between subjects, **indicates significance at $p > .01$ (corrected for multiple comparisons, $.05/5 = .01$), *indicates trend level significance.

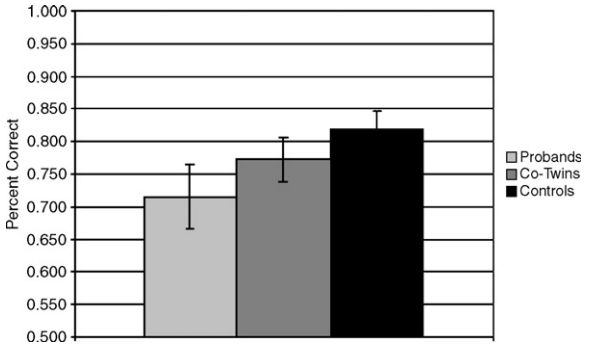

Fig. 3. Behavioral working memory performance.

(Glahn et al., 2003). A one-way ANOVA across all groups showed only trend level significance ($p = .062$, 1-tailed), however the difference between probands and control subjects was significant when assessed with a *t*-test ($p = .0476$, 1 tailed).

3.2. Functional imaging data

Given the small sample, MZ and DZ co-twin groups did not significantly differ, so were combined. There were no significant differences in the group × load whole brain voxelwise analysis or in an ROI analysis comparing activation within the ROIs across groups. In the ROI regression analysis the slope of the relationship between fMRI signal and behavior differed between probands and controls in the left DLPFC and left PPC, with trends in the right DLPFC and right PPC. Unaffected co-twins did not significantly differ from probands in any region examined. Unaffected co-twins did not differ from controls in left or right DLPFC or right parietal lobe, although they did differ in the left PPC. No group differences were found in the OCC control region (see Fig. 2).

4. Discussion

The finding that probands showed decreased BOLD activation relative to controls with decreasing performance in DLPFC and PPC, and increased relative activation with increasing performance, supports our hypothesis that the activation-performance relationship is disrupted in schizophrenia in a way consistent with an inefficiency model. Low performing patients were "hypoactive" relative to controls and high performing patients were "hyperactive". Previous work has categorized patients, with low performers demonstrating hypofrontality and higher performers hyperfrontality (Callicott et al., 2003a). We expand on this by examining a continuum of performance. We believe that while performance matching can provide a snapshot of activation differences at a specific performance level, it may be less informative than testing across a range of behavior. The finding that the effects are more significant on the left than the right supports the idea that the left hemisphere is more strongly associated with verbal processing and thus with performance on this verbal task.

It is noteworthy that the patterns observed in these data were linear, rather than the quadratic effects seen in within-subject investigations and that are hypothesized in the shifted inverted U model of inefficiency. The pattern seen here supports the idea that high performers are hyperactive and low performers hypoactive overall, which does not preclude the possibility that these subjects' activations might also change as their performance changes, in a way consistent with a double-U function, due to the fact that between-subjects analysis requires averaging across within-subjects variance and within subjects performance-activation curves. It is possible that in individual subjects, higher performing patients have an overall higher set point for the curve than higher performing controls, reflecting a more global inefficiency and lower performing patients have an overall lower set point reflecting an overall inability to activate. What this indicates is that in addition to investigations within subjects, future studies in many modalities should compare high and low performing patients with schizophrenia to assess whether there is some overall change in neural function above and beyond a shift in the averaged inverted-U curves.

The pattern of results for unaffected co-twins was intermediate between patients and controls, suggesting that the inefficiency pattern may be related to genetic rather than disease-specific factors. This is consistent with indications that DLPFC-related cognitive functions are disordered in unaffected relatives (Conklin et al., 2005; Egan et al., 2001), and that brain regions supporting WM are altered as well (Breier et al., 1992; Cannon et al., 2002). Further, previous fMRI studies in relatives of schizophrenics have been subject to the same hypo- (Keshavan et al., 2002) and hyper-activation (Callicott et al., 2003b; Thermenos et al., 2004) discrepancies as have case-control studies. While the analysis of the co-twins should be considered preliminary, given the small sample size, it potentially indicates that the differences in the relationship of performance and activation in co-twins may stem from the same alteration in the performance-activation relationship found in probands.

The fact that this pattern of activation was not observed in OCC indicates that the group differences are specific to WM circuitry and are task-related, they are not global activation differences. Additionally, as this task is sufficiently difficult to show a range of performance in

all groups, not just in patients, we were able to assess functional activation at many levels of performance within each group.

Our study did have some limitations. First, the sample size, which necessitated combining MZ and DZ co-twins for analysis. The small sample size also limits our conclusions about heritability, and future work addressing this in larger samples with matched twin pairs is necessary to fully address this issue. Secondly, analyzing individual loads (within-subjects) would allow fuller assessment of the functional/behavioral relationship and would allow the comparison of between and within subjects effects. Our study was also limited by the lack of a non-task baseline, which resulted in the lowest load being used as the baseline. While the use of a task-based baseline does circumvent some issues relating to subtraction, which may arise with a non-task baseline, future studies with resting baselines would also be informative. And finally, our patients had a relatively long duration of illness, and long history of medication. The question of whether this phenomena is also present in the early stages of the illness can be addressed by doing similar studies in recent onset patients.

Overall, these findings lend empirical support to the neural inefficiency model of working memory in schizophrenia, which has implications for the previously described hypo/hyperfrontality discrepancies in the literature. Further, this study can give preliminary evidence that neural processing changes observed in schizophrenics may be a heritable aspect of the disorder, and may be present in unaffected relatives even without a behavioral deficit, which may help inform our conceptualization of the nature and origin of WM deficits in schizophrenia.

Acknowledgements

Thanks to Lauren Ellman, Jacquie Horwitz, Vikas Rao, and David Shirinyan for help with data analysis, Russell Poldrack, Robert Bilder, and Joaquin Fuster for input on the project, Carl-Gustaf Standertskjold-Nordenstam, Ulla Mustonen and the participants. This work was supported in part by National Institutes of Mental Health Grant MH52857 to T.D.C. and National Research Service Award 1F31MH068111-01A2 to K.H.K.

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