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Re-evaluating Dorsolateral Prefrontal Cortex Activation During Working Memory in Schizophrenia

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Abstract

Previous neuroimaging studies of working memory (WM) in schizophrenia have generated conflicting findings of hypo- and hyper-frontality, discrepancies potentially driven by differences in task difficulty and/or performance. This study proposes and tests a new model of the performance-activation relationship in schizophrenia by combining changes by load with overall individual differences in performance. Fourteen patients with recent-onset schizophrenia and eighteen controls underwent functional magnetic resonance imaging while performing a parametric verbal WM task. Group level differences followed a linear “cross-over” pattern, such that in controls, activation in the dorsolateral prefrontal cortex (DLPFC) increased as performance decreased, while patients showed the opposite. Overall, low performing patients were hypoactive and high performing patients hyperactive relative to controls. However, patients and controls showed similar functions of activation by load in which activation rises with task difficulty but levels off or slightly decreases at higher loads. Moreover, across all loads and at their own WM capacity, higher performing patients showed greater DLPFC activation than controls, while lower performing patients activated least. This study establishes a novel framework for predicting the relationship between functional activation and WM performance by combining changes of activation by WM load occurring within each subject with the overall differences in activation associated with general WM performance. Essentially, increasing task difficulty correlates asymptotically with increasing activation in all subjects, but depending on their behavioral performance, patients show overall hyper-versus hypofrontality, a pattern potentially derived from individual differences in underlying cellular changes that may relate to levels of functional disability.

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Keywords

prefrontal cortex; magnetic resonance imaging; efficiency; task performance; memory; schizophrenia; brain; cognition

1. Introduction

Functional neuroimaging studies of working memory (WM) in schizophrenia have generated apparently conflicting findings of hypo- (e.g. (Barch et al. 2003; Cannon et al. 2005; Driesen et al. 2008; Ragland et al. 1998; Stevens et al. 1998)) and hyper-activation (Callicott et al. 2000; Manoach et al. 2000; Manoach et al. 1999) in the dorsolateral prefrontal cortex (DLPFC). One interpretation of this pattern combines the hypothesis of lower processing capacity in schizophrenia with an extrapolation of the Yerkes-Dodson law (Yerkes and Dodson 1908) to WM. In this model, the relationship of fMRI activation with WM load is represented by overlapping inverted U-curves, with the patient curve shifted to reflect lower capacity, thus providing points of both hyper- and hypo-frontality (Callicott et al. 2003; Manoach 2003) [see Figure 1.a]. Essentially, an individual's activation is likely to be low when task difficulty, in this case WM load, is low and fewer resources are needed and highest when task difficulty is at that individual's capacity and resource need is maximal. When task difficulty exceeds capacity, activation may decline (e.g., if effort diminishes, as in the inverted U model) or asymptote (e.g., if effort persists but at no further improvement, as in an inverted L).

However, the inverted U models are inherently most appropriate for describing variation in activation based on changes in task difficulty within individual subjects. While this is useful, there are also likely to be individual differences between subjects (e.g. behavioral performance differences) that also contribute to the effects we see on the group level. Although prior work has assessed groups of high and low performers, the relationship of these findings to existing models of WM in schizophrenia has not been discussed. For instance, in healthy control samples, low performers show increased activation compared to high performers (Rypma and D'Esposito 1999; Rypma and D'Esposito 2000; Tan et al. 2006). However in patients, decreased performance correlated with decreased DLPFC activation (Manoach et al. 1999), high performers activate more than low performers (Tan et al. 2006), and relative to similarly performing controls low performers are hypoactive and high performers are hyperactive (Callicott et al. 2003). Therefore, while a U may occur within subjects, across differently performing subjects an inverted-U seems less plausible. Instead, a linear rather than curvilinear function seems more likely, and moreover, the pattern may differ in patients and controls. That is, if the task is more difficult for them, generally lower performing healthy subjects with less cognitive capability may need greater neural resources than higher performers, a pattern confirmed in a sample of healthy subjects in which BOLD activation increased linearly with decreasing overall performance on a Sternberg-style WM task (Karlsgodt et al. 2007). However, the opposite pattern was observed in chronic schizophrenia patients, who also showed a linear performance-activation relationship, but it was in the opposite direction, such that BOLD activation decreased linearly with decreasing performance and high performing patients were hyperfrontal, and low performing patients hypofrontal, relative to similarly performing controls (Karlsgodt et al. 2007) (Fig 1b). This pattern may suggest that the variance we see in behavioral performance is not simply noise, but a systematic and explainable feature of the data. Accordingly, variations along a gradient of disrupted cellular connectivity may determine both the degree of possible brain activation and ability to perform a WM task. Patients with higher WM performance and less compromised cellular microcircuitry may be able to activate the WM circuitry more than patients with lower performance who have significantly compromised cellular microcircuitry thus resulting in group-level hyper and hypoactivation.

The above model for explaining the effects of individual variability in performance does not preclude the existence of an inverted curve function for activation (either U or asymptote) and load within a given subject. We propose that the subject's behavior determines their position on the linear pattern, setting the range within which their activation will vary as task difficulty changes. The range in which higher performing patients activate will have a higher center compared with higher performing controls, reflecting a need for greater activation to produce similar WM output. In contrast, the range for lower performing patients would have a lower center than lower performing controls. This reflects decreased ability to activate WM circuitry overall, while still showing task related relative changes across load, within their own lowered range. Combining activation differences both based on individual variation and on task related changes results in a multi-level model (Figure 1c), in which a series of within-subject inverted curves are placed along the linear gradient of between-subjects changes that are based on differences in overall performance.

To test this model we used a parametric Sternberg style verbal WM task. We first tested whether an inverted curve describes the within-subjects change in activation as load changes in groups of healthy controls and recent-onset patients. Second, we examined individual differences between subjects, in particular, the hypothesized relationship between subjects' overall performance and overall activation. Although both are important, no prior study has simultaneously addressed predictions about the overall task independent differences based on individual subject characteristics and the task imposed activation changes seen within subjects. Finally, we tested activation at capacity, which is differently predicted by the multilevel model (1c) and the double inverted-U model (1a). The double-U predicts equal activation when different groups are measured at capacity. The multilevel model predicts differences at capacity based on the interaction between diagnostic status and performance. By testing this directly we were able to see if either model better predicts group differences. These analyses focus on the DLPFC because it has the persistent cellular activity presumed to be the neural basis of WM (Fuster 1973), shows cytoarchitectural changes in schizophrenia (Selemon et al. 2003), and is where the inverted-U pattern has been most investigated (Callicott et al. 1999).

2. Materials and Methods

2.1 Participants

Fourteen volunteers with recent-onset schizophrenia and 18 healthy control volunteers (Table 1) gave written informed consent. Participants under 18 years completed written assent while a parent or legal guardian provided written consent. Patients with schizophrenia were recruited from the Aftercare Research Program and Adolescent Brain-Behavior Research Clinic (ABBRC) at UCLA. Inclusion criteria were: onset of psychosis within 2 years, and a DSM-IV diagnosis of schizophrenia or schizo affective disorder (depressive subtype) (First et al. 1997). Research participants are between 12–17 (ABBRC) or 18–45 years old (Aftercare); however, only participants aged 16–25 years were included. Community control subjects age-matched to participants with schizophrenia and no evidence of any major mental disorder (Structured Clinical Interview for DSM-IV (Spitzer et al. 1979)) were recruited via advertisement. Both patients and controls were excluded for known neurological disorders, diagnosis of substance abuse or dependence in the last 6 months, premorbid IQ lower than 70, and insufficient English fluency.

2.2 Cognitive Paradigm

We used a Sternberg-style item recognition task (Sternberg 1966). A target set of yellow uppercase consonants was displayed for 2s, followed by a 3s fixation cross. A green lowercase probe then appeared for 2s, followed by 2s of fixation before the next trial. Subjects indicated whether or not each probe matched any letters from the previous target set by pressing

designated buttons. WM load was manipulated by increasing set size (3, 5, 7 or 9 consonants). The task included 12 trials per load, for a total of 48 trials with 50% match trials. Trials were arranged into blocks of 2 trials from the same load. Six additional 18s fixation blocks were interspersed throughout, providing baseline. Trial randomization was optimized using Optimize Design 10 software (Wager and Nichols 2003). The experiment was run using E-Prime Software (Psychology Software Tools); images were displayed using goggles (Resonance Technologies, Inc), and responses collected via button box.

2.3 Functional Imaging Parameters

Scans were acquired on a 3T Siemens Allegra scanner at UCLA. A T2 weighted image with 1.5mm in-plane resolution was taken using a set of high-resolution EPI localizers (TR/TE 5000/33ms, 33 3-mm slices with 1mm gap, 128×128 matrix, 200mm FOV). To match any B0-related distortions, the high-resolution images had readout bandwidth along the phase encoding direction identical to that in the functional scans. Functional slices matched the AC-PC aligned slices in the T2 image, and utilized an echo planar (EPI) sequence (TR/TE 3000/45ms, 90 degree flip angle, 33 3mm slices). The task consisted of 180 scans, lasting 9 minutes.

2.4 Image Processing

A study-specific group averaged T2-weighted brain was created using the Automated Image Registration (AIR) package (Woods, 1998). This average brain was used as the common space to which all subjects were registered and in which group statistics were performed. This minimizes mis-registration of the functional data during spatial normalization and avoids causing relatively greater warping in the patient group than in the control group.

Functional analysis was performed using FSL (FMRIB's Software Library v3.3; Smith et al, 2004). Each BOLD image in the time series was registered (using a 3D co-registration, 6 parameter rigid-body) to the middle data point. Data were then registered, first the EPI to the subject's individual T2-weighted structural image, then the T2 to the study specific common brain (Jenkinson et al. 2002; Jenkinson and Smith 2001). Individual subject analyses employed FEAT (FMRI Expert Analysis Tool) using a 5mm (FWHM) Gaussian smoothing kernel and 72s high-pass filter. Time-series statistical analysis on each subject was carried out using FILM (FMRIB's Improved Linear Model) with local autocorrelation correction (Woolrich et al. 2001). Each load was modeled separately, and each trial was modeled in its entirety in a block design fashion. Motion parameters were entered as covariates in the analysis. A univariate General Linear Model was applied on a voxel-by-voxel basis so that each voxel's time course was individually fit to the resulting model, with local autocorrelation correction that was applied within tissue type to improve the estimation of temporal smoothness (Smith et al. 2004; Woolrich et al. 2001). Goodness-of-fit of each voxel was estimated, and the resulting parameter estimates indicated the degree to which the change in fMRI signal could be explained by each model.

The group analysis was carried out using FLAME (FMRIB's Local Analysis of Mixed Effects) (Behrens et al. 2003; Smith et al. 2004). Subjects with average translational motion greater than 3mm were excluded. Motion parameters did not differ between groups. Each subject's data, including the parameter and variance estimates for each contrast from the lower level analysis, was entered. To correct for multiple comparisons, resulting Z-statistic images were thresholded using clusters determined by $Z > 2.3$ and a (corrected) cluster significance threshold of $P = 0.01$ (Forman et al.; Friston et al.; Worsley et al.). Cluster p-values were determined using a spatial smoothness estimation implemented in Feat (Jenkinson and Smith 2001) (Forman et al. 1995) (Friston et al. 1994).

2.5 Region of Interest

Function regions of interest (ROI's) were defined in the study-specific average brain space using the all-subjects all-loads omnibus contrast. The t-statistic map for this contrast was thresholded at $T_{30} > 3.285$ (2 tailed, $p < .005$) and clusters in the DLPFC were identified using Brodmann's (areas 9 and 46) and anatomical landmarks. All contiguous voxels above the threshold were included in the ROI (see Figure 2E). The Featquery (fmrib.ox.ac.uk/fsl/feat5/featquery.html) program applied the inverse of the initial transformation matrix from individual to the average brain to warp the ROI's back into each subject's individual space for analysis. The motion corrected, smoothed, and filtered data across each entire ROI were probed for percent signal change from baseline.

2.6 Statistical Analyses

To assess behavioral performance, a repeated measures ANOVA was performed (SPSS, v13) with group (patient or control) as the between subjects factor, load as the within subjects repeated measures factor, and percent correct at each load as the dependent variable (Analysis I).

For the performance-activation analysis, a robust regression was performed (Stata 2003) with behavioral performance (across the entire task) predicting BOLD activation in left and right DLPFCs (each averaged across the entire task), covarying for age. The data for each regression were tested for outliers, and subjects with high studentized residuals (> 2) were excluded. For both left and right DLPFCs, one control subject had to be eliminated. Group differences were tested using the interaction between the slopes of the regression lines for each group, and tested for significance using a Wald test. (Analysis II).

In order to examine the effect of performance on changes in activation across load, we then divided patients at the median behavioral performance into high and low performers. Repeated measures ANOVAs were performed with group as the between subjects factor and load as the within-subjects repeated-measures factor for activation in each ROI (Analysis III).

Even within groups, the load best approximating each subject's capacity may still vary. To address this issue we calculated the WM capacity for each subject (Cowan 2001) at each load using the following formula where k =capacity, n =# items in the display, H =hit rate, CR =correct rejection rate:

$$k = n * (H + CR - 1) \quad (1)$$

The subject's capacity was set to the highest capacity among those calculated. We then compared ROI activation when the activation for each subject was taken from the load closest to their own capacity (Analysis IV). All analyses are 2-tailed unless otherwise indicated.

3. Results

3.1 Analysis I: Behavioral Performance

A repeated measures ANOVA showed a main effect of WM load [$F(3,90)=49.38$, $p < .001$] but no main effect of group [$F(1,30)=2.805$, $p=.104$] or load by group interaction [$F(3,90)=.660$, $p=.579$] (See Figure 2).

3.2 Analysis II: Overall Group Comparison

In the between-subjects linear regression analysis in left DLPFC, the overall model was significant [$F(4,25)=4.35$, $p=.0083$], and slopes estimating the behavior-activation relationship

for each group differed as shown by a test of the interaction ($p=.001$) such that controls increased activation with decreased performance, while patients showed the opposite. In the right DLPFC the overall model was significant [$F(4,25)=5.46$, $p=.0027$] but with only trend level differences between slopes for patients and controls ($p=.068$, n.s.). (See Figures 3a, 3b).

3.3 Analysis III: fMRI Analysis by Load

We divided the patient group into high and low performers at the median for overall performance (87.5% correct). Controls were not divided due to the relatively restricted range of performance in this young healthy sample. The three groups (low performing patients, high performing patients, and controls) showed similar patterns in BOLD signal by load, resembling the leftmost portion of an inverted-U shaped function in the left DLPFC. The right DLPFC is similar, although the high performing patients appear to differ, albeit non-significantly. In both hemispheres, the location of the curve on the y axis (BOLD activation) was shifted between groups indicating that the range of activation for each group differed, despite the similarly shaped curves (Figure 3b, 3d). In left DLPFC there was a significant main effect of load [$F(3, 87)=11.637$, $p<.001$] and of group [$F(2, 29)=5.64$, $p=.009$] but no load $\times$ group interaction [$F(6, 87)=.286$, $p=.954$]. In the right DLPFC there was a main effect of load [$F(3, 87)=13.868$, $p<.001$] but not of group [$F(2, 29)=.389$, $p=.681$], and there was no significant load $\times$ group interaction [$F(6, 87)=.1650$, $p=.143$].

3.4 Analysis IV: fMRI Analysis Adjusting for Capacity

In the capacity analysis (Equation 1), an univariate ANOVA of performance group and BOLD activation was significant in the left DLPFC [$F(2, 29)=6.432$, $p=.005$], but not right DLPFC [$F(2, 29)=.722$, $p=.494$]. Post-hoc t-tests in left DLPFC indicated that even when matched on WM capacity, high performing patients had higher activation than low performers [$t=-3.08$, $df=12$, $p=0.009$, 2-tailed] and than controls [$t=2.980$, $df=23$, $p=0.007$, 2-tailed], while low performing patients did not significantly differ from controls [$t=-.8$, $df=23$, $p=0.432$, 2-tailed] (Figure 4). In addition to the analysis at capacity, a one-way ANOVA was performed to test whether the absolute range of activation (maximum activation out of the four loads minus minimum activation) was the same for the groups. There was no significant difference in either DLPFC for the range in which the activation was changing (left: $F(2, 29)=.487$, $p=.619$; right: $F(2,29)=.141$, $p=.867$).

4. Discussion

These results support our proposed multi-level model combining within subjects changes by load with group level variability in performance, and provide novel information regarding the relationship between functional activation and behavioral performance in schizophrenia. Both patient and control groups express similar inverted-curved functions as WM load changes. However, the analysis of the performance-activation relationship across subjects, together with our previous findings, support the linear “cross-over model” in which higher overall performance equates with higher overall DLPFC activity in patients, with the opposite in controls. Here we show the same between-subjects cross-over pattern in the first episode, prior to long term effects of medication or disease process, as previously demonstrated among unaffected genetically high risk individuals (Karlsgodt et al. 2007). Together, these results indicate that this novel finding of an altered performance-activation relationship may be a core feature of WM function in schizophrenia.

Furthermore, when controlling for individual differences in WM capacity, high performing patients remained hyperactive compared to controls, while low performing patients were not, indicating that despite showing similar relative functions of change with load, the peaks of their inverted-curves differed. This supports the current model more than the previous double-

inverted-U model in which the only group difference is a leftward shift in the patients. This activation difference is not secondary to a difference in the overall height of the peaks of the inverted-curves between groups (Johnson et al. 2006), as we found no difference in the absolute range of activation changes. Essentially, the patient group showed normal within-subjects curve functions by load (as previously theoretically suggested (Callicott et al. 2003)), but with the curve shifted higher or lower based on WM performance.

Schizophrenia is a spectrum disorder, with a range of deficits and impairments. This is not only evident at the level of psychiatric symptoms, cognitive impairment has been correlated with neurophysiological measures such as D1 binding potential and fMRI activation (Abi-Dargham et al. 2002) (Karlsgodt et al. 2007; Manoach et al. 2000). The degree of impairment may thus relate to the degree of underlying neural change (e.g. decreased dendritic arborization or dysfunctional cellular microcircuitry). Low performing patients may have more severe changes, while the high performing patients are intermediate, such that the high performers have sufficient remaining circuitry to enable compensation, which is precluded in low performers. Thus, the degree of hyperfrontality as measured by fMRI may reflect the degree of ability to compensate and index underlying changes. Studies assessing structural, pathological, or neural signaling changes as related to cognitive performance differences would further inform this issue.

This study was limited by the sample size, although power was adequate to detect significant, hypothesized effects. Secondly, although the limited range of performance in controls precluded dividing them by performance, the distribution was continuous and the linear regression interaction analysis statistically supports the cross-over model, as does previously reported data [Karlsgodt et al, 2007; Figure 5] that includes a full range of control performance. Nevertheless, future studies with both low and high performing controls and first-episode patients would be informative. Further, although treatment duration was relatively brief and patients were relatively uniformly treated with atypical antipsychotics, studies of medication-naïve patients would confirm the independence of the observed differences from medication effects.

In conclusion, this work demonstrates that there is a fundamental difference in neural functioning during WM performance in schizophrenic patients with greater cognitive impairment. This pattern may have important clinical implications, as it may indicate that these groups require different approaches for both treatment and cognitive remediation.

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Figure 1.

Proposed model: 1a. Inverted-U shaped curve representing the hypothetical signal change in DLPFC as a response to increasing working memory load in patients with schizophrenia and controls (Callicott et al, 2003; Manoach, 2003), 1b Between-subjects crossover model (based on Karlsgodt, 2007), plotting individual differences in overall performance (averaged across the entire task) against individual differences in overall functional activation (averaged across the entire task), 1c Proposed Multi-level model. Each inverted curve shaped function represents the change in activation of an individual subject as load changes. The placement of the curves is determined by individual differences in performance, which influence the range of activation within which the subject changes. As a group, controls increase activation as performance decreases, while patients do the opposite. Independently of this, all subjects show similar functions of activation changes with load.

Figure 2.

Behavioral performance (percent correct $\pm$ standard error) on the verbal working memory task across memory load (number of letters presented). The patient group is divided at the median to constitute “low performing” and “high performing” subgroups.

Figure 3.

Between-subjects linear regression investigating the relationship in working memory performance (percent correct) and functional activation (percent change in BOLD signal $\pm$ standard error) in patient and control groups in left (A) and right (C) DLPFC. Within-subjects functional activation across working memory load in left (B) and right (D) DLPFC ROIs. All subject groups demonstrate similar functions, however high performing patients are hyperactive to controls while low performing patients are hypoactive. Functionally defined regions of interest in left and right DLPFC (E).

Figure 4.

Analysis of functional activation (percent change in BOLD signal $\pm$ standard error) in each group, calculated by pooling across the activation observed at each subjects individually calculated working memory capacity (Equation 1).

Figure 5.

DLPFC performance-activation data from the current first episode sample and previously analyzed chronic sample (Karlsgodt, 2007) demonstrating the replicability of the cross-over pattern in these two samples.

Table 1

Subject Demographics

	Patients	Controls
Age (years $\pm$ stdev) *	20.27 $\pm$ 2.53	20.43 $\pm$ 2.25
Gender (m/f) *	6/8	6/12
Years Education *	12.46 $\pm$ 2.69	13.41 $\pm$ 1.19
Estimated I.Q. **	111.87 $\pm$ 10.17	111.46 $\pm$ 9.29
Age of Onset	18.46 $\pm$ 3.50	
Antipsychotic Medication (typical/atypical)	0/14	

* Groups did not significantly differ on age [$t(30)=-.688$, $p=.497$], gender [$\chi^2=1.033$, $p=.310$], years of education [$t(29)=-1.261$, $p=.217$], or I.Q. [$t(24)=-.1075$, $p=.915$]

** IQ data was not available for 4 subjects (2 patients and 2 controls)

Table 2

Regions of Functional activation based on omnibus contrast of all subjects across all loads.

Region	MNI Coordinates	Max Z-score
Anterior Cingulate	-4, 6, 53	8.50
Left DLPFC	-40, 26, 25	5.37
Right DLPFC	44, 40, 22	5.46
Left Frontal Eye Field	-28, -5, 67	5.79
Right Frontal Eye Field	28, -1, 63	5.47
Left Thalamus	-10, -21, 3	5.31
Left Visual Cortex	-10, -81, 2	5.40
Right Visual Cortex	14, -79, 7	5.39
Left Parietal Lobe	-26, -60, 46	6.51
Right Parietal Lobe	30, -56, 50	5.44