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Reduced Frontoparietal Activity in Schizophrenia Is Linked to a Specific Deficit in Goal Maintenance: A Multisite Functional Imaging Study

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Patients with schizophrenia (SZ) previously demonstrated specific deficits in an executive function known as goal maintenance, associated with reduced middle frontal gyrus (MFG) activity. This study aimed to validate a new tool—the Dot Pattern Expectancy (DPX) task—developed to facilitate multisite imaging studies of goal maintenance deficits in SZ or other disorders. Additionally, it sought to arrive at recommendations for scan length for future studies using the DPX. Forty-seven SZ and 56 healthy controls (HC) performed the DPX in 3-Tesla functional magnetic resonance imaging (fMRI) scanners at 5 sites. Group differences in DPX-related activity were examined with whole brain voxelwise analyses. SZs showed the hypothesized specific performance deficits with as little as 1 block of data. Reduced activity in SZ compared with HC was observed in bilateral frontal pole/MFG, as well as left posterior parietal lobe. Efficiency analyses found significant group differences in activity using 18 minutes of scan data but not 12 minutes. Several behavioral and imaging findings from the goal maintenance literature were robustly replicated despite the use of different scanners at different sites. We did not replicate a previous correlation with disorganization symptoms among patients. Results were consistent with an executive/attention network dysfunction in the higher levels of a cascading executive system responsible for goal maintenance. Finally, efficiency analyses found that 18 minutes of scanning during the DPX task is sufficient to detect group differences with a similar sample size.

Key words: fMRI/GLM/cognitive/context processing/executive/DPX

Introduction

Cognitive deficits represent a debilitating and difficult to treat facet of schizophrenia (SZ), and they involve many aspects of cognition including memory, attention/concentration, and executive functioning.[1] Although these deficits remain largely unaffected by traditional psychotherapeutic and pharmacological interventions, recent initiatives in both these domains hold promise for effective treatments.[2,3] Therapeutic efforts depend on accurate and reliable measures of deficits in specific cognitive functions to chart treatment-related changes.[4] The Cognitive Neuroscience Test Reliability and Clinical applications for Serious mental illness (CNTRaCS) Consortium was organized to develop and evaluate novel cognitive neuroscience-based measures of cognitive deficits in SZ that tap specific brain-based mechanisms.[4,5]

In addition to the cognitive domains of visual integration[6] and relational encoding and retrieval,[7] CNTRaCS sought a valid measure for goal maintenance, which is the ability to retain and use relevant contextual information when pursuing a novel goal. For example, goal maintenance is required to overcome one's habitual route home from work given an errand that must be completed on the way. This requires more than remembering the errand itself; rather, it is keeping the context of the errand in mind to alter the overlearned habit. Deficits in goal maintenance can impede life functioning in multiple domains, including employment, education, socializing, and recreation because it is required to complete tasks that necessitate responses to be modified based on differing contexts. Specific deficits in goal maintenance have been observed in SZ[8,9] and their unaffected relatives.[10,11]

To measure goal maintenance, Cohen and Servan-Schreiber[9] modified the traditional AX-CPT paradigm by changing the expectancy of AX pairings. The Dot Pattern Expectancy (DPX) task further modified this paradigm by using dot patterns instead of letters, thereby manipulating

difficulty by varying the similarity of target and nontarget stimuli.[12] The DPX also addressed the issue that overlearned representation of letters might reduce the sensitivity of the letter-based expectancy AX-CPT. The DPX has been shown to reliably measure goal maintenance[8,13] and has been optimized for use with SZ by reducing the length of the task while maintaining its level of reliability.[14] Maximizing the efficiency and reliability of DPX also enhanced its treatment utility, as shorter measures are less cumbersome to administer and less prone to participant fatigue.

Previous studies demonstrated that healthy controls (HC) activated middle frontal gyrus (MFG) on trials of the expectancy AX task that required goal maintenance.[15,16] Activation differences have been observed in this region when comparing HC with SZ[15,17] and their unaffected relatives.[11] Regions within MFG have been theorized to instantiate premotor representations based on external contextual cues accompanying stimuli,[18] so hypoactivation in this region may indicate impairment in that ability. One previous report of DPX neuroimaging findings exists in HC,[19] which showed activation of the same brain regions when completing the DPX as when performing the expectancy AX. However, the DPX has never been used to examine brain activation in SZ.

Using tasks such as the DPX to examine cognition and brain activation changes to treatment response would be facilitated if the task could be used successfully across many sites. Early studies of multisite functional magnetic resonance imaging (fMRI)[20–22] found good reproducibility between sites, as did later multisite studies that included SZ.[23,24] Multisite imaging allows for greater sample sizes and more power to detect group differences and treatment effects. Thus, the current study involved 5 CNTRaCS sites and included standardized imaging protocols to reduce between-site differences.

The use of imaging tasks to study treatment changes is also facilitated by having short and efficient protocols. Thus, to produce a more efficient and reliable measure of goal maintenance for evaluating treatment success, we sought to quantify a minimum length of fMRI scan capable of detecting group differences in goal maintenance. This is a practical question for future studies, as shorter scans may reduce participant fatigue, lower per subject costs, and allow for larger sample sizes. Therefore, the aims of the present study were 3-fold. First, we wished to replicate the regional localization of specific goal maintenance deficits in SZ compared with HC using an optimized DPX paradigm. Second, we wished to determine whether this task could be successfully implemented in a multisite context. Third, we wished to establish a recommended scan length to observe activation differences in groups of this size.

Methods

Subjects

Data were collected across 5 CNTRaCS sites. A complete methodology for the current study can be found in the supplementary methods. A complete subject recruitment protocol has been previously published,[14] and the current sample has been previously described.[6,25] The final sample consisted of 103 subjects (56 HCs, 47 SZs). There were no significant differences between included and excluded controls or patients on demographic, behavioral, or symptom indices (Ps > .08). The final groups were demographically similar on age, and they did not differ on any measured demographic variable with the exception of education (table 1). Subject groups did not differ on average relative or absolute head movement after removing subjects with excessive movement (both Ps > .45).

DPX Task and Analysis

The DPX task has been described previously.[8,14] The task was performed in 4 blocks by each subject, with each trial consisting of a cue dot pattern followed by a probe dot pattern. One dot pattern was identified as a valid cue ("A" cue), and another as a valid probe ("X" probe). All other cues were invalid ("B" cues), and all other probes were invalid ("Y" probes). Besides the valid "AX" target trials, 3 other possible combinations of cues and probes ("AY," "BX," and "BY") made up 3 distinct nontarget trial types enabling the identification of a specific deficit in a subject's ability to maintain goal-relevant information throughout a trial. Each block of the DPX task consisted of 40 trials: 24 AX (60%), 6 AY (15%), 6 BX trials (15%), and 4 BY (10%).

For the DPX behavioral data, we employed 2 primary analyses. Groups were first compared using an independent samples t test on d′-context,[9] a measure of general impairment on the DPX task. To establish a specific deficit, we fit a mixed effects logistic regression within a hierarchical model. Accuracy data were predicted using a small number of variables, with the minimum being the "group" variable. Additional variables were added to the model, such as "trial type (ie, AX, AY, BX, BY)" and "CNTRaCS site." Each model was assessed using the Akaike Information Criterion (AIC) to determine the simplest model that predicted the data, as well as or better than any other. Once a model was chosen, main effects and interactions of the variables were evaluated with a particular emphasis on "BX" trial type and the comparison of "BX" and "AY" trials.

fMRI Data Acquisition and Preprocessing

Three CNTRaCS sites used Siemens Trio 3 Tesla scanners (Minnesota, Washington University, UC Davis), one site used a Siemens Allegra 3 Tesla scanner (Rutgers), and the fifth site employed a Phillips 3 Tesla scanner (MPRC). Scanning details can be found in the supplementary methods. The scan session included the collection of four, 180-volume scans during 4 blocks of the DPX task. Quality control "phantom" scans were also collected on each scanner at the time of each subject's data collection.

Preprocessing using FMRIB Software Library (FSL v. 4.1.8)[27] included motion correction,[28] brain extraction,[29]

Table 1. Demographic and Clinical Characteristics

	Group		
	Patients	Controls	Test
N	47	56	
Mean age (y)	35.6 (12.1)	34.8 (11.9)	$t(101) = 0.33$
% Male	74.5	75	$\chi^2(1) = 0.00$
% Caucasian	55.3	62.5	$\chi^2(1) = 0.29$
% Right-handed	85.1	83.9	$\chi^2(1) = 0.00$
Mean education (y)	13.9 (2.0)	15.3 (2.6)	$t(101) = -2.89$*
Premorbid functioning[a]	36.3 (9.6)	37.5 (10.6)	$t(99) = 0.58$
Mean parental education (y)	14.0 (2.5)	13.8 (2.7)	$t(92) = 0.33$
BPRS total	40.3 (10.1)	n/a	
Positive symptoms[b]	9.6 (5.3)	n/a	
Negative symptoms[c]	7.2 (2.3)	n/a	
Disorganization[d]	5.0 (1.7)	n/a	
Antipsychotic meds			
Typical/atypical/none	2/44/1	n/a	

Note: BPRS refers to the Brief Psychiatric Rating Scale. Parenthetical numbers following means represent SDs. Asterisks following test statistics represent $P < .05$.
[a]Wechsler Test of Adult Reading.[26]
[b]BPRS items 8, 9, 10, and 11.
[c]BPRS items 13, 16, 17, and 18.
[d]BPRS items 12, 14, 15, and 24.

prewhitening,[27] high-pass temporal filtering with sigma of 100 s; B_0 field unwarping, spatial smoothing with a 5 mm FWHM Gaussian kernel, and spatial normalization and linear registration[30] to the Montreal Neurological Institute (MNI) 152 standard brain. Subjects with poor data quality were removed from the analysis (see supplementary methods for details).

General Linear Model

Following preprocessing, functional data were analyzed with a general linear model approach using the fMRI Expert Analysis Tool (FEAT) within the FSL software library. The following events from correct trials were modeled for each subject: "A" Cues, "B" Cues, "AX" Probes, "AY" Probes, "BX" Probes, and "BY" Probes. Cue Errors and Probe Errors were also modeled, although they were not used in further analyses. Variation in the neural response was accounted for using the default FMRIB Linear Optimal Basis Set (FLOBS)[27] included with FSL.

Whole-brain analyses were performed at the group level in a voxelwise general linear model (GLM) analysis within FEAT. The primary contrast of interest at this group level was a comparison of SZ with HC on the lower level contrast of B Cue activation minus A Cue activation, although within-group analyses were also conducted to determine typical activation patterns for each group. Based on goal maintenance literature,[16,17,19,31–35] the contrast of B cues with A cues was chosen because B trials require the ability to maintain goal-relevant information to overcome the prepotent "target" response in the event of an X probe. Site membership, as well as estimates of the data smoothness, signal-to-fluctuation-noise ratio (SFNR), average relative movement, and average absolute movement were also included as explanatory variables in the analysis. Their inclusion was intended to assess the effect of, and control for cross-site differences. A threshold of $z > 3.09$ and whole-brain corrected cluster extent threshold of $P < .05$ were employed for all group-level tests.

Scan Length Analysis

Additionally, we analyzed the functional data in a stepwise fashion to determine how long a scan must be to detect group differences in brain activation patterns. Data were analyzed with 2 and 3 scans (12 and 18 min, respectively), and the results of these were compared with the full, 4-scan data analysis (24 min). Qualitative analysis of the results was used to indicate whether the effects seen in the full data analysis were present in the reduced data analyses. Additionally, quantitative analyses using the Dice coefficient[36] were conducted to measure the extent of overlap.

Results

Behavioral Results

To investigate sensitivity to context on the DPX, we calculated the signal-detection metric d′-context and compared HCs to SZs using an independent samples *t* test. Figure 1A shows that HCs had significantly higher d′-context scores ($M = 3.38$, SD = 0.77) than SZs did ($M = 2.80$, SD = 0.97; $t(86.99) = 3.30$, $P = .001$). The mixed-effects logistic regression included group and trial type as fixed explanatory variables and subject as a random variable. As displayed

in figure 1B, the interaction of group and trial type showed that compared with AY trials, HCs were significantly more accurate on BX trials than SZs ($z = -3.16$, $P = .002$).

To evaluate the association between psychiatric symptoms and performance on the DPX, we performed correlation tests between d′-context scores and BPRS positive ($M = 9.6$, SD = 5.3), negative ($M = 7.2$, SD = 2.3), and disorganization ($M = 4.9$, SD = 1.7) subscale scores, as well as total BPRS scores ($M = 40.3$, SD = 10.1) for SZs. No significant correlations were observed in this sample (all tests: $|r| < .19$, $P > .21$).

Behavioral Efficiency Analysis Results

The mixed effects logistic regression model used with the whole dataset was also applied in a stepwise manner with 1, 2, and 3 blocks of the DPX behavioral data. As illustrated in figure 2, the significant group by trial-type effect (BX compared with AY trials) was present regardless of the number of blocks used (1 block: $z = -3.8$, $P < .001$; 2 blocks: $z = -3.8$, $P < .001$; 3 blocks: $z = -3.4$, $P < .001$; 4 blocks: $z = -3.2$, $P < .002$).

fMRI Results

The fMRI analyses indicated there were no significant effects of site as measured by group level F tests of contrasts including CNTRaCS site as an explanatory variable. Additionally, no regions showed significant activation associated with SFNR, smoothness, and relative or absolute movement estimates.

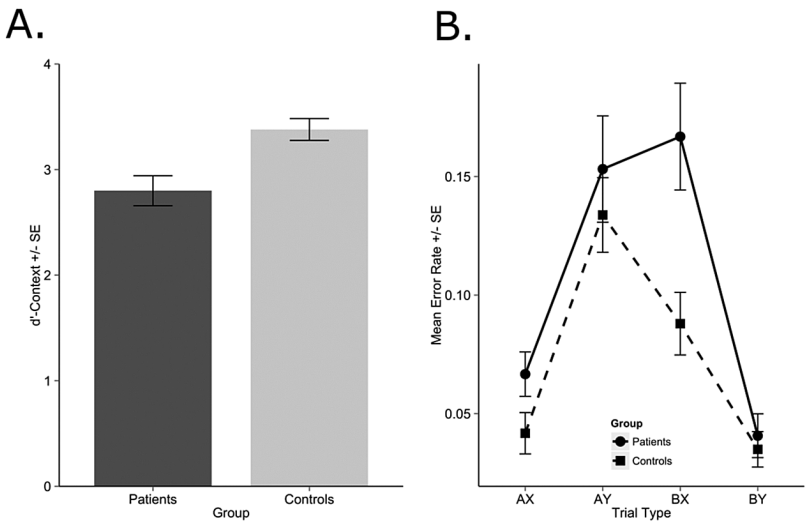

Fig. 1. Dot Pattern Expectancy (DPX) behavioral results. A. d′-context scores on the DPX task. B. Error rates separated by group, trial type. Error bars represent standard error of the mean.

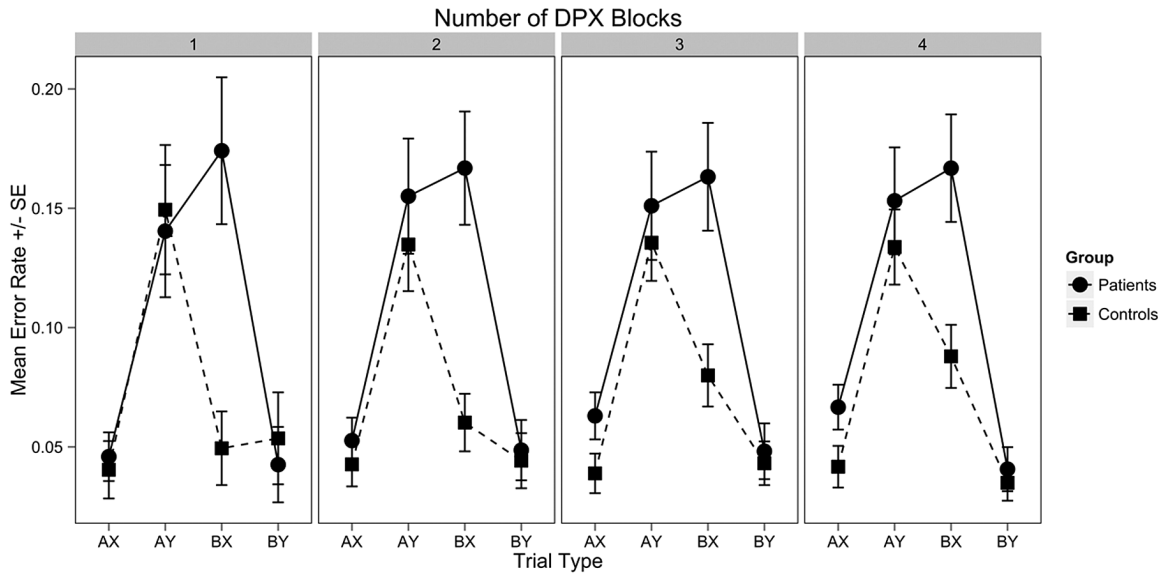

Fig. 2. Behavioral efficiency analysis. Error rates on the Dot Pattern Expectancy (DPX) task calculated from 4 amounts of data. The first figure represents only the first block (40 trials) of data, the second represents the first and second blocks (80 trials), etc.

The exploratory whole-brain analyses yielded significant differences in activation in the contrast of "B" cues with "A" cues. SZ displayed activation in left MFG and bilateral lateral occipital lobes, whereas HC activated in various regions of the cortex (peak in right lateral occipital lobe). When comparing groups, HC activated more compared to SZ in right MFG/frontal pole, left posterior parietal lobe, and left MFG/frontal pole, as displayed in figure 3. No significant correlations were observed between activation and BPRS subscale scores (all tests: $|r| < .21$, $P > .16$). Full statistical results are presented in supplementary table S1.

fMRI Efficiency Analysis

In an effort to determine the minimum necessary scan length to detect experimental effects in groups of this size on the DPX task, we conducted a series of stepwise analyses. In the "B" cues minus "A" cues contrast (illustrated in figure 4 and supplementary figure S1), the results showed remarkable consistency across all 3 analysis conditions (Dice coefficients of 0.72, 0.73, and 0.89). However, in the HC > SZ contrast illustrated in supplementary figure S2, there were more varied results. There were no significant group differences in the 12-minute analysis. In the 18-minute analysis, there was some overlap in group differences in activation in the left frontal lobe with the 24-minute analysis; however, the 18-minute results included left parietal activation not seen in the 24-minute analysis (Dice coefficient of 0.40).

To rule out the possibility that the efficiency results were driven by changes as the study progressed as opposed to the amount of data in the analysis, we performed a sliding window analysis. Specifically, we analyzed 2 blocks at a time according to the following chunks: first and second, second and third, third and fourth. Again, the significant activation associated with the "B" cues greater than "A" cues contrast retained its consistency and had Dice coefficients greater than .78 among them. The maps of HC and SZ activation to this contrast are presented in supplementary figure S3.

Discussion

The DPX task was previously established as a reliable measure of goal maintenance that can discern specific deficits in SZ compared with HC.[8,13,14] The current study is the first to employ fMRI and the DPX to determine the neural underpinnings of goal maintenance deficits in SZ compared with HC and was able to do so across 5 sites with different scanners. The study replicated previous behavioral findings[17] of a specific deficit in goal maintenance in SZ compared with HC and found the deficit to be consistent across blocks. The study also

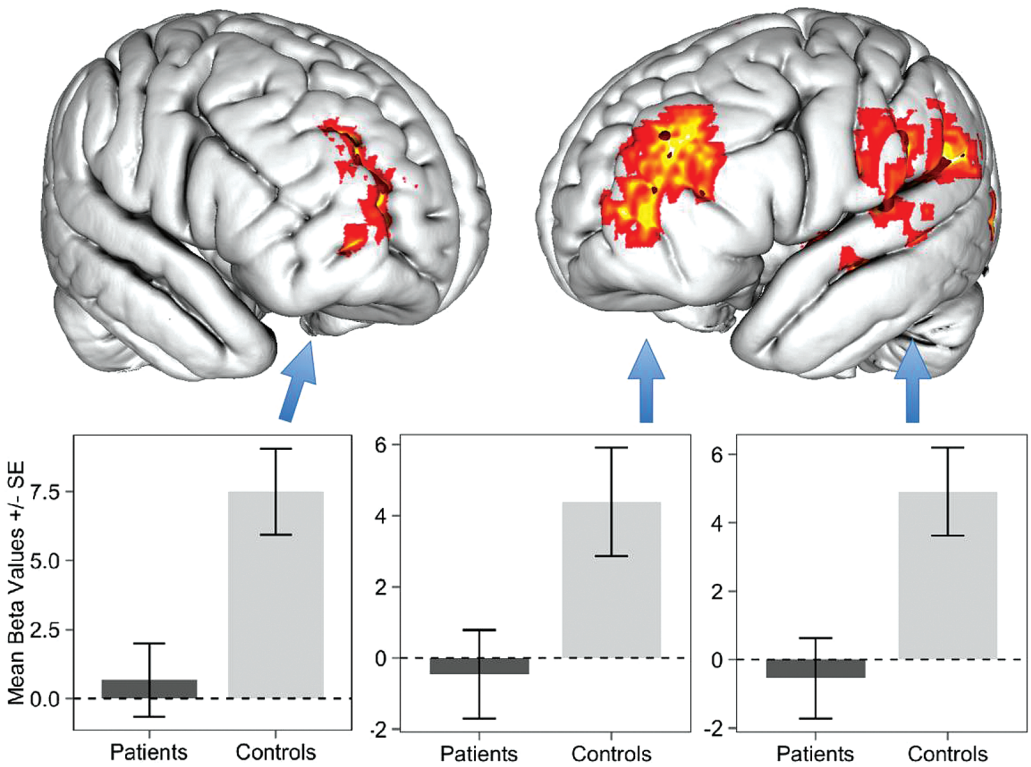

Fig. 3. Whole brain functional magnetic resonance imaging (fMRI) GLM results. Beta values represent B Cues – A Cues contrast. Regions with greater activation in healthy controls (HC) than schizophrenia (SZ; 3 clusters). Cluster 1 had a peak voxel Z score of 4.28, volume = 11 056 mm^3, and MNI coordinates (x, y, z) of 26, 54, 14. Cluster 2 had a peak voxel Z score of 4.43, volume = 30 664 mm^3, and coordinates of −40, 4, 12. Cluster 3 had a peak voxel Z score of 4.31, volume = 23 408 mm^3, and coordinates of −50, −40, 22.

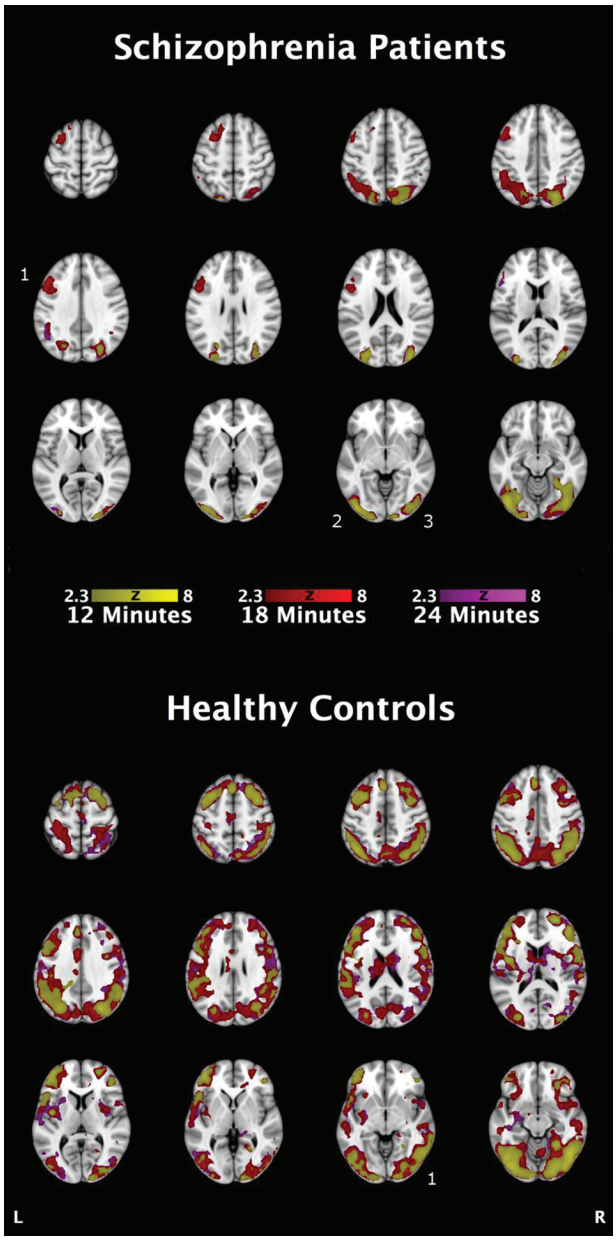

Fig. 4. Functional magnetic resonance imaging (fMRI) efficiency analysis, B Cues – A Cues. Top portion displays schizophrenia (SZ) activation (3 clusters). Cluster 1 had a peak voxel Z score of 4.39, volume = 10 152 mm^3, and MNI coordinates (x, y, z) of −50, 12, 42. Cluster 2 had a peak voxel Z score of 6.09, volume = 39 408 mm^3, and coordinates of −44, −82, −10. Cluster 3 had a peak voxel Z score of 5.91, volume = 48 856 mm^3, and coordinates of 38, −76, −16. The bottom displays healthy controls (HC) activation (1 cluster). That cluster had a peak voxel Z score of 6.78, volume = 495 912 mm^3, and coordinates of 46, −66, −14. The scan lengths that define the color of activation are cumulative, such that 18-minute data includes 12-minute data, and 24-minute data includes the previous 2.

replicated the findings from previous research with drug-naïve patients performing the expectancy AX task[17] who showed reduced activity in middle frontal cortex during goal maintenance. The current study showed lower activity in SZ compared with HC in an executive/attention network consisting of bilateral frontal pole/MFG, as well as left posterior parietal lobe. Finally, a recommended scan length was estimated for future studies employing samples of a comparable size.

In terms of behavior, SZ demonstrated the hypothesized specific deficit in goal maintenance previously observed on the DPX[8,14] and the expectancy AX.[9,10,17] This group difference was first observed after only 6 minutes (40 trials) and it remained throughout the administration (24 min; 160 trials total). This result suggests the DPX is sufficiently sensitive for efficient studies of goal maintenance in this population. Further, the analysis suggests this is not merely the result of differential effects of learning or fatigue, allowing us to examine the efficiency of the imaging analysis with knowledge that the behavioral effect was consistent over time. For reference, a previous imaging study of expectancy AX in SZ patients[17] had a task duration of 40 minutes as compared to 24 minutes for the longest analyses conducted in the current study.

FMRI analyses showed that HC had larger activation differences between "B" cues and "A" cues compared with SZ in bilateral MFG. These results agree with previous literature with regard to the MFG's importance in successfully utilizing goal maintenance and SZs' deficits in that region. Hypofrontality in left[16] and right[17,37] MFG has been reported in SZ during the performance of the expectancy AX task.

In addition to group differences in bilateral MFG, differences in superior/posterior parietal lobes were also detected. There are several possible mechanisms that could lead to the increased parietal activation during B cues compared with A cues. The dorsal visual stream has been associated with processing spatial relationships (including dot patterns[38]), and therefore HC's increased activation to B cues may reflect increased processing related to identifying or categorizing the group of "B" patterns, that are less familiar, compared to patients. These regions are also associated with visuomotor control,[39] and an alternative explanation is that B cue-related activity may reflect the preparation needed to inhibit a prepotent response, activity that is reduced in SZ. A third explanation, which is not entirely distinct, is that this difference in posterior parietal activation reflects its role in a more general executive functioning network.[33,40] This region's covariation with dorsolateral prefrontal cortex reflects the demands for the representation and maintenance of contextual goals. The relative contributions of visual cognitive, response preparation, and goal maintenance functions to the parietal activation observed during the DPX are in need of further clarification. Together with MFG, these regions are consistent with a visuospatial reasoning and attentional control network.[41,42] This network is thought to be integral to top-down control and managing responses given changing demands. Left MFG and posterior parietal cortex compose an executive network has been associated with language tasks, as well

as working and explicit memory tasks. SZ have demonstrated disrupted functional[43] and white matter connectivity[44] in this network, and these changes were associated with deficits in working memory and performance IQ, respectively. Functional dysconnectivity in a frontoparietal network has previously been observed in SZ and their healthy first-degree relatives while performing the expectancy AX task.[45] Although the present study does not identify a network per se, it does implicate the same regions as being deficiently activated by SZ.

We also observed group differences in bilateral frontal pole, a region that has been shown to underpin the maintenance, monitoring, and processing of subgoals during a working memory task.[46,47] The frontal pole is theorized to perform this action as one facet of a cascading executive system whereby information from the environment provides contextual cues that are interpreted and acted upon to achieve some goal.[48]

The results observed in the present study were robust to site effects. No significant effects of site were observed in the fMRI analyses. This finding highlights the practicality of combining imaging data from multiple sites, thereby allowing for larger sample sizes in fMRI patient studies.

The efficiency analyses undertaken to establish a recommended scan length for future fMRI studies of the DPX task with similar sample sizes found that 18 minutes of scanning is required to observe group differences. However, the within-group task activation patterns seen in the full 24 minutes could be observed almost undiminished in half that time. It was further determined that these effects are unlikely due to changes in the scanning session over time, as there were few if any differences among a set of 3 sliding window analyses employing 2 blocks of data each.

Limitations

Previous research[17,34] demonstrated an association between BOLD activation in dlPFC/MFG and disorganization symptoms in SZ, but no such association was observed in the current study. However, other studies of the AX-CPT in SZ either did not observe a correlation between dlPFC activity and disorganization symptoms[16,35,49] or did not report any such correlations,[15,37,50,51] and this generally tracks with a less extensive assessment of disorganization symptoms as used in the current study.

Conclusions and Future Directions

The present study, the first imaging study of the DPX task in SZ, provides support for the task as a cross-site probe of goal maintenance-related activity of the MFG and other related executive control regions. It replicated previous studies showing a specific deficit in goal maintenance in SZ. The imaging analyses replicated previous findings of MFG hypoactivation and also found significantly less parietal activation in addition to frontal regions when comparing SZ with HC on context-intensive trials of the DPX task. This was also a multisite study that incorporated data from 5 sites and different scanners and found no significant effects of site in the imaging analyses. The behavioral and imaging efficiency analyses showed that the DPX is an efficient tool for assessing goal maintenance ability in imaging studies. Of interest for future research are questions about the reliability of the BOLD activations and group differences observed in the current study, as well as whether there are functional connectivity differences that may explain performance on the DPX task. Also of import is whether there is plasticity in the regions or networks that underlie goal maintenance and whether such regions and networks may act as targets for training or pharmacological treatment in the future. Treatments such as cognitive remediation[52] or cognitive enhancing medication[53] might be capable of ameliorating impaired network activity underlying goal maintenance deficits in SZ, which could then improve goal maintenance ability and functional outcomes. We hope this work is useful in future endeavors to answer those questions.

Supplementary Material

Supplementary material is available at http://schizophreniabulletin.oxfordjournals.org.

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