

Neural Correlates of Prospective Memory in Individuals With Schizotypal Personality Features

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Objective: Prospective memory (PM) refers to the ability to remember to perform actions in the future. Schizophrenia spectrum disorders show impairments in PM but neural correlates of these impairments remain unclear. The present study aimed to examine brain activation during PM to identify impairments in individuals with schizotypal personality features. **Method:** Nineteen participants with schizotypal features and 22 healthy controls participated in a functional MRI experiment while performing a PM task. **Results:** Results showed that the prefrontal cortex (including Brodmann Area [BA] 10), middle temporal gyrus, and precuneus were activated when performing the PM task compared with baseline. The schizotypal and control groups did not differ in behavioral PM performance. However, participants with schizotypal features showed decreased activations in the inferior and medial frontal lobes (BA 45, and 8). **Conclusions:** These results confirmed that the PM network involves prefrontal cortex, including BA 10. The lower activation in prefrontal cortex of individuals with schizotypal features when performing a PM task indicates brain activation abnormality. Notably, this abnormality may occur in the absence of any behavioral manifestation. Our findings support the hypothesis of frontal lobe involvement in PM deficits observed in individuals with schizotypal features.

Keywords: prospective memory, schizotypal personality feature, functional imaging

This article was published Online First November 11, 2013.

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This study was supported by grants from the National Science Foundation of China (81088001, 91132701, and 30900403), the National Key Basic Research Program of China (973 Program) (2012CB720704), Youth Innovation Promotion Association Funding of Chinese Academy of Sciences (Y1CX131003), the Young Investigator Scientific Fund of Institute of Psychology, Chinese Academy of Sciences (O9CX073007), Key Laboratory of Mental Health, Institute of Psychology, Chinese Academy of Sciences, the Knowledge Innovation Project of the Chinese Academy of Sciences (KSCX2-EW-J-8), and a grant from the initiation fund of the CAS/SAFEA International Partnership Programme for Creative Research Team (Y2CX131003), Endeavor Fellowship of Australian government, and the Smart Futures Fund (QLD), National and International Research Alliances Programme.

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Prospective memory (PM) refers to the ability to remember to perform actions at a particular moment in the future (Ellis, 1996). PM is critical for many daily activities such as remembering to pay utility bills on time or switching off the gas after cooking. Categorized by the cues that trigger the actions, PM can be divided into three types: event-, time-, and activity-based (Kvavilashvili & Ellis, 1996). Event-based PM refers to executing an intended action when an overt cue appears. Time-based PM refers to executing an intended action at a particular time. Activity-based PM refers to executing an intended action at the completion of an activity. Among its roles in daily life, PM is important in medication adherence (Zogg, Woods, Saucedo, Wiebe, & Simoni, 2012).

Prospective Memory in Schizophrenia Spectrum

Schizophrenia is a serious, worldwide disorder that affects about 1% of the general population and causes much social and economic burden (Shastri, 2002). It is no longer considered a single entity but a spectrum of disorders including high-risk individuals prone for psychosis such as schizotypal personality disorders (Cadenhead, Perry, Shafer, & Braff, 1999). Schizophrenia spectrum disorders are characterized by social dysfunction and cognitive impairment (Heinrichs & Zakzanis, 1998; McCleery et al., 2012; Raine, 2006). Schizophrenia spectrum disorders also have genetic causes reflected by different degrees of proneness in patients' first-degree relatives (Gottesman & Shields, 1973; Greenwood et al., 2007).

PM deficits have been found in patients with schizophrenia at different stages of the illness, including both early and chronic stages (Chan et al., 2008; Elvevåg, Maylor, & Gilbert, 2003; Henry, Rendell, Kliegel, & Altgassen, 2007; Lui et al., 2011; Shum, Ungvari, Tang, & Leung, 2004; Wang, Chan, Hong, et al., 2008; Wang, Chan, Yu et al., 2008; Woods, Twamley, Dawson, Narvaez, & Jeste, 2007). A meta-analysis (Wang et al., 2009) has also shown medium to large degrees of impairments for event-, time-, and activity-based PM in this clinical group. Notably, studies reported similar but attenuated PM deficits in both the genetically at-risk individuals, such as nonpsychotic first-degree relatives of patients (Lui et al., 2011; Wang et al., 2010) and clinically at-risk individuals with schizotypal features (Chan et al., 2008; Wang, Chan, Yu et al., 2008).

The dysfunctions and impairments of schizophrenia spectrum disorders have been related to brain abnormalities. Structural and functional neuroimaging studies have demonstrated that patients with schizophrenia show abnormalities in the frontal and temporal lobes and connections between the frontal lobes and other brain areas (Kindermann, Karimi, Symonds, Brown, & Jeste, 1997; Kubicki et al., 2007; Pearson & Marsh, 1999; Satterthwaite et al., 2010). Participants with clinically diagnosed schizotypal personality disorder showed prefrontal, temporal impairments and fronto-temporal disconnectivity (Nakamura et al., 2005; Raine et al., 2002; Raine, Sheard, Reynolds, & Lencz, 1992). Similar abnormalities in the prefrontal and temporal regions have been found in Individuals with schizotypal features (Aichert, Williams, Möller, Kumari, & Ettinger, 2012; Ettinger et al., 2012; Modinos et al., 2010; Premkumar et al., 2012; Raine et al., 1992).

Neural Basis of Prospective Memory

A number of studies have demonstrated the importance of prefrontal cortex for PM, particularly rostral (Brodmann Area 10, BA 10) and dorsolateral regions (DLPFC; Burgess, Gonen-Yaacovi, & Volle, 2011; Burgess, Quayle, & Frith, 2001). Brain lesion studies showed that patients with prefrontal lesions are impaired on PM tasks (Burgess, Veitch, Costello, & Shallice, 2000; Daum & Mayes, 2000; Volle, Gonen-Yaacovi, de Lacy Costello, Gilbert, & Burgess, 2011). Neuroimaging studies with healthy participants supported the important role of BA10 in PM. These studies included stimuli such as letters, words, digits, and pictures (Burgess, Quayle, & Frith, 2001; Burgess, Scott, & Frith, 2003), with both event- and time-based PM tasks (Okuda et al., 2007), and measures of different stages of PM processing such as encoding, storage, cue identification and intention retrieval (Gilbert, 2011; Poppenk, Moscovitch, McIntosh, Ozcelik, & Craik, 2010; Simons, Scholvinck, Gilbert, Frith, & Burgess, 2006). Results suggested that BA 10 was activated in PM across types of stimuli and processing stages. In addition to BA 10, other brain regions such as the temporal lobe and precuneus have been involved in PM in neuroimaging studies with healthy participants (Burgess et al., 2011; Okuda et al., 1998).

The Present Study

Despite the extensive literature concerning the neural mechanisms of PM in healthy volunteers, and the evidence on behavioral deficits of PM in schizophrenia spectrum disorders, there is a lack of studies examining the neural mechanism of PM in schizophrenia spectrum disorders. The present study aimed to address this gap by examining neural activation during an event-based PM task to test for impairments in individuals with schizotypal features. Thus, we compared brain activations measures from fMRI between individuals with schizotypal features and matched controls while undertaking a PM task. Given the important role of the frontal lobes (especially BA 10) and its related brain regions, we hypothesized that individuals with schizotypal features would demonstrate abnormal prefrontal activations while performing the PM task compared with the controls.

Method

Participants

Twenty-two individuals with schizotypal features and 22 controls participated in this study. These two groups were selected from a larger group of 426 university students screened using a Chinese version of the Schizotypal Personality Questionnaire (SPQ; Chen, Hsiao, & Lin, 1997; Raine, 1991) in Shanghai, China. Participants with schizotypal features (i.e., the schizotypal group) were randomly selected from those students who scored the highest 10% ($n = 42$) on the SPQ, and participants without schizotypal features (i.e., the control group) were randomly selected from those who scored the lowest 50% ($n = 213$) on the same questionnaire. IQ of the participants were estimated by prorating scores on four subscales (Information, Arithmetic, Similarities, and Digit Span) of the Wechsler Adult Intelligence Scale-Chinese Version (Gong, 1992). Three participants in the schizotypal group were excluded from the analyses because of excessive

head movements during scanning, resulting in a total of 19 participants in the schizotypal group. The two groups did not differ in age, gender ratio, education, and IQ (see Table 1). All participants had normal or corrected to normal vision, no history of psychiatric or neurological disorders, and no drug/alcohol abuse. They were all right-handed as assessed by the Annett Handedness Questionnaire (Annett, 1970). This study was approved by the ethics committee of the Institute of Psychology, Chinese Academy of Sciences. All participants provided their written informed consent before the study.

Materials and Procedure

Design. Because event-based PM is most widely used in neuroimaging studies, we also incorporated this paradigm in the present study. We used a combination of block and event-related design based on the approach of (Simons et al., 2006). The task consisted of four sessions: a baseline session and three PM sessions. In the baseline session, participants were asked to perform an idiom-judgment task that did not have any PM instructions. The baseline session was always conducted first. After the baseline session was finished, PM instructions were given to participants and then they performed three PM blocks including PM trials and ongoing trials. We compared the brain activities evoked by PM trials (trials with PM cues and responses embedded in the judgment task) and baseline trials uncontaminated by PM instructions (judgment tasks that did not have any PM instructions).

Stimuli and task. The stimuli were four-character phrases presented in white color at the center of the screen against a black background. During the baseline session, participants were asked to judge whether each phrase was a Chinese idiom or not, without mentioning the PM task. If the phrase was an idiom, they were instructed to press the left button on the response box, otherwise to press the right button. During the three PM sessions, participants were again asked to judge whether each phrase was an idiom or not (i.e., the ongoing task). In addition, they were also asked to monitor whether or not there was an animal name in the phrase. If they saw an animal name while doing the ongoing task, they were instructed to press both response keys together (i.e., the PM task). There were 32 trials in the baseline session, and 52 trials in each of the

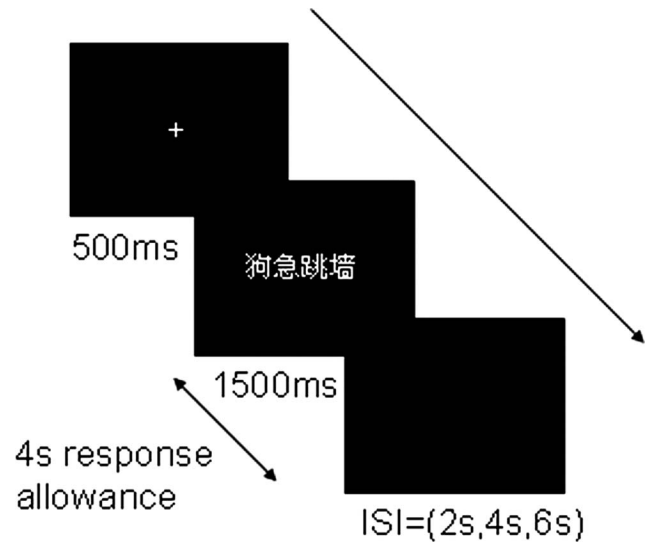


Figure 1. Illustration of a trial of the PM task.

three PM sessions. There were 10 PM trials and 42 ongoing trials in the first PM session, and 11 PM trials and 41 ongoing trials in the second and third PM session. There were at least three ongoing trials between two adjacent PM trials in order to keep participants' attention focused on the ongoing task. For each trial, there was a 500-ms fixation followed by a 1500-ms stimulus, and then a blank screen. The duration of the blank screen was jittered at 2 s, 4 s, or 6 s (see Figure 1). Thus, the average duration of a trial was 6 s. We were mainly interested in the contrast of PM trials with baseline trials.

Imaging Data Acquisition

Functional and structural MRI data were acquired (SIEMENS 3T-Trio A Tim, Erlangen, Germany) using a 32-channel head coil. Functional images were obtained using a T2-weighted single-shot gradient EPI sequence (TR: 2000, TE: 30, 90° flip angle, FOV: 210 mm, matrix: 64 × 64, voxel size: 3.3 × 3.3 × 4 mm³). Each volume included 32 axial slices (thickness 4 mm with 0 mm gap), which covered the whole brain, acquired in sequential order. The baseline session contained 106 volumes, and each PM session contained 166 volumes. The first two volumes of each session were discarded to allow for T1 equilibration. In addition, T1-weighted anatomical MR images were acquired using a magnetization-prepared rapid gradient-echo (MP-RAGE) 3D MRI sequence (192 slices, sagittal acquisition, TR: 2300ms, TE: 3.01ms, flip angle: 9°, FOV: 240 × 256, matrix: 256 × 256, voxel size: 1 × 1 × 1 mm³).

Image Data Analyses

Image data were preprocessed and analyzed using the Statistical Parametric Mapping software package (SPM8; Wellcome Department of Imaging Neuroscience, London, U.K.) implemented in MATLAB 2008b (Mathworks Inc., Sherborn, MA). Preprocessing of the EPI volumes of the four fMRI sessions included motion correction (realign), slice timing correction,

Table 1
Demographic Information of Participants

	Control (n = 22)		Schizotypal (n = 19)		t/χ^2	p
	Mean	SD	Mean	SD		
Male:female	12:10		10:9		0.02	0.902
Age	19.68	0.72	19.37	1.07	1.12	0.270
Education	13.32	0.72	13.05	1.13	0.91	0.367
IQ	127.00	8.04	125.83	9.22	0.43	0.671
SPQ_total	16.64	4.86	39.53	3.63	-16.87	<0.001
SPQ_cognitive	8.23	3.39	18.53	4.09	-8.82	<0.001
SPQ_interpersonal	5.73	3.34	14.05	4.29	-6.98	<0.001
SPQ_disorganization	3.77	2.71	10.68	2.79	-8.04	<0.001

Note. Control = participants without schizotypal personality features; Schizotypal = participants with schizotypal personality features; SPQ = Schizotypal Personality Questionnaire.

Table 2
Behavioral Performance Comparison Between Groups

	Control (<i>n</i> = 22)		Schizotypal (<i>n</i> = 19)		<i>t</i>	<i>p</i>
	Mean	SD	Mean	SD		
Baseline accuracy	0.86	0.07	0.84	0.05	1.09	0.283
Baseline RT	950.87	175.06	977.22	385.9	−0.29	0.775
PM accuracy	0.9	0.07	0.9	0.1	0.03	0.976
PM RT	879.95	152.19	872.3	264.43	0.12	0.909
Ongoing accuracy	0.84	0.03	0.84	0.05	0.47	0.638
Ongoing RT	985.18	206.75	1007.13	350.5	−0.25	0.805

Note. Control = participants without schizotypal personality features; Schizotypal = participants with schizotypal personality features; PM = prospective memory; RT = reaction time.

coregistration to the T1 anatomical image, normalization to Montreal Neurological Institute (MNI) reference space with a $3 \times 3 \times 3$ mm resolution, and spatial smoothing with 8 mm FWHM Gaussian kernel.

At the first level, statistical analysis was based on General Linear Model (GLM) fitted to each participant. The design matrix of GLM consisted of one session with two regressors for the baseline session (baseline trials and time derivatives) and three sessions with four regressors (PM trials, ongoing trials and relevant time derivatives) for PM sessions. They were used to derive contrast images for the second-level group analysis. A high-pass filter of 1/128 Hz was used to remove low-frequency noise. Parameters were estimated for each voxel using weighted least squares estimates to provide maximum likelihood based on the nonsphericity assumption of the data to get identical and independently distributed error residual terms. Contrast images were then obtained by subtracting baseline trials from PM trials or vice versa.

For the second level analysis, we first examined the two contrasts (PM > baseline and baseline > PM) in the control group. One-sample *t* test was carried out for every voxel to

compare the BOLD activity between PM trials and baseline trials. This comparison aimed to investigate the brain activations related to PM. We then compared the schizotypal and the control groups on the PM > baseline contrast using an independent sample *t* test. This comparison aimed to explore the difference in brain activation between the two groups when performing the PM task. The statistical threshold of $p < .001$ with alphasim correction was used for both analyses, which resulted in a threshold cluster size of 22. This controls for the whole-brain multiple comparisons. We applied a gray matter mask with a threshold of 0.2 in the second level analysis.

Results

Behavioral Data

The behavioral performances of the two groups are summarized in Table 2. The schizotypal and the control groups did not show any significant differences in accuracy and reaction time (RT) for baseline, ongoing, and PM tasks.

fMRI Data

Results for the control group. The contrast comparing the PM and the baseline trials revealed activation in several brain regions including the superior frontal gyrus (BA 8, 9, 10), precuneus (BA 31), postcentral gyrus (BA 40), middle temporal gyrus (BA 39), medial frontal gyrus (BA 8), and paracentral lobule (BA 6). The reverse contrast revealed that the postcentral gyrus (BA 2) and inferior parietal lobule (BA 40) showed more activation in the baseline than PM trials (see Table 3 and Figure 2). Parameter estimates for PM and baseline in left BA10, right BA10, and left inferior parietal lobe were presented in Figure 3.

Comparison between schizotypal and control groups. Group comparisons showed that the schizotypal group had significantly less activation in the inferior frontal gyrus (BA 45) and medial frontal gyrus (BA 8) than the control group for the

Table 3
Significant Brain Activations of PM in Control Group

Anotamical label	Hemisphere	Brodmann area	Peak MNI coordinates			T	Cluster size (voxels)
			<i>x</i>	<i>y</i>	<i>z</i>		
PM > baseline							
Superior frontal gyrus	L	10	−18	59	16	6.11	48
Precuneus	L	31	−15	−58	34	5.98	304
Middle temporal gyrus	L	39	−42	−64	34	5.15	78
Superior frontal gyrus	R	9/10	18	65	16	4.89	115
Postcentral gyrus	R	40	33	−31	61	4.85	136
Medial frontal gyrus	R	8	15	41	34	4.53	33
Paracentral lobule	R	6	12	−19	49	4.51	41
Superior frontal gyrus	R	8	24	38	46	4.32	22
Medial frontal gyrus	L	8	−9	53	34	4.29	38
Superior frontal gyrus	L	8	−24	32	49	4.19	27
Baseline > PM							
Postcentral gyrus	L	2	−66	−19	25	6.42	73
Inferior parietal lobule	L	40	−48	−34	61	6.39	165

Note. $p < .001$ with alphasim correction. For the labeling, the MNI coordinates were transformed to Talairach space and labeled using Talairach Client 2.4.2 (Lancaster et al., 2000).

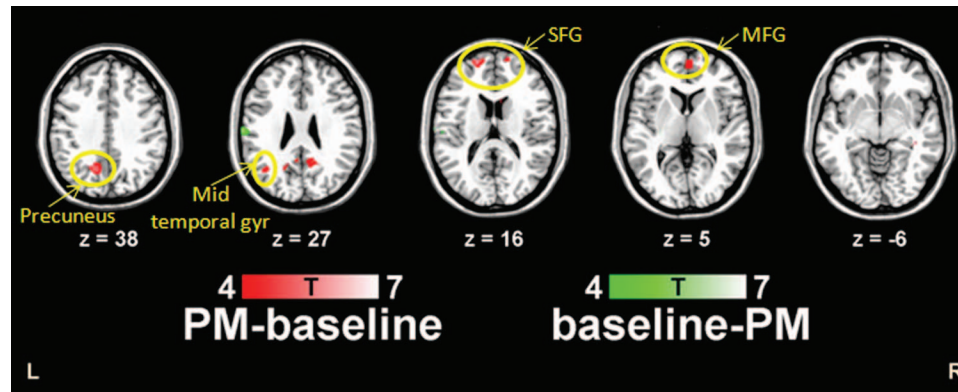


Figure 2. Brain activations and deactivations in PM for the control group. Mid temporal gyr = middle temporal gyrus; SFG = superior frontal gyrus; MFG = medial frontal gyrus.

PM compared with baseline trials. The schizotypal group did not show any significantly higher activation than the control group (see Table 4 and Figure 4). Parameter estimates for PM and baseline in inferior frontal gyrus (BA 45) and medial frontal gyrus (BA 8) are presented in Figure 5.

Discussion

To our knowledge, this is the first neuroimaging study of PM in individuals with schizotypal features. The main findings of the study are as follows: (1) participants with schizotypal features did not show behavioral impairments in the PM task; (2) PM was associated with activations in the prefrontal cortex, precuneus, middle temporal gyrus, postcentral gyrus, and paracentral lobe; (3) participants with schizotypal features showed decreased activations in the inferior and medial frontal gyrus compared to controls while performing the PM task.

Behavioral Results

The finding that the schizotypal group did not show PM impairments is not consistent with those reported by previous behavioral studies (Chan et al., 2008; Wang, Chan, Yu et al., 2008). This could be because the frequency of PM trials was higher in the current study

(about 20%) than in previous studies (about 5%). For example, Czernochowski, Horn, and Bayen (2012) showed that the frequency of PM trials could affect the performance of PM, that is, more frequent PM trials would result in a better PM performance, likely because of increased salience for the PM task and enhanced cognitive control. The absence of group difference in behavioral results might be attributable to a ceiling effect for the PM task (both groups showed a mean accuracy of 0.9). High proportion of PM trials might have reduced the difference in PM task performance between the schizotypal and the control groups in our study. The inclusion of a relatively larger number of PM trials in an imaging study was inevitable because a sufficient number of trials are required for stable and reliable fMRI analyses. Another reason for the absence of group difference in this study might be the longer time allowed for participants to respond in this study (6 s on average) compared with that in previous studies (3.5 s on average). From the standpoint of functional neuroimaging methodology, the similar performance level for the two groups is an advantage because it removes performance as a potential confound when interpreting group differences in activation (Gur et al., 1997).

Imaging Results

Imaging results showed that event-based PM activated several brain regions, including superior frontal gyrus, medial

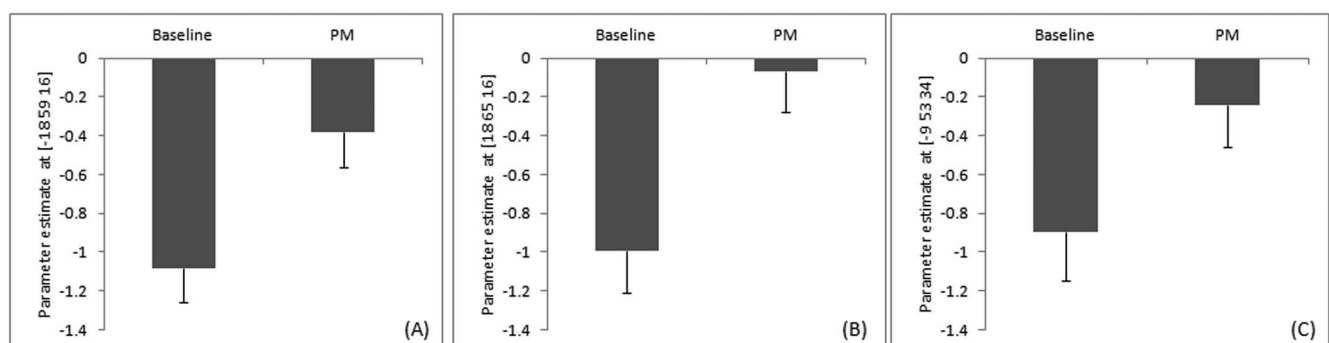


Figure 3. Parameter estimates for PM and baseline in superior frontal gyrus centered at [-18 59 16] (A), superior frontal gyrus centered at [18 65 16] (B), and medial frontal gyrus centered at [-9 53 34] (C) for the control group.

Table 4
Comparison Between Schizotypal and Control Group for PM-Baseline Comparison

Anatomical label	Hemisphere	Brodmann area	Peak MNI coordinates			<i>t</i>	Cluster size
			<i>x</i>	<i>y</i>	<i>Z</i>		
Control > schizotypal							
Inferior frontal gyrus	R	45	51	23	7	4.64	26
Medial frontal gyrus	R	8	15	41	34	3.98	29
Schizotypal > control							
none							

Note. $p < .001$ with alphasim correction. For the labeling, the MNI coordinates were transformed to Talairach space and labeled using Talairach Client 2.4.2 (Lancaster et al., 2000).

frontal gyrus, middle frontal gyrus, precuneus, and middle temporal gyrus, in the control group. These results are consistent with those reported in previous studies (Burgess et al., 2011; Burgess, Quayle, & Frith, 2001; Burgess, Scott, & Frith, 2003; Okuda et al., 1998). The BA 10 has been widely reported to be activated when performing PM tasks, and many components of PM (e.g., dual processing, PM encoding, attentional preparatory process, monitoring, disengagement, attention switching, maintenance of the PM intention in the context of ongoing task, and intention execution) are considered to be related to this brain area (Benoit, Gilbert, Frith, & Burgess, 2012; Hashimoto, Umeda, & Kojima, 2011; Poppenk et al., 2010; Reynolds, West, & Braver, 2009). The precuneus is another brain area activated and involved in PM, particularly in the encoding or maintenance (Burgess, Quayle, & Frith, 2001; Burgess, Gonen-Yaacovi, & Volle, 2011; Okuda et al., 2011). Finding activations in the BA 10 and precuneus supports the validity of our PM paradigm.

Schizotypal participants had hypo-activation in the inferior and medial frontal gyrus (BA 45 and BA 8). In Aron's (2011) review, he suggested that the right inferior frontal cortex (BA 45) is involved in inhibitory control (inhibiting motor response) and attentional detection of stop signals. Hampshire, Chamberlain, Monti, Duncan, and Owen (2010) further suggested that right inferior frontal gyrus plays a role in attentional switching—the process that the focus of attention is moved from one locus to another. This is consistent with the inhibitory control

hypothesis, because the right inferior frontal gyrus facilitates the attentional switch by inhibiting the previously attended object or dimension, thereby allowing attention to disengage and relocate. Thus the decreased activation in these brain areas for the schizotypal group may indicate impairment in switching attention from the ongoing to the PM task and inhibiting their ongoing response impulse, although this subtle impairment did not manifest behaviorally.

Rushworth, Walton, Kennerley, and Bannerman (2004) suggested that the medial frontal gyrus (BA 8) is involved in motor sequencing and cognitive control. Passingham, Bengtsson, & Lau (2010) suggested that the medial frontal cortex is crucially involved in self-generated action and self-reflection. Thus the decreased activation in BA 8 found in the schizotypal group may indicate impairments in inhibiting ongoing task response sequence and in making a PM response when the PM cue was detected. For both BA 45 and BA 8, the schizotypal group showed more activation in the baseline condition and less activation in the PM condition compared to controls, suggesting that schizotypal individuals process the PM task differently, that is, they need more resources to perform the idiom decision task, and have less additional resources to accomplish the PM task. Such a potential difference in processing pattern in schizotypal participants merits further study.

The present results are generally consistent with findings in patients with schizophrenia in showing decreased activation in the frontal cortex (Hill et al., 2004; Whalley et al., 2008).

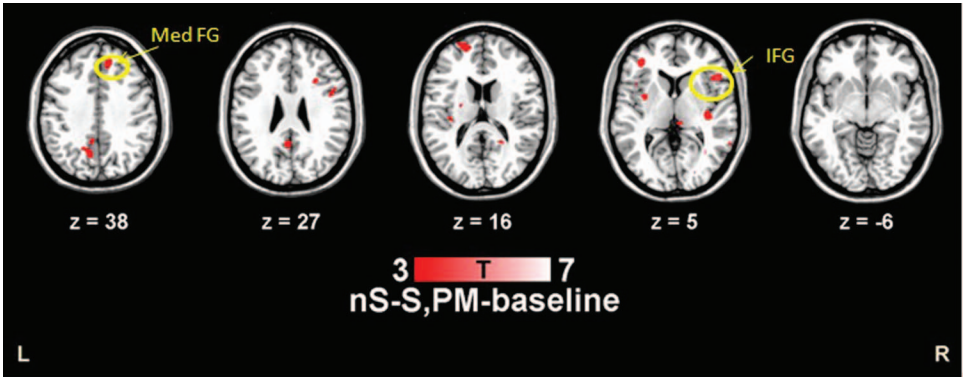


Figure 4. Comparison of brain activations between schizotypal and control group for PM and baseline contrast. NS = control group; S = schizotypal group; Med FG = medial frontal gyrus; IFG = inferior frontal gyrus.

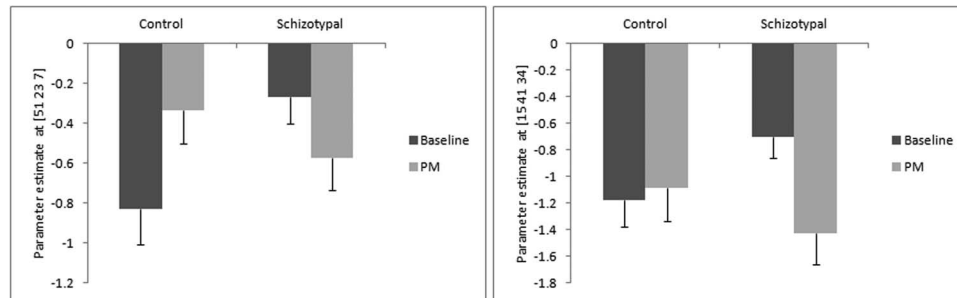


Figure 5. Parameter estimates for PM and baseline in inferior frontal gyrus centered at [51 23 7] (left) and medial frontal gyrus centered at [15 41 34] (right) for control and schizotypal groups.

Furthermore, individuals at high risk for schizophrenia also showed decreased activations in the frontal lobes. For example, Broome et al. (2009) found that high risk individuals showed decreased activation compared with healthy controls in the inferior frontal and dorsolateral prefrontal cortex during a semantic working memory task (letter n-back task). In another study, they found high-risk individuals showed less activation in the medial and superior frontal gyrus when performing a visual-spatial working memory task (Broome et al., 2010). Allen et al. (2011) found that high-risk participants showed decreased activations in the medial frontal gyrus and middle frontal gyrus (BA 8) while performing a verbal episodic memory task. Choi et al. (2012) found that compared with controls, ultra high-risk group showed a decreased activation in the dorsolateral and ventrolateral frontal cortex when performing a spatial working memory task, without showing behavioral impairments. Egerton et al. (2011) concluded that decreased prefrontal cortex activation was apparent during mnemonic tasks performance in high-risk subjects for psychosis, which may underlie subtle memory impairments. Furthermore, the finding that the schizotypal group showed abnormal activations indicates that brain activity is more sensitive than behavioral measures in detecting vulnerability to PM impairments, and is consistent with the view that neuroimaging methods may have additional value for identifying psychosis risk (Egerton et al., 2011).

Contrary to our expectation, the schizotypal group did not show significant differences in temporal cortex activations compared to the control group. This might be because prefrontal cortex is more vulnerable than temporal cortex in individuals with schizotypal features. However, these issues need further study.

Limitations and Future Directions

This study has a number of limitations. First, we only studied event-based PM, and previous studies (e.g., Okuda et al., 2007) have shown that time-based PM may have a different neural basis than event-based PM. Thus to obtain a more complete picture of neural basis of PM in individuals with schizotypal features, future studies should include a time-based PM task. Second, we did not isolate different processing stages of PM. Previous studies (Allen et al., 2011; Choi et al., 2012) found that impairment may be different in other stages such as en-

coding and recognition phase of episodic memory, encoding, maintenance, and retrieval phase of working memory. Thus different stages of PM may show different impairments in individuals with schizotypal features and this needs to be investigated further. Third, we did not distinguish subtypes of schizotypy. Previous studies (Barrantes-Vidal et al., 2003; Dinn, Harris, Aycicegi, Greene, & Andover, 2002) reported that subtypes of schizotypy (e.g., positive, negative) showed different neurocognitive profiles. Because these subtypes might have different locations or extent of neural impairments, further studies are needed to address this question. Fourth, the combined block and event-related design could rule out contamination of PM instructions. However, it entails other limitations, such as the temporal order, that cannot be randomized. Furthermore, PM was a specific event while the baseline was a block. Future studies can use other designs to provide convergent evidence.

Conclusions

The current study showed that individuals with schizotypal features have reduced brain activations in the prefrontal cortex, suggesting a subtle impairment in switching attention from ongoing task to PM task and inhibiting ongoing response impulse to make a PM response. Notably, brain abnormality as assessed by fMRI activations occurred without behavioral manifestations in these individuals.

References

- Aichert, D. S., Williams, S. C. R., Möller, H. J., Kumari, V., & Ettinger, U. (2012). Functional neural correlates of psychometric schizotypy: An fMRI study of antisaccades. *Psychophysiology*, 49, 345–356. doi:10.1111/j.1469-8986.2011.01306.x
- Allen, P., Seal, M. L., Valli, I., Fusar-Poli, P., Perlani, C., Day, F., . . . McGuire, P. K. (2011). Altered prefrontal and hippocampal function during verbal encoding and recognition in people with prodromal symptoms of psychosis. *Schizophrenia Bulletin*, 37, 746–756. doi:10.1093/schbul/sbp113
- Annett, M. (1970). A classification of hand preference by association analysis. *British Journal of Psychology*, 61, 303–321. doi:10.1111/j.2044-8295.1970.tb01248.x
- Aron, A. R. (2011). From reactive to proactive and selective control: Developing a richer model for stopping inappropriate responses. *Biological Psychiatry*, 69, e55–e68. doi:10.1016/j.biopsych.2010.07.024

- Barrantes-Vidal, N., Fañanás, L., Rosa, A., Caparrós, B., Dolors Riba, M., & Obiols, J. E. (2003). Neurocognitive, behavioural and neurodevelopmental correlates of schizotypy clusters in adolescents from the general population. *Schizophrenia Research*, 61, 293–302. doi:10.1016/S0920-9964(02)00321-3
- Benoit, R. G., Gilbert, S. J., Frith, C. D., & Burgess, P. W. (2012). Rostral prefrontal cortex and the focus of attention in prospective memory. *Cerebral Cortex*, 22, 1876–1886. doi:10.1093/cercor/bhr264
- Broome, M. R., Fusar-Poli, P., Matthiasson, P., Woolley, J. B., Valmaggia, L., Johns, L. C., . . . Brammer, M. J. (2010). Neural correlates of visuospatial working memory in the 'at-risk mental state'. *Psychological Medicine*, 40, 1987–1999. doi:10.1017/S0033291710000280
- Broome, M. R., Matthiasson, P., Fusar-Poli, P., Woolley, J. B., Johns, L. C., Tabraham, P., . . . Brammer, M. J. (2009). Neural correlates of executive function and working memory in the 'at-risk mental state'. *The British Journal of Psychiatry*, 194, 25–33. doi:10.1192/bjp.bp.107.046789
- Burgess, P. W., Gonen-Yaacovi, G., & Volle, E. (2011). Functional neuroimaging studies of prospective memory: What have we learnt so far? *Neuropsychologia*, 49, 2246–2257. doi:10.1016/j.neuropsychologia.2011.02.014
- Burgess, P. W., Quayle, A., & Frith, C. D. (2001). Brain regions involved in prospective memory as determined by positron emission tomography. *Neuropsychologia*, 39, 545–555. doi:10.1016/S0028-3932(00)00149-4
- Burgess, P. W., Scott, S. K., & Frith, C. D. (2003). The role of the rostral frontal cortex (area 10) in prospective memory: A lateral versus medial dissociation. *Neuropsychologia*, 41, 906–918. doi:10.1016/S0028-3932(02)00327-5
- Burgess, P. W., Veitch, E., Costello, A. L., & Shallice, T. (2000). The cognitive and neuroanatomical correlates of multitasking. *Neuropsychologia*, 38, 848–863. doi:10.1016/S0028-3932(99)00134-7
- Cadenhead, K., Perry, W., Shafer, K., & Braff, D. (1999). Cognitive functions in schizotypal personality disorder. *Schizophrenia Research*, 37, 123–132. doi:10.1016/S0920-9964(98)00147-9
- Chan, R. C. K., Wang, Y., Ma, Z., Hong, X., Yuan, Y., Yu, X., . . . Gong, Q. (2008). Objective measures of prospective memory do not correlate with subjective complaints in schizophrenia. *Schizophrenia Research*, 103, 229–239. doi:10.1016/j.schres.2008.02.019
- Chen, W. J., Hsiao, C. K., & Lin, C. C. H. (1997). Schizotypy in community samples: The three-factor structure and correlation with sustained attention. *Journal of Abnormal Psychology*, 106, 649–654. doi:10.1037/0021-843X.106.4.649
- Choi, J. S., Park, J. Y., Jung, M. H., Jang, J. H., Kang, D. H., Jung, W. H., . . . Kwon, J. S. (2012). Phase-specific brain change of spatial working memory processing in genetic and ultra-high risk groups of schizophrenia. *Schizophrenia Bulletin*, 38, 1189–1199. doi:10.1093/schbul/sbr038
- Czernochowski, D., Horn, S., & Bayen, U. J. (2012). Does frequency matter? ERP and behavioral correlates of monitoring for rare and frequent prospective memory targets. *Neuropsychologia*, 50, 67–76. doi:10.1016/j.neuropsychologia.2011.10.023
- Daum, I., & Mayes, A. R. (2000). Memory and executive function impairments after frontal or posterior cortex lesions. *Behavioural Neurology*, 12, 161–173.
- Dinn, W. M., Harris, C. L., Aycicegi, A., Greene, P., & Andover, M. S. (2002). Positive and negative schizotypy in a student sample: Neurocognitive and clinical correlates. *Schizophrenia Research*, 56, 171–185. doi:10.1016/S0920-9964(01)00230-4
- Egerton, A., Borgwardt, S. J., Tognin, S., Howes, O. D., McGuire, P., & Allen, P. (2011). An overview of functional, structural and neurochemical imaging studies in individuals with a clinical high risk for psychosis. *Neuropsychiatry*, 1, 477–493. doi:10.2217/npv.11.51
- Ellis, J. A. (1996). Prospective memory or the realization of delayed intentions: A conceptual framework for research. In M. Brandimonte, G. O. Einstein, & M. A. McDaniel (Eds.), *Prospective memory: Theory and Applications* (pp. 1–22). Mahwah, NJ: Erlbaum.
- Elvevåg, B., Maylor, E. A., & Gilbert, A. L. (2003). Habitual prospective memory in schizophrenia. *BMC Psychiatry*, 3, 3–9.
- Ettinger, U., Williams, S. C. R., Meisenzahl, E. M., Möller, H. J., Kumari, V., & Koutsouleris, N. (2012). Association between brain structure and psychometric schizotypy in healthy individuals. *The World Journal of Biological Psychiatry*, 13, 544–549. doi:10.3109/15622975.2011.559269
- Gilbert, S. J. (2011). Decoding the content of delayed intentions. *The Journal of Neuroscience*, 31, 2888–2894. doi:10.1523/JNEUROSCI.5336-10.2011
- Gong, Y. X. (1992). *Manual of Wechsler Adult Intelligence Scale-Chinese version*. Changsha, China: Chinese Map Press.
- Gottesman, I. I., & Shields, J. (1973). Genetics theorizing and schizophrenia. *The British Journal of Psychiatry*, 122, 15–30. doi:10.1192/bjp.122.1.15
- Greenwood, T. A., Braff, D. L., Light, G. A., Cadenhead, K. S., Calkins, M. E., Dobie, D. J., . . . Schork, N. J. (2007). Initial heritability analyses of endophenotypic measures for schizophrenia: The consortium on the genetics of schizophrenia. *Archives of General Psychiatry*, 64, 1242–1250. doi:10.1001/archpsyc.64.11.1242
- Gur, R. C., Ragland, J. D., Mozley, L. H., Mozley, P. D., Smith, R., Alavi, A., . . . Gur, R. E. (1997). Lateralized changes in regional cerebral blood flow during performance of verbal and facial recognition tasks: Correlations with performance and "effort". *Brain and Cognition*, 33, 388–414. doi:10.1006/brcg.1997.0921
- Hampshire, A., Chamberlain, S. R., Monti, M. M., Duncan, J., & Owen, A. M. (2010). The role of the right inferior frontal gyrus: Inhibition and attentional control. *NeuroImage*, 50, 1313–1319. doi:10.1016/j.neuroimage.2009.12.109
- Hashimoto, T., Umeda, S., & Kojima, S. (2011). Neural substrates of implicit cueing effect on prospective memory. *NeuroImage*, 54, 645–652. doi:10.1016/j.neuroimage.2010.07.047
- Heinrichs, R. W., & Zakzanis, K. K. (1998). Neurocognitive deficit in schizophrenia: A quantitative review of the evidence. *Neuropsychology*, 12, 426–445. doi:10.1037/0894-4105.12.3.426
- Henry, J. D., Rendell, P. G., Kliegel, M., & Altgassen, M. (2007). Prospective memory in schizophrenia: Primary or secondary impairment? *Schizophrenia Research*, 95, 179–185. doi:10.1016/j.schres.2007.06.003
- Hill, K., Mann, L., Laws, K. R., Stephenson, C. M. E., Nimmo-Smith, I., & McKenna, P. J. (2004). Hypofrontality in schizophrenia: A meta-analysis of functional imaging studies. *Acta Psychiatrica Scandinavica*, 110, 243–256. doi:10.1111/j.1600-0447.2004.00376.x
- Kindermann, S. S., Karimi, A., Symonds, L., Brown, G. G., & Jeste, D. V. (1997). Review of functional magnetic resonance imaging in schizophrenia. *Schizophrenia Research*, 27, 143–156. doi:10.1016/S0920-9964(97)00063-7
- Kubicki, M., McCarley, R., Westin, C.-F., Park, H.-J., Maier, S., Kikinis, R., . . . Shenton, M. E. (2007). A review of diffusion tensor imaging studies in schizophrenia. *Journal of Psychiatric Research*, 41, 15–30. doi:10.1016/j.jpsychires.2005.05.005
- Kvavilashvili, L., & Ellis, J. A. (1996). Variety of intentions: Some distinctions and classifications. In M. Brandimonte, G. O. Einstein, & M. A. McDaniel (Eds.), *Prospective memory: Theory and applications* (pp. 23–51). Mahwah, NJ: Erlbaum.
- Lancaster, J. L., Woldorff, M. G., Parsons, L. M., Liotti, M., Freitas, C. S., Rainey, L., . . . Fox, P. T. (2000). Automated Talairach atlas labels for functional brain mapping. *Human Brain Mapping*, 10, 120–131.
- Lui, S. S. Y., Wang, Y., Liu, A. C. Y., Chui, W. W. H., Gong, Q.-y., Shum, D., . . . Chan, R. C. K. (2011). Prospective memory in patients with

- first-onset schizophrenia and their non-psychotic siblings. *Neuropsychologia*, 49, 2217–2224. doi:10.1016/j.neuropsychologia.2011.04.002
- McCleery, A., Divilbiss, M., St-Hilaire, A., Aakre, J. M., Seghers, J. P., Bell, E. K., & Docherty, N. M. (2012). Predicting social functioning in schizotypy: An investigation of the relative contributions of theory of mind and mood. *Journal of Nervous and Mental Disease*, 200, 147–152. doi:10.1097/NMD.0b013e3182439533
- Modinos, G., Mechelli, A., Ormel, J., Groenewold, N. A., Aleman, A., & McGuire, P. K. (2010). Schizotypy and brain structure: A voxel-based morphometry study. *Psychological Medicine*, 40, 1423–1431. doi:10.1017/S0033291709991875
- Nakamura, M., McCarley, R. W., Kubicki, M., Dickey, C. C., Niznikiewicz, M. A., Voglmaier, M. M., . . . Kikinis, R. (2005). Fronto-temporal disconnectivity in schizotypal personality disorder: A diffusion tensor imaging study. *Biological Psychiatry*, 58, 468–478. doi:10.1016/j.biopsych.2005.04.016
- Okuda, J., Fujii, T., Ohtake, H., Tsukiura, T., Yamadori, A., Frith, C. D., & Burgess, P. W. (2007). Differential involvement of regions of rostral prefrontal cortex (Brodmann area 10) in time- and event-based prospective memory. *International Journal of Psychophysiology*, 64, 233–246. doi:10.1016/j.ijpsycho.2006.09.009
- Okuda, J., Fujii, T., Yamadori, A., Kawashima, R., Tsukiura, T., Fukatsu, R., . . . Fukuda, H. (1998). Participation of the prefrontal cortices in prospective memory: Evidence from a PET study in humans. *Neuroscience Letters*, 253, 127–130. doi:10.1016/S0304-3940(98)00628-4
- Okuda, J., Gilbert, S. J., Burgess, P. W., Frith, C. D., & Simons, J. S. (2011). Looking to the future: Automatic regulation of attention between current performance and future plans. *Neuropsychologia*, 49, 2258–2271. doi:10.1016/j.neuropsychologia.2011.02.005
- Passingham, R. E., Bengtsson, S. L., & Lau, H. C. (2010). Medial frontal cortex: From self-generated action to reflection on one's own performance. *Trends in Cognitive Sciences*, 14, 16–21. doi:10.1016/j.tics.2009.11.001
- Pearlson, G. D., & Marsh, L. (1999). Structural brain imaging in schizophrenia: A selective review. *Biological Psychiatry*, 46, 627–649. doi:10.1016/S0006-3223(99)00071-2
- Poppenk, J., Moscovitch, M., McIntosh, A. R., Ozcelik, E., & Craik, F. I. M. (2010). Encoding the future: Successful processing of intentions engages predictive brain networks. *NeuroImage*, 49, 905–913. doi:10.1016/j.neuroimage.2009.08.049
- Premkumar, P., Ettinger, U., Inchley-Mort, S., Sumich, A., Williams, S. C. R., Kuipers, E., & Kumari, V. (2012). Neural processing of social rejection: The role of schizotypal personality traits. *Human Brain Mapping*, 33, 695–706. doi:10.1002/hbm.21243
- Raine, A. (1991). The SPQ: A scale for the assessment of schizotypal personality based on *DSM-III-R* criteria. *Schizophrenia Bulletin*, 17, 555–564. doi:10.1093/schbul/17.4.555
- Raine, A. (2006). Schizotypal personality: Neurodevelopmental and psychosocial trajectories. *Annual Review of Clinical Psychology*, 2, 291–326. doi:10.1146/annurev.clinpsy.2.022305.095318
- Raine, A., Lencz, T., Yarlalian, P., Bihle, S., LaCasse, L., Ventura, J., & Colletti, P. (2002). Prefrontal structural and functional deficits in schizotypal personality disorder. *Schizophrenia Bulletin*, 28, 501–513. doi:10.1093/oxfordjournals.schbul.a006957
- Raine, A., Sheard, C., Reynolds, G. P., & Lencz, T. (1992). Pre-frontal structural and functional deficits associated with individual differences in schizotypal personality. *Schizophrenia Research*, 7, 237–247. doi:10.1016/0920-9964(92)90018-Z
- Reynolds, J. R., West, R., & Braver, T. (2009). Distinct neural circuits support transient and sustained processes in prospective memory and working memory. *Cerebral Cortex*, 19, 1208–1221. doi:10.1093/cercor/bhn164
- Rushworth, M. F. S., Walton, M. E., Kennerley, S. W., & Bannerman, D. M. (2004). Action sets and decisions in the medial frontal cortex. *Trends in Cognitive Sciences*, 8, 410–417. doi:10.1016/j.tics.2004.07.009
- Satterthwaite, T. D., Wolf, D. H., Loughhead, J., Ruparel, K., Valdez, J. N., Siegel, S. J., . . . Gur, R. C. (2010). Association of enhanced limbic response to threat with decreased cortical facial recognition memory response in schizophrenia. *The American Journal of Psychiatry*, 167, 418–426. doi:10.1176/appi.ajp.2009.09060808
- Shastri, B. S. (2002). Schizophrenia: A genetic perspective. *International Journal of Molecular Medicine*, 9, 207–212.
- Shum, D., Ungvari, G. S., Tang, W. K., & Leung, J. P. (2004). Performance of schizophrenia patients on time-, event-, and activity-based prospective memory tasks. *Schizophrenia Bulletin*, 30, 693–702. doi:10.1093/oxfordjournals.schbul.a007123
- Simons, J. S., Scholvinck, M. L., Gilbert, S. J., Frith, C. D., & Burgess, P. W. (2006). Differential components of prospective memory? Evidence from fMRI. *Neuropsychologia*, 44, 1388–1397. doi:10.1016/j.neuropsychologia.2006.01.005
- Volle, E., Gonen-Yaacovi, G., de Lacy Costello, A., Gilbert, S. J., & Burgess, P. W. (2011). The role of rostral prefrontal cortex in prospective memory: A voxel-based lesion study. *Neuropsychologia*, 49, 2185–2198. doi:10.1016/j.neuropsychologia.2011.02.045
- Wang, Y., Chan, R. C. K., Cui, J., Deng, Y., Huang, J., Li, H., . . . Shum, D. (2010). Prospective memory in non-psychotic first-degree relatives of patients with schizophrenia. *Psychiatry Research*, 179, 285–290. doi:10.1016/j.psychres.2009.07.011
- Wang, Y., Chan, R. C. K., Hong, X., Ma, Z., Yang, T., Guo, L., . . . Shum, D. (2008). Prospective memory in schizophrenia: Further clarification of nature of impairment. *Schizophrenia Research*, 105, 114–124. doi:10.1016/j.schres.2008.07.002
- Wang, Y., Chan, R. C. K., Yu, X., Shi, C., Cui, J., & Deng, Y. (2008). Prospective memory deficits in subjects with schizophrenia spectrum disorders: A comparison study with schizophrenic subjects, psychometrically defined schizotypal subjects, and healthy controls. *Schizophrenia Research*, 106, 70–80. doi:10.1016/j.schres.2007.07.020
- Wang, Y., Cui, J., Chan, R. C. K., Deng, Y., Shi, H., Hong, X., . . . Shum, D. (2009). Meta-analysis of prospective memory in schizophrenia: Nature, extent, and correlates. *Schizophrenia Research*, 114, 64–70. doi:10.1016/j.schres.2009.07.009
- Whalley, H. C., Mowatt, L., Stanfield, A. C., Hall, J., Johnstone, E. C., Lawrie, S. M., & McIntosh, A. M. (2008). Hypofrontality in subjects at high genetic risk of schizophrenia with depressive symptoms. *Journal of Affective Disorders*, 109, 99–106. doi:10.1016/j.jad.2007.11.009
- Woods, S. P., Twamley, E. W., Dawson, M. S., Narvaez, J. M., & Jeste, D. V. (2007). Deficits in cue detection and intention retrieval underlie prospective memory impairment in schizophrenia. *Schizophrenia Research*, 90, 344–350. doi:10.1016/j.schres.2006.11.005
- Zogg, J. B., Woods, S. P., Saucedo, J. A., Wiebe, J. S., & Simoni, J. M. (2012). The role of prospective memory in medication adherence: A review of an emerging literature. *Journal of Behavioral Medicine*, 35, 47–62. doi:10.1007/s10865-011-9341-9

Received June 1, 2013

Revision received August 12, 2013

Accepted September 2, 2013 ■