Author(s): M. R. Broome, P. Fusar-Polia, P. Matthiasson, J. B. Woolley, L. Valmaggia, L. C. Johns, P. Tabraham, E. Bramon, S. C. R. Williams, M. J. Brammer, X. Chitnis, F. Zelaya and P. K. McGuire

Article Title: Neural correlates of visuospatial working memory in the 'at-risk mental state'
Year of publication: 2010
Link to published article: http://dx.doi.org/10.1017/S0033291710000280

Psychological Medicine (2010), **40**, 1987–1999. © Cambridge University Press 2010
doi:10.1017/S0033291710000280

ORIGINAL ARTICLE

Neural correlates of visuospatial working memory in the 'at-risk mental state'

M. R. Broome[1,2]*, P. Fusar-Poli[1,3], P. Matthiasson[1], J. B. Woolley[1], L. Valmaggia[1,4], L. C. Johns[1], P. Tabraham[1], E. Bramon[1], S. C. R. Williams[5], M. J. Brammer[6], X. Chitnis[6], F. Zelaya[5] and P. K. McGuire[1]

[1] *Psychosis Clinical Academic Group, Institute of Psychiatry, King's College London, UK*
[2] *Health Sciences Research Institute, Warwick Medical School, University of Warwick, Coventry, UK*
[3] *Department of Applied and Psychobehavioural Health Sciences, University of Pavia, Italy*
[4] *Department of Psychiatry and Neuropsychology, Maastricht University, The Netherlands*
[5] *Neuroimaging Research Group, Department of Neurology, Institute of Psychiatry, King's College London, UK*
[6] *Brain Image Analysis Unit, Department of Biostatistics and Computing, Institute of Psychiatry, King's College London, UK*

Background. Impaired spatial working memory (SWM) is a robust feature of schizophrenia and has been linked to the risk of developing psychosis in people with an at-risk mental state (ARMS). We used functional magnetic resonance imaging (fMRI) to examine the neural substrate of SWM in the ARMS and in patients who had just developed schizophrenia.

Method. fMRI was used to study 17 patients with an ARMS, 10 patients with a first episode of psychosis and 15 age-matched healthy comparison subjects. The blood oxygen level-dependent (BOLD) response was measured while subjects performed an object–location paired-associate memory task, with experimental manipulation of mnemonic load.

Results. In all groups, increasing mnemonic load was associated with activation in the medial frontal and medial posterior parietal cortex. Significant between-group differences in activation were evident in a cluster spanning the medial frontal cortex and right precuneus, with the ARMS groups showing less activation than controls but greater activation than first-episode psychosis (FEP) patients. These group differences were more evident at the most demanding levels of the task than at the easy level. In all groups, task performance improved with repetition of the conditions. However, there was a significant group difference in the response of the right precuneus across repeated trials, with an attenuation of activation in controls but increased activation in FEP and little change in the ARMS.

Conclusions. Abnormal neural activity in the medial frontal cortex and posterior parietal cortex during an SWM task may be a neural correlate of increased vulnerability to psychosis.

Received 19 January 2009; Revised 26 January 2010; Accepted 26 January 2010; First published online 10 March 2010

Key words: ARMS, imaging, memory, prodrome, psychosis, visuospatial.

Introduction

Although it is known that schizophrenia is associated with neurocognitive dysfunction, the extent to which this is related to the disorder, as opposed to vulnerability to schizophrenia, is unclear. There is also increasing evidence that neuroimaging abnormalities may change over the course of psychotic disorders (Lieberman, 1999; Rapoport *et al*. 1999; Lieberman *et al*. 2001; Pantelis *et al*. 2003) and can be affected by treatment (Chakos *et al*. 2005; Dazzan *et al*. 2005). Determining variables that are linked to vulnerability to schizophrenia, rather than to the disorder itself, is important for identifying those who may benefit from interventions that may prevent the onset of the disorder, and also allows understanding of how the disorder develops and progresses. One way of clarifying the relative contribution of these factors is to compare individuals who are at very high risk of psychosis, patients who have just developed schizophrenia and have had minimal treatment, and healthy volunteers.

People with 'prodromal' symptoms of psychosis have a 25–40% risk of developing a psychotic disorder in the next 12 months (Yung *et al*. 2003) and thus have an 'at-risk mental state' (ARMS). However, this rate of transition has not remained the same in other centres or, indeed, over time. Other groups have reported higher rates of transition (Miller *et al*. 2002), and the

* Address for correspondence: Dr M. R. Broome, Warwick Medical School, University of Warwick, Gibbet Hill, Coventry CV4 7AL, UK.
(Email: m.r.broome@warwick.ac.uk)

Melbourne Personal Assessment and Crisis Evaluation (PACE) service has recently reported a transition rate of less than 10% (Yung *et al*. 2007). Within our own service, OASIS, current transition rates are at approximately 21% (Valmaggia *et al*. 2009). Knowledge of neurocognitive function in this group is growing rapidly. Neuropsychological studies point to an impairment of executive and memory functions (Brewer *et al*. 2005) with some deficits only evident when the task demands are relatively high (Broome *et al*. 2007). In general, neuropsychological performance in ARMS subjects has been found to be at an intermediate level relative to patients with schizophrenia and controls (Wood *et al*. 2003; Brewer *et al*. 2005; Lencz *et al*. 2006; Wagner *et al*. 2006; Pukrop *et al*. 2007), with evidence suggesting that spatial working memory (SWM) is impaired. Structural magnetic resonance imaging (MRI) studies suggest that the ARMS is associated with reduced grey matter volumes in the prefrontal, cingulate and temporal cortex (Pantelis *et al*. 2003) whereas functional MRI (fMRI) studies have reported differential prefrontal activation in ARMS subjects relative to controls and patients with schizophrenia during a visual oddball paradigm (Morey *et al*. 2005) and during verbal fluency and the N-back verbal working memory tasks (Broome *et al*. 2009). In both these studies, the clinical high-risk group demonstrated activations intermediate between those with schizophrenia and healthy controls, with the control subjects typically showing greatest activation and those with psychosis, the least.

Working memory refers to the retention of information in conscious awareness when it is not present in the environment. Working memory has been implicated as an important contributor to language processing, learning, planning, reasoning and general fluid intelligence (Postle, 2006). It can be subdivided into a memory component (holding information 'online') and a manipulation component (working on the information being held). It has been further subdivided according to the form of the information involved (verbal *versus* non-verbal; spatial *versus* non-spatial; verbal *versus* object memory) (Pollmann & von Cramon, 2000). In our previous imaging work with the ARMS groups we studied verbal working memory (Broome *et al*. 2009). In the present study our focus is on SWM. SWM impairments have been well documented in schizophrenia (Park & Holzman, 1992; Fleming *et al*. 1997) and have been highlighted as a neuropsychological dysfunction that is core to the disorder (Silver *et al*. 2003; Joyce & Huddy, 2004). Impairments in visuospatial working memory are evident early in the course of schizophrenia (Wood *et al*. 2002, 2003; Smith *et al*. 2006; Vance *et al*. 2006), but it is unclear whether impairments in SWM predate the onset of psychosis. Studies of monozygotic and dizygotic twins pairs discordant for schizophrenia (Cannon *et al*. 2000; Glahn *et al*. 2005) indicate that SWM deficits are associated with increased genetic risk for schizophrenia, and it has been suggested that a higher genetic loading for disease-related traits is linked to greater cognitive impairment (Saperstein *et al*. 2006). Impaired spatial memory performance has also been reported in subjects with high levels of schizotypy (Park *et al*. 1995) or schizotypal personality disorder (Farmer *et al*. 2000), and in those with a history of very preterm birth (Narberhaus *et al*. 2009).

Several studies have reported impaired memory performance in the ARMS (Wood *et al*. 2003; Brewer *et al*. 2005; Francey *et al*. 2005; Lencz *et al*. 2006; Pukrop *et al*. 2007). Brewer *et al*. (2005) found that ARMS subjects showed impairments on measures of visual reproduction and verbal memory, and that this deficit was specific to the subgroup that went on to develop psychosis. Brewer and colleagues performed a paired-associate task, but one that assessed verbal, rather than spatial, memory. To date, functional neuroimaging studies of working memory in the ARMS have been limited to the verbal domain (Broome *et al*. 2009). However, SWM has been studied in the offspring of people with schizophrenia using a memory-guided saccade task; this genetically high-risk group showed decreased activation in the dorsolateral prefrontal and inferior parietal cortex while performing the task relative to controls (Keshavan *et al*. 2002).

In the present study, we used fMRI to assess cortical activation during an object–location paired-associate memory task. This task is complex, comprising elements of encoding, recognition, learning and discrimination (Narberhaus *et al*. 2009). Interpretation of data from non-verbal associative learning tests can be compromised if the stimuli are easy to verbalize (Goldstein *et al*. 1988). Paired-associate learning (PAL) tasks attempt to overcome this problem by pairing abstract designs with spatial locations (Brewer *et al*. 2005). The paradigm we used also incorporated different levels of mnemonic load, which allowed us to examine whether functional deficits were related to the demands on working memory. In addition, the repetition of trials over the course of the study enables us to examine whether abnormalities were related to the ability to learn the relationship between the pairs of stimuli and their spatial location. We studied three groups: (1) patients with a first episode of schizophrenia, (2) subjects with an ARMS, and (3) healthy controls. We hypothesized that, relative to controls, individuals with an ARMS would show qualitatively similar functional abnormalities to patients with first-episode psychosis (FEP) but that the magnitude of these abnormalities would be less severe. More

specifically, we predicted that group differences in activation would be evident in the frontal and parietal cortex (Curtis, 2006), with the superior frontal cortex implicated in the maintenance of spatial information and the dorsolateral cortex implicated in its manipulation (Postle *et al*. 2000), and that these differences would become more apparent as the mnemonic demands of the task were increased (Gould *et al*. 2003). A further prediction was that differential frontal and parietal activation would be evident in association with differential learning across repeated trials of the task (Brewer *et al*. 2005; Lencz *et al*. 2006).

Method

Subjects

ARMS group

Individuals meeting PACE criteria for the ARMS were recruited from Outreach and Support in South London (OASIS; Broome *et al*. 2005*a*). The diagnosis was based on assessment by two experienced clinicians using the Comprehensive Assessment for the ARMS (CAARMS; Yung *et al*. 1998, 2003) and a consensus meeting with the clinical team. None of the subjects had ever received antipsychotic medication. An individual can meet criteria for the ARMS in one or more of three ways: first, a recent decline in function coupled with either schizotypal personality disorder or a first-degree relative with psychosis; second, 'attenuated' positive symptoms; and third, a brief psychotic episode of less than 1 week's duration that resolves without antipsychotic medication.

FEP group

Patients who had recently presented with a first episode of psychosis ($n=10$) were recruited from Lambeth Early Onset (LEO) Services (www.slam.nhs.uk/services/). All met ICD-10 criteria for schizophreniform psychosis at the time of scanning and met OPCRIT criteria (McGuffin *et al*. 1991) for schizophrenia when subsequently reassessed 12 months after first presentation. Three of these patients were unmedicated. The other seven had been treated with either oral risperidone or quetiapine for a mean of 10 days [95% confidence interval (CI) 4.7–16.3] at mean doses of 1.7 and 63.75 mg respectively.

Controls

Healthy volunteers ($n=15$) were recruited through advertisements in the local media. All subjects lived in the borough of Lambeth (London), were native speakers of English and were right-handed. The groups were matched on sociodemographic variables (Table 1), including age ($F=0.35$, $p=0.71$) and handedness. Subjects were excluded if there was a history of neurological disorder or they met DSM-IV criteria for a substance misuse disorder. General intellectual function was estimated in all subjects using the National Adult Reading Test (NART). The severity of symptoms in the clinical groups was assessed with the Positive and Negative Syndrome Scale (PANSS; Kay, 1990) on the day of scanning by a psychiatrist (M.R.B. or P.M.) trained in its use.

Table 1. *Age, IQ, gender and psychopathology ratings*

	Controls ($n=15$)	ARMS ($n=17$)	FEP ($n=10$)
Age (years)	25.4 (4.9)	24.2 (4.1)	25.5 (5.9)
NART IQ	111.2 (7.2)	102.9 (11.9)	103.6 (9.2)
Gender (M:F)	11:4	12:5	7:3
PANSS Total	N.A.	51. 9 (12.7)	58.1 (9.5)
PANSS Positive	N.A.	11.7 (3.4)	18.5 (4.6)
PANSS Negative	N.A.	10.6 (4.1)	10.0 (2.3)
PANSS General	N.A.	20.9 (9.2)	29.6 (5.9)

NART, National Adult Reading Test; M, male; F, female; PANSS, Positive and Negative Syndrome Scale; ARMS, at-risk mental state; FEP, first-episode psychosis; N.A., not applicable.

Values given as mean (standard deviation).

Experimental task

Stimuli were presented in 22.5 s epochs, alternating with 34.5 s epochs of cross-hair fixation; this cycle was repeated 12 times (for a total of 24 epochs) so the total duration of the experiment was 686 s or 343 images [repetition time (TR) = 2 s]. Cognitive load was manipulated by presenting trials at one of three levels of difficulty (easy, intermediate, and hard) in a block design, with four blocks of each level of difficulty. Thus, there were a total of 12 blocks of trials alternating with 12 blocks of cross-hair fixation. The blocks of trials were always presented in the same sequence with respect to level of difficulty: easy, intermediate, and then hard. Each block comprised seven trials.

In an easy trial, two stimuli (highly discriminable coloured shapes) were shown either side (left and right) of a central cross-hair, followed by the central cross-hair alone, then the central presentation of one of the two original stimuli. Subjects had been trained to move a joystick with their right hand in the direction of the location originally occupied by the central stimulus. Intermediate and hard trials were the same except that four and eight stimuli were presented around the central cross-hair respectively. The speed

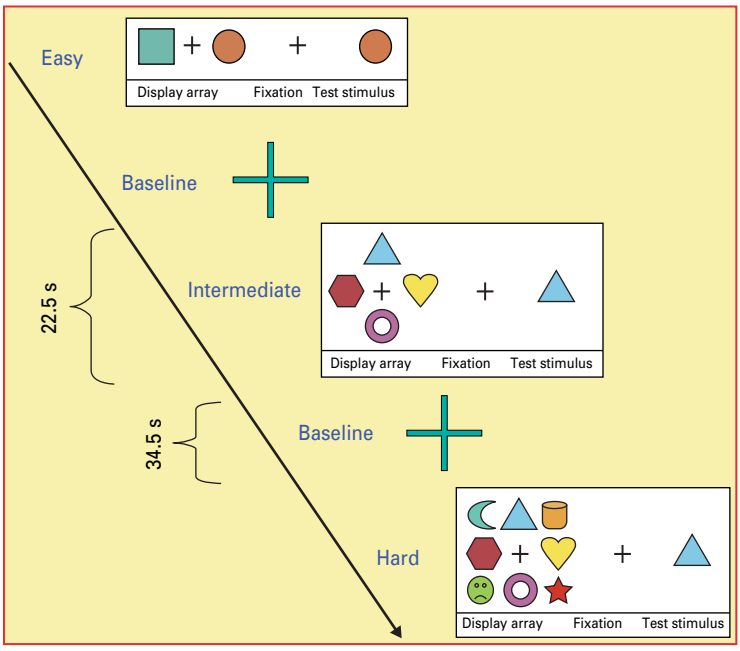


Fig. 1. The paired-associate learning task.

and accuracy of the joystick movements were recorded during scanning. To avoid habituation of the subject, every stimulus had a randomly varied time of presentation, either between stimuli or before the presentation of the probe. As the stimuli were jittered randomly in every block, we did not need to take account of this in the block design analysis (Fig. 1).

Behavioural data

All behavioural data, response accuracy and response latency, were recorded on a personal computer using Visual Basic (Microsoft Corp., USA) and analysed in SPSS version 11.0 (SPSS Inc., USA).

Image acquisition

Images were acquired on a 1.5-T Signa (GE) system at the Maudsley Hospital, London. T2*-weighted images were acquired in 38×3 mm slices, with a 0.3 mm gap in 14 axial planes, and a TR of 2 s, echo time (TE) 40 ms, and flip angle 90°. To facilitate anatomical localization of activation, a high-resolution inversion recovery image dataset was also acquired, with 3 mm contiguous slices and an in-plane resolution of 3 mm [TR 1600 ms, inversion time (TI) 180 ms, TE 80 ms].

Image analysis

Individual brain activation maps

The data were analysed with software developed at the Institute of Psychiatry, using a non-parametric approach. Data were realigned (Bullmore *et al*. 1999*b*) and then smoothed using a Gaussian filter [full-width at half-maximum (FWHM) 7.2 mm]. Responses to the experimental paradigms were detected by convolving each component of the design with each of two gamma variate functions (peak responses at 4 and 8 s respectively). The best fit between the weighted sum of these convolutions and the time series at each voxel was computed using the constrained blood oxygen level-dependent (BOLD) effect model (Friman *et al*. 2003). A goodness-of-fit statistic comprising the ratio of the sum of squares of deviations from the mean image intensity (over the whole time series) divided by the sum of squares of deviations due to the residuals (SSQratio) was then computed at each voxel.

The data were then permuted by a wavelet-based method (Bullmore *et al*. 2001) to calculate the null distribution of SSQratios under the assumption of no experimentally determined response. This was used to calculate the critical value of SSQratio needed to threshold the maps at a type I error rate of <1. The detection of activated voxels was then extended from voxel to cluster level (Bullmore *et al*. 1999*a*). To minimize the potential confounding effects of between-group and between-condition variation in task performance, in the analysis of data from the task the BOLD response in each subject was modelled using only trials associated with correct responses. In addition to the SSQratio, the size of the BOLD response to each experimental condition was computed for each individual at each voxel as a percentage of the mean resting image intensity level. To calculate the BOLD

effect size, the difference between the maximum and minimum values of the fitted model for each condition was expressed as a percentage of the mean image intensity level over the whole time series.

Group maps

The SSQratio maps for each individual were transformed into the standard space of Talairach & Tournoux (1988) using a two-stage warping procedure (Brammer *et al*. 1997). Group activation maps were computed by determining the median SSQratio at each voxel (across all individuals) in the observed and permuted data maps. The distribution of median SSQratios from the permuted data was used to derive the null distribution of SSQratios and the critical SSQratio to threshold group activation maps at a cluster level threshold of <1 expected type I error cluster per brain.

Linear trend analysis

Two different types of linear trend analysis were performed to assess linear change in neural activation dependent on group (analysis 1) and on mnemonic load (analysis 2). In the first analysis, for each mnemonic load (easy, intermediate, hard), control, ARMS and FEP subjects were respectively coded with dummy variables -1, 0 and 1. A linear model was selected to test the hypothesis that activation in the ARMS group would be intermediate between that in the controls and FEP subjects. In the second analysis, for each group (ARMS, control, FEP), the easy, intermediate and difficult levels of the task were respectively coded with dummy variables -1, 0 and 1. In this case a linear model was selected to test the hypothesis that activation at the intermediate level would be intermediate between that during the easy and hard levels. To minimize the potential confounding effects of between-group and between-condition variation in task performance, in each subject the BOLD response was covaried with the performance score. To ensure that we examined whether the middle group was intermediate in both the linear trend analyses (ARMS group in comparison to FEP and controls; medium mnemonic load in comparison to easy or hard load), an additional quadratic trend analysis was performed using the dummy variables (-1, 2, -1). Data that failed to fit this model, but that fitted the linear model, would hence have a middle group that was indeed intermediate between the other groups.

ANOVA was carried out on the effect size maps representing percentage change in BOLD response in standard space by first computing the difference in median SSQratio between groups at each voxel. Subsequent inference of the probability of this difference under the null hypothesis was made by reference to the null distribution obtained by repeated random permutation of group membership and recomputation of the difference in median SSQratios between the two groups obtained from the resampling process. Cluster-level maps were then obtained as described above. We set a voxel-wise p value of 0.05 and a cluster-wise p value of 0.01. This method ensured a total number of false-positive clusters of <1. Corrections for multiple comparisons were not required, as thresholds were set on an image-wide, not a voxel-wise, basis.

Group comparison

Given the possible limitations of the linear trend analysis described above, and to identify more precisely the relationship between groups (ARMS, FEP, control), task loads (two objects, four object, eight objects), or the effects of task repetition (comparing the first half of the run with the latter half), *post-hoc* comparisons were made between the respective conditions. Comparison of responses between groups or experimental conditions was performed by fitting the data at each intracerebral voxel at which all subjects had non-zero data using a linear model of the type $Y=a+bX+e$, where Y is the vector of BOLD effect sizes for each individual, X is the contrast matrix for the particular inter-condition/group contrasts required, a is the mean effect across all individuals in the various conditions/groups, b is the computed group/condition difference and e is a vector of residual errors. The model was fitted by minimizing the sum of absolute deviations rather than the sums of squares to reduce outlier effects. The null distribution of b was computed by permuting data between conditions/groups (assuming the null hypothesis of no effect of experimental condition or group membership) and refitting the above model. Group difference maps were computed using BOLD effect maps rather than standardized measures such as SSQratio, F or t as these contain explicit noise components (error SSQ or error variance), raising the possibility that group differences resulting from F, SSQratio or t comparisons could reflect differences in noise rather than signal.

Statistical significance

We have consistently adopted stringent levels of statistical significance for all the hypothesis tests reported on imaging data. For all between-group ANOVAs we set a voxel-wise p value of 0.05 and a cluster-wise p value of 0.01. For trend analysis conducted at cluster level, we set a voxel-wise p value of 0.05 and a cluster-wise probability p value of 0.01. This method ensured

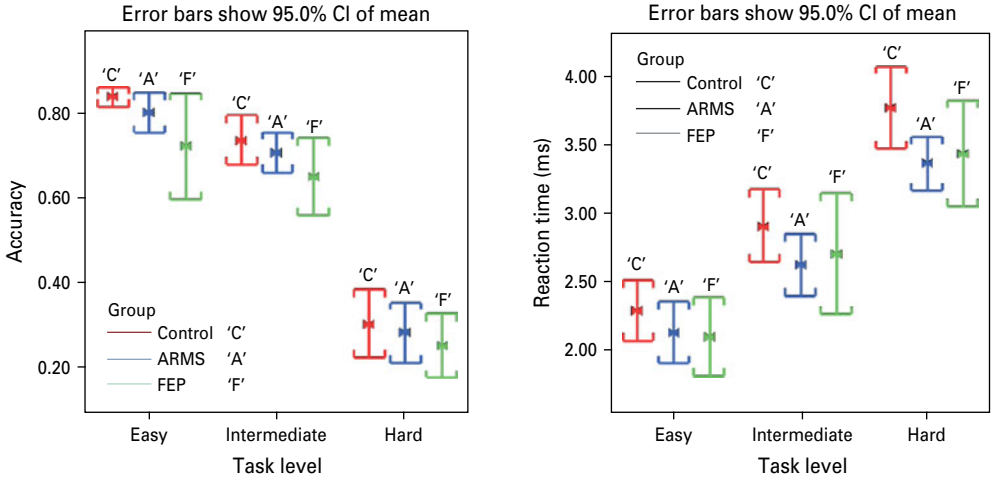


Fig. 2. Performance during the paired-associate learning (PAL) task. ARMS, 'At-risk mental state'; FEP, first-episode psychosis.

a total number of false-positive clusters of <1. Corrections for multiple comparisons were not required, as thresholds were set on an image-wide, not a voxel-wise, basis.

The method of analysis we used (XBAM) makes use of median statistics to control outlier effects and permutation rather than normal theory-based inference. The main test statistic is computed by standardizing for individual differences in residual noise before embarking on second-level, multi-subject testing using robust permutation-based methods. Approaches using a mixed effects analysis and permutation-based and cluster-level inference seem to be more valid than analyses involving simple random effects and voxel-level inference (Thirion *et al*. 2007).

Results

Behavioural data

Repeated-measures ANCOVA showed a main effect for task difficulty with respect to accuracy ($F=154.29$, $p<0.00$) and latency ($F=229.47$, $p<0.00$). As the mnemonic load increased, response latency increased and response accuracy decreased in an approximately linear fashion (Fig. 2). No main effect for group was observed with respect to accuracy ($F=1.59$, $p=0.271$) or latency ($F=1.7$, $p=0.247$). However, *post-hoc* analysis revealed that, compared to controls, FEP showed impaired accuracy during the intermediate and hardest level of the task (t tests <0.05). No significant interactions of group by task load were observed with respect to accuracy ($F=0.226$, $p=0.013$) or latency ($F=1.19$, $p=0.415$) (Fig. 2).

To explore the effect for learning, we compared the accuracy in the first half of the run with accuracy in the second half of the run. During the easiest level of the task, there were no significant differences in accuracy between the first and the last blocks (paired t tests >0.05). Conversely, when performing the more demanding levels of the task (intermediate plus hard level), subjects performed better during the second half of the run than the first. This effect was evident for all three groups, FEP, ARMS and controls (all t tests <0.05).

fMRI results

Main effect of task (independent of group and mnemonic load): group analysis

Across all groups and levels of task demand, relative to baseline (cross-hair fixation), the task was associated with activation in a wide region spanning the cerebellum and occipital cortex bilaterally (precuneus $x=-25$, $y=-70$, $z=37$). Conversely, cross-hair fixation was associated with activation in the left posterior cingulate gyrus ($x=-7$, $y=-63$, $z=15$) (voxel $p=0.05$, cluster $p=0.001$, type I error $p<1$).

Activation associated with mnemonic load: linear trend analysis

Independent of group, increasing the number of stimuli (from two to four to eight) was associated with activation in the left medial frontal/superior frontal and precentral gyrus, the cerebellum bilaterally and the right cuneus (voxel $p=0.05$, cluster $p=0.01$, type I error, $p<1$). After controlling for response accuracy, the activation in the left medial frontal/superior frontal gyrus and right precuneus remained significant (voxel $p=0.05$, cluster $p=0.01$). In both these regions the intermediate level of the task showed less activation than the most demanding level but greater activation than the easy level (all t tests <0.05) (Fig. 3).

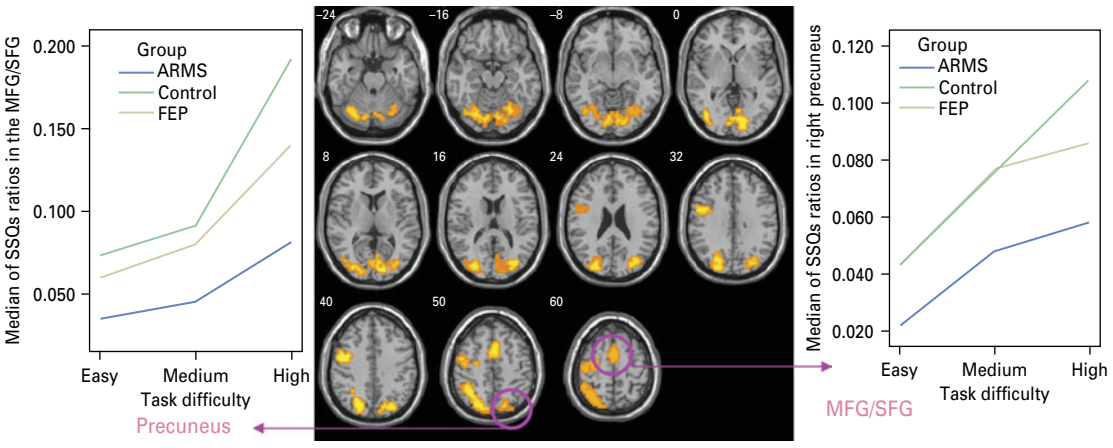


Fig. 3. Main effect for task difficulty across all groups. Areas shown in yellow revealed increasing activation as task demand was increased (high level > medium level > easy level). MFG, medial frontal gyrus; SFG, superior frontal gyrus; ARMS, 'at-risk mental state'; FEP, first-episode psychosis.

Changes in activation dependent upon group: linear trend analyses

Easy level (*two objects*). While performing the easiest level of the PAL task, there was differential activation across the three groups in a cluster spanning the medial frontal and anterior cingulate gyrus (voxel $p<0.05$, cluster $p<0.01$) (Fig. 4*a*). In this region the magnitude of activation in the ARMS group was similar to that in controls, whereas the FEP group showed less activation than both other groups. *Post-hoc* paired comparisons confirmed that the FEP group showed significantly less activation than both the ARMS and control groups (t tests <0.05), with no significant difference between the latter two groups (t tests >0.05) (Fig. 4*a*). These differences remained significant after covarying for accuracy (voxel $p<0.05$, cluster $p<0.01$).

Intermediate level (*four objects*). While performing the intermediate level of the PAL task, we detected differential activation across the three groups in the right cerebellum, right precuneus [Brodmann area (BA) 19] and medial frontal/superior frontal gyrus (BA 6/32) (voxel $p<0.05$, cluster $p<0.025$; Fig. 4*b*). In these regions the magnitude of activation in the ARMS group was intermediate between that of the controls and FEP subjects, with the FEP group showing less activation than both other groups, and control subjects the greatest activation.

Hard level (*eight objects*). While subjects were performing the most demanding level of the PAL task, there was differential activation across the three groups in the medial frontal gyrus/superior frontal gyrus (BA 32/6) and right precuneus (19) (voxel $p<0.05$, cluster $p<0.01$; Fig. 4*c*). In these regions the magnitude of activation in the ARMS group was intermediate between that of both controls and FEP subjects, with the FEP group showing less activation than both other groups and the control subjects the greatest (Fig. 5). These differences remained significant after covarying for accuracy (voxel $p<0.05$, cluster $p<0.01$).

Main effect of task repetition (*independent of group*): *group analysis*

Across all groups, processing the most demanding levels of the task (intermediate plus hard) was associated with a greater activation in the right precuneus ($x=21$, $y=-59$, $z=36$) during the second half of the run than that in the first half (voxel $p=0.01$, cluster $p=0.0075$). There were no brain areas that showed greater activation in the first half of the run compared with the second (Fig. 5).

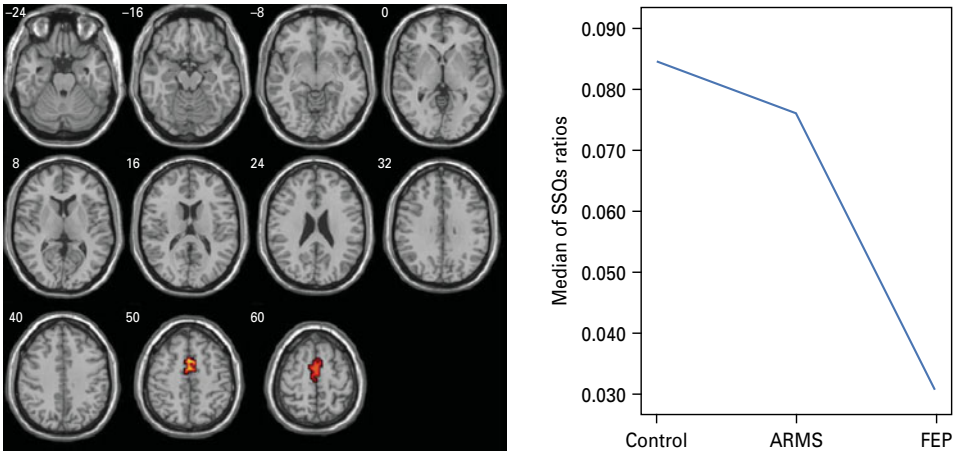
Group differences in effect of task repetition

There was also a difference between the groups in the effect of repetition of the most demanding levels of the task in a region spanning the left cuneus/precuneus (BA 7/19, $x=-10$, $y=-74$, $z=31$). In this region, there was a greater response during the second half of the run relative to the first, with the magnitude of the within-group difference greatest in the FEP group, smallest in the controls and intermediate in the ARMS (all t tests <0.05).

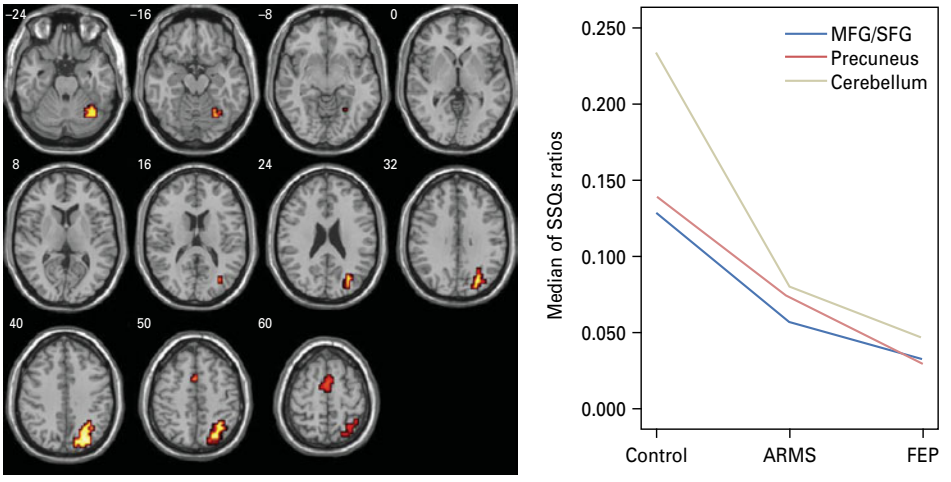
Effects of antipsychotic medication: correlational analysis

Within the FEP group (which was the only group that included subjects on antipsychotic medication), for all levels of task demand, there was no correlation

(*a*)



(*b*)



(*c*)

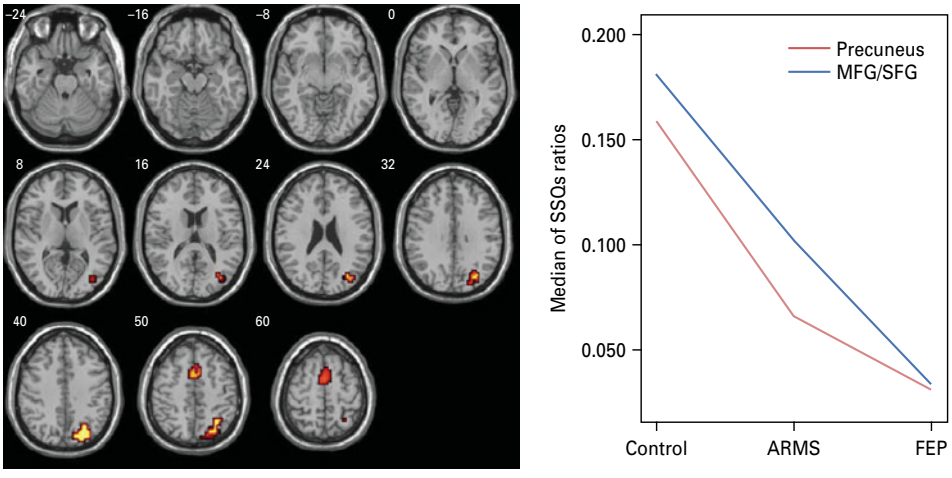


Fig. 4. (*a*) Easy level: between-group difference in activation (controls > ARMS > FEP) in the medial frontal gyrus (voxel $p = 0.05$, cluster $p = 0.01$). The left side of the brain is shown on the left of the picture. (*b*) Intermediate level: between-group differences in activation (controls > ARMS > FEP) in the middle frontal gyrus, right precuneus and right cerebellum (voxel $p = 0.05$, cluster $p = 0.01$). (*c*) Hard level: between-group differences in activation (controls > ARMS > FEP) in the medial frontal gyrus and right precuneus (voxel $p = 0.05$, cluster $p = 0.01$). MFG, medial frontal gyrus; SFG, superior frontal gyrus; ARMS, 'at-risk mental state'; FEP, first-episode psychosis.

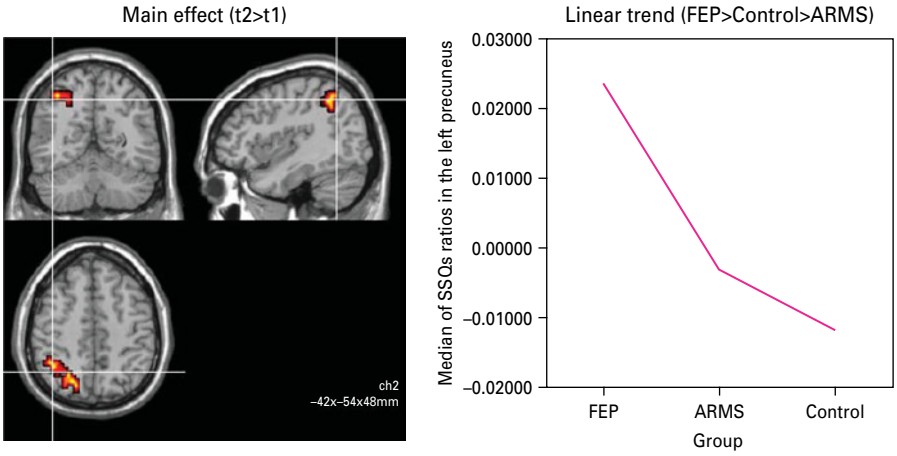


Fig. 5. Effect of learning on activation. There was a main effect across all groups in the right precuneus, with greater activation during the second half of the experiment (voxel $p=0.05$, cluster $p=0.01$). t1 = intermediate and hard level of the paired-associate learning (PAL) task during the first half of the run; t2 = intermediate and hard level of the task during the second half of the run. ARMS, 'At-risk mental state'; FEP, first-episode psychosis.

(Pearson's r, $n=10$, $p>0.05$) between activation in brain areas that were differentially engaged in the FEP group relative to the other two groups and measures of antipsychotic treatment (daily and cumulative dose in chlorpromazine equivalents, or exposure).

Discussion

The present study used fMRI to study the neural substrate of SWM in subjects with an ARMS. In line with our hypothesis, there was a consistent pattern of differential activation across the groups on all levels of difficulty of the task, with an additional differential response across the groups on the analysis to examine the effects of learning.

The differential activation was not attributable to impairments in task performance, as there were no significant differences in the speed or accuracy of responses across groups, and the analysis selectively modelled the BOLD response to those trials associated with correct responses. Hence, any remaining difference in activation is likely to be due to the disorder of interest.

Similarly, the findings are unlikely to be related to effects of antipsychotic medication as both the ARMS subjects and controls were antipsychotic medication naive, and in the first-episode group there was no relationship between medication exposure and activation in the regions that were differentially engaged across groups.

When quadratic trend analysis was carried out, there were no significant clusters activated differentially across the groups, indicating that there was a predominantly linear relationship in activation across the groups on all the tasks.

Neural network underlying object and SWM

Compared to cross-hair fixation, PAL engaged a wide area spanning the cerebellum and visual cortex bilaterally. We also manipulated task difficulty by parametrically varying memory load in the task. We found that the medial frontal/superior frontal gyrus and the right precuneus showed a linear response. These brain areas have been extensively implicated in spatial and object working memory (McCarthy *et al*. 1996; LaBar *et al*. 1999; Rypma *et al*. 1999).

A medial superior frontal gyrus region, centred on the supplementary motor area (SMA), has been traditionally associated with motor control necessary in the selection of action sets and in monitoring of response conflict (Rushworth *et al*. 2004) and also speech expression and memory (Chung *et al*. 2005). The anterior part of the SMA is known to interconnect with the prefrontal cortex and to play a role in the more complex components of movement (Exner *et al*. 2006). As such, the role of the SMA is likely to be key in performing the SWM task. The absence of hippocampal activation may suggest that such activation does not distinguish the groups or the effect of mnemonic load. However, imaging data have demonstrated both over- and underactivation of the hippocampus in memory tasks in schizophrenia (Boyer *et al*. 2007).

Functional imaging findings in healthy subjects evidenced a central role for the precuneus, in visuospatial imagery, episodic memory retrieval (Krause *et al*. 1999; Wagner *et al*. 2005) and self-processing operations (Cavanna & Trimble, 2006). Nagahama *et al*. (1999) showed that the precuneus may process spatial attention and attention shift between object features. Lesion studies suggest that the dorsal stream of the 'visuospatial sketchpad' involves the

precuneus, and this may enable spatial operations (Muller & Knight, 2006). Hence, our finding implicating differential precuneus activation may be due to its probable role in visual imagery, spatial behaviour and spatial attention, all functions relevant for the SWM task.

Group differences in activation

Consistent with our first hypothesis, during both the intermediate and the hard versions of the task, activation in the medial frontal cortex and precuneus in the ARMS group was intermediate relative to that in the FEP group and controls. The localization of the group differences in activation in the medial frontal cortex and precuneus is consistent with data from previous neuroimaging studies of SWM in schizophrenia (Gould *et al*. 2003; Curtis, 2006). A different pattern of activation across groups was evident during the least demanding ('easy') version of the task. In this case there were no significant differences in activation between the ARMS and the control subjects, and differences in activation were limited to the medial frontal cortex, which responded more weakly in the FEP than the other groups. This suggests that functional abnormalities in the ARMS group became more evident as the task demands were increased, as has been reported in behavioural studies of other paradigms (Broome *et al*. 2007).

SWM as a neurocognitive vulnerability marker for psychosis

Kuperberg *et al*. (2003) found significant cortical thinning in the medial frontal areas of adult schizophrenic patients, and grey matter reductions have been reported in the medial premotor cortex (Honey *et al*. 2003). Imaging studies suggest that the medial frontal gyrus (Stevens *et al*. 1998; Paillere-Martinot *et al*. 2001) and the medial prefrontal cortex (Ananth *et al*. 2002) are affected early in psychosis. Suzuki *et al*. (2005) found the SMA to be reduced in subjects with recent-onset schizophrenia whereas Exner *et al*. (2006) showed that reduced volume of the SMA in FEP subjects was related to impaired implicit learning. Medial frontal cortex dysfunction is compatible with the hypothesis of a core deficit in early stages of psychosis involving a failure to monitor actions generated internally (Exner *et al*. 2006). Activation in the cuneus and precuneus increased in the second half of the run, during the harder versions of the task, in all three groups. However, this increase itself was greatest in the FEP group, least in the controls, and intermediate in the ARMS cohort. Given that behavioural performance improved, it is likely that this differential activation of the precuneus may underpin such a learning effect, and, furthermore, that greater activation in the FEP group is required than in the control group (with the ARMS group intermediate) to enable the same degree of learning. Barnett *et al*. (2005) suggested that visuospatial PAL failure may be a marker of clinical severity, in a first-episode cohort, whereas executive dysfunction may reflect more stable, trait-like impairment. However, in our data there seems to be some relationship between executive function and clinical course in the at-risk sample (Fusar-Poli *et al*. 2009) and we are currently undertaking longitudinal studies of the PAL task in the at-risk cohort.

Conclusions

This study suggests that the ARMS is associated with a dysfunction in the neural substrate for SWM. This is not attributable to an effect of psychotic illness, as none of the subjects were psychotic, nor an effect of antipsychotic treatment, as all of the ARMS subjects were medication naive. These observations are consistent with independent neuroimaging and neuropsychological evidence that the ARMS is associated with neurofunctional abnormalities that are qualitatively similar to, but less severe than, those seen in patients with schizophrenia (Broome *et al*. 2005*b*, 2007, 2009; Fusar-Poli *et al*. 2007). As those in the ARMS group had a high risk of developing a psychotic disorder but were not psychotic, the functional abnormalities they displayed can be seen as a correlate of their increased vulnerability to psychosis.

Limitations of the study

This study reports cross-sectional data, from a modestly sized sample, on ARMS, FEP and control subjects. The findings in the ARMS group may be a correlate of the subjects' increased vulnerability to psychosis. However, to determine this formally will require a longitudinal study, a study informed by the findings presented here and, in particular, whether the pattern and degree of activation during visuospatial working memory tasks predict transition to psychosis in a clinical high-risk group. We hope to report longitudinal fMRI data, and particularly the relationship to clinical outcomes such as transition to psychosis, in the future.

Acknowledgements

OASIS is supported by the Guy's and St Thomas' Charitable Foundation and the South London and Maudsley National Health Service (NHS) Trust. We thank all the clients, staff and referrers of both OASIS and LEO.

Declaration of Interest

None.

References

Ananth H, Popescu I, Critchley HD, Good CD, Frackowiak RS, Dolan RJ (2002). Cortical and subcortical gray matter abnormalities in schizophrenia determined through structural magnetic resonance imaging with optimized volumetric voxel-based morphometry. *American Journal of Psychiatry* **159**, 1497–1505.

Barnett JH, Sahakian BJ, Werners U, Hill KE, Brazil R, Gallagher O, Bullmore ET, Jones PB (2005). Visuospatial learning and executive function are independently impaired in first-episode psychosis. *Psychological Medicine* **35**, 1031–1041.

Boyer P, Phillips JL, Rousseau FL, Ilivitsky S (2007). Hippocampal abnormalities and memory deficits: new evidence of a strong pathophysiological link in schizophrenia. *Brain Research Reviews* **54**, 92–112.

Brammer M, Bullmore E, Simmons A, Williams S, Grasby PM, Howard RJ, Woodruff PW, Rabe-Hesketh S (1997). Generic brain activation mapping in functional magnetic resonance imaging: a nonparametric approach. *Magnetic Resonance Imaging* **15**, 763–770.

Brewer WJ, Francey SM, Wood SJ, Jackson HJ, Pantelis C, Phillips LJ, Yung AR, Anderson VA, McGorry PD (2005). Memory impairments identified in people at ultra-high risk for psychosis who later develop first-episode psychosis. *American Journal of Psychiatry* **162**, 71–78.

Broome MR, Johns LC, Valli I, Woolley JB, Tabraham P, Brett C, Valmaggia L, Peters E, Garety PA, McGuire PK (2007). Delusion formation and reasoning biases in those at clinical high risk for psychosis. *British Journal of Psychiatry* **191**, s38–s42.

Broome MR, Matthiasson P, Fusar-Poli P, Woolley JB, Johns LC, Tabraham P, Bramon E, Valmaggia L, Williams SCR, Brammer MJ, Chitnis X, McGuire PK (2009). Neural correlates of executive function and working memory in the 'at-risk mental state'. *British Journal of Psychiatry* **194**, 25–33.

Broome MR, Woolley JB, Johns LC, Valmaggia LR, Tabraham P, Gafoor R, Bramon E, McGuire PK (2005*a*). Outreach and support in South London (OASIS): implementation of a clinical service for prodromal psychosis and the at risk mental state. *European Psychiatry* **20**, 372–378.

Broome MR, Woolley JB, Tabraham P, Johns LC, Bramon E, Murray GK, Pariante C, McGuire PK, Murray RM (2005*b*). What causes the onset of psychosis? *Schizophrenia Research* **79**, 23–34.

Bullmore E, Long C, Suckling J, Fadili J (2001). Coloured noise and computational inference in neurophysiological (fMRI) series analysis: resampling methods in time and wavelet domains. *Human Brain Mapping* **12**, 61–78.

Bullmore ET, Suckling J, Overmeyer S, Rabe-Hesketh S, Taylor E, Brammer MJ (1999*a*). Global, voxel and cluster tests, by theory and permutation, for a difference between two groups of structural MR images of the brain. *Transcranial Medical Imaging* **18**, 32–42.

Bullmore ET, Brammer MJ, Rabe-Hesketh S, Curtis VA, Morris RG, Williams SC, Sharma T, McGuire PK (1999*b*). Methods for diagnosis and treatment of stimulus-correlated motion in generic brain activation studies using fMRI. *Human Brain Mapping* **7**, 38–48.

Cannon TD, Huttunen MO, Lonnqvist J, Tuulio-Henriksson A, Pirkola T, Glahn D, Finkelstein J, Hietanen M, Kaprio J, Koskenvuo M (2000). The inheritance of neuropsychological dysfunction in twins discordant for schizophrenia. *American Journal of Human Genetics* **67**, 369–382.

Cavanna AE, Trimble MR (2006). The precuneus: a review of its functional anatomy and behavioural correlates. *Brain* **129**, 564–583.

Chakos MH, Schobel SA, Gu H, Gerig G, Bradford D, Charles C, Lieberman JA (2005). Duration of illness and treatment effects on hippocampal volume in male patients with schizophrenia. *British Journal of Psychiatry* **186**, 26–31.

Chung GH, Han YM, Jeong SH, Jack Jr. CR (2005). Functional heterogeneity of the supplementary motor area. *American Journal of Neuroradiology* **26**, 1819–1823.

Curtis CE (2006). Prefrontal and parietal contributions to spatial working memory. *Neuroscience* **139**, 173–180.

Dazzan P, Morgan KD, Orr K, Hutchinson G, Chitnis X, Suckling J, Fearon P, McGuire PK, Mallett RM, Jones PB, Leff J, Murray RM (2005). Different effects of typical and atypical antipsychotics on grey matter in first episode psychosis: the AESOP study. *Neuropsychopharmacology* **30**, 765–774.

Exner C, Weniger G, Schmidt-Samoa C, Irle E (2006). Reduced size of the pre-supplementary motor cortex and impaired motor sequence learning in first-episode schizophrenia. *Schizophrenia Research* **84**, 386–396.

Farmer CM, O'Donnell BF, Niznikiewicz MA, Voglmaier MM, McCarley RW, Shenton ME (2000). Visual perception and working memory in schizotypal personality disorder. *American Journal of Psychiatry* **157**, 781–788.

Fleming K, Goldberg TE, Binks S, Randolph C, Gold JM, Weinberger DR (1997). Visuospatial working memory in patients with schizophrenia. *Biological Psychiatry* **41**, 43–49.

Francey SM, Jackson HJ, Phillips LJ, Wood SJ, Yung AR, McGorry PD (2005). Sustained attention in young people at high risk of psychosis does not predict transition to psychosis. *Schizophrenia Research* **79**, 127–136.

Friman O, Borga P, Lundberg P (2003). Adaptive analysis of fMRI data. *NeuroImage* **19**, 837–845.

Fusar-Poli P, Broome MR, Matthiasson P, Woolley JB, Mechelli A, Johns LC, Tabraham P, Bramon E, Valmaggia L, Williams S, McGuire P (2009). Prefrontal response during executive functioning directly related to twelve months clinical outcome in people at ultra high risk of psychosis. *Schizophrenia Bulletin*. Published online: 7 August 2009. doi:10.1093/schbul/sbp074.

Fusar-Poli P, Perez J, Broome M, Borgwardt S, Placentino A, Caverzasi E, Cortesi M, Veggiotti P, Politi P, Barale F,

McGuire P (2007). Neurofunctional correlates of vulnerability to psychosis: a systematic review and meta-analysis. *Neuroscience and Biobehavioral Reviews* **31**, 465–484.

Glahn DC, Ragland JD, Abramoff A, Barrett J, Laird AR, Bearden CE, Velligan DI (2005). Beyond hypofrontality: a quantitative meta-analysis of functional neuroimaging studies of working memory in schizophrenia. *Human Brain Mapping* **25**, 60–69.

Goldstein LH, Canavan AG, Polkey CE (1988). Verbal and abstract designs paired associate learning after unilateral temporal lobectomy. *Cortex* **24**, 41–52.

Gould RL, Brown RG, Owen AM, ffytche DH, Howard RJ (2003). fMRI BOLD response to increasing task difficulty during successful paired associates learning. *NeuroImage* **20**, 1006–1019.

Honey GD, Sharma T, Suckling J, Giampietro V, Soni W, Williams SC, Bullmore ET (2003). The functional neuroanatomy of schizophrenic subsyndromes. *Psychological Medicine* **33**, 1007–1018.

Joyce E, Huddy V (2004). Defining the cognitive impairment in schizophrenia. *Psychological Medicine* **34**, 1151–1155.

Kay SR (1990). Positive-negative symptom assessment in schizophrenia: psychometric issues and scale comparison. *Psychiatry Quarterly* **61**, 163–178.

Keshavan MS, Diwadkar VA, Spencer SM, Harenski KA, Luna B, Sweeney JA (2002). A preliminary functional magnetic resonance imaging study in offspring of schizophrenic parents. *Progress in Neuropsychopharmacology and Biological Psychiatry* **26**, 1143–1149.

Krause BJ, Schmidt D, Mottaghy FM, Taylor J, Halsband U, Herzog H, Tellmann L, Muller-Gartner HW (1999). Episodic retrieval activates the precuneus irrespective of the imagery content of word pair associates. A PET study. *Brain* **122**, 255–263.

Kuperberg GR, Broome MR, McGuire PK, David AS, Eddy M, Ozawa F, Goff D, West WC, Williams SC, van der Kouwe AJ, Salat DH, Dale AM, Fischl B (2003). Regionally localized thinning of the cerebral cortex in schizophrenia. *Archives of General Psychiatry* **60**, 878–888.

LaBar KS, Gitelman DR, Parrish TB, Mesulam MM (1999). Neuroanatomic overlap of working memory and spatial attention networks: a functional MRI comparison within subjects. *NeuroImage* **10**, 695–704.

Lencz T, Smith CW, McLaughlin D, Auther A, Nakayama E, Hovey L, Cornblatt BA (2006). Generalized and specific neurocognitive deficits in prodromal schizophrenia. *Biological Psychiatry* **59**, 863–871.

Lieberman J, Chakos M, Wu H, Alvir J, Hoffman E, Robinson D, Bilder R (2001). Longitudinal study of brain morphology in first episode schizophrenia. *Biological Psychiatry* **49**, 487–499.

Lieberman JA (1999). Is schizophrenia a neurodegenerative disorder? A clinical and neurobiological perspective. *Biological Psychiatry* **46**, 729–739.

McCarthy G, Puce A, Constable T, Krystal JH, Gore JC, Goldman-Rakic P (1996). Activation of human prefrontal cortex during spatial and nonspatial working memory tasks measured by functional MRI. *Cerebral Cortex* **6**, 600–611.

McGuffin P, Farmer A, Harvey I (1991). A polydiagnostic application of operational criteria in studies of psychotic illness. Development and reliability of the OPCRIT system. *Archives of General Psychiatry* **48**, 764–770.

Miller TJ, McGlashan TH, Rosen JL, Somjee L, Markovich PJ, Stein K, Woods SW (2002). Prospective diagnosis of the initial prodrome for schizophrenia based on the Structured Interview for Prodromal Syndromes: preliminary evidence of interrater reliability and predictive validity. *American Journal of Psychiatry* **159**, 863–865.

Morey RA, Inan S, Mitchell TV, Perkins DO, Lieberman JA, Belger A (2005). Imaging frontostriatal function in ultra-high-risk, early, and chronic schizophrenia during executive processing. *Archives of General Psychiatry* **62**, 254–262.

Muller NG, Knight RT (2006). The functional neuroanatomy of working memory: contributions of human brain lesion studies. *Neuroscience* **139**, 51–58.

Nagahama Y, Okada T, Katsumi Y, Hayashi T, Yamauchi H, Sawamoto N, Toma K, Nakamura K, Hanakawa T, Konishi J, Fukuyama H, Shibasaki H (1999). Transient neural activity in the medial superior frontal gyrus and precuneus time locked with attention shift between object features. *NeuroImage* **10**, 193–199.

Narberhaus A, Lawrence E, Allin MP, Walshe M, McGuire P, Rifkin L, Murray R, Nosarti C (2009). Neural substrates of visual paired associates in young adults with a history of very preterm birth: alterations in fronto-parieto-occipital networks and caudate nucleus. *NeuroImage* **47**, 1884–1893.

Paillere-Martinot M, Caclin A, Artiges E, Poline JB, Joliot M, Mallet L, Recasens C, Attar-Levy D, Martinot JL (2001). Cerebral gray and white matter reductions and clinical correlates in patients with early onset schizophrenia. *Schizophrenia Research* **50**, 19–26.

Pantelis C, Velakoulis D, McGorry PD, Wood SJ, Suckling J, Phillips LJ, Yung AR, Bullmore ET, Brewer W, Soulsby B, Desmond P, McGuire PK (2003). Neuroanatomical abnormalities before and after onset of psychosis: a cross-sectional and longitudinal MRI comparison. *Lancet* **361**, 281–288.

Park S, Holzman PS (1992). Schizophrenics show spatial working memory deficits. *Archives of General Psychiatry* **49**, 975–982.

Park S, Holzman PS, Lenzenweger MF (1995). Individual differences in spatial working memory in relation to schizotypy. *Journal of Abnormal Psychology* **104**, 355–363.

Pollmann S, von Cramon DY (2000). Object working memory and visuospatial processing: functional neuroanatomy analyzed by event-related fMRI. *Experimental Brain Research* **133**, 12–22.

Postle BR (2006). Working memory as an emergent property of the mind and brain. *Neuroscience* **139**, 23–38.

Postle BR, Berger JS, Taich AM, D'Esposito M (2000). Activity in human frontal cortex associated with spatial working memory and saccadic behavior. *Journal of Cognitive Neuroscience* **12**, 2–14.

Pukrop R, Ruhrmann S, Schultze-Lutter F, Bechdolf A, Brockhaus-Dumke A, Klosterkotter J (2007). Neurocognitive indicators for a conversion to psychosis: comparison of patients in a potentially initial prodromal

state who did or did not convert to a psychosis. *Schizophrenia Research* **92**, 116–125.

Rapoport JL, Giedd JN, Blumenthal J, Hamburger S, Jeffries N, Fernandez T, Nicolson R, Bedwell J, Lenane M, Zijdenbos A, Paus T, Evans A (1999). Progressive cortical change during adolescence in childhood-onset schizophrenia. A longitudinal magnetic resonance imaging study. *Archives of General Psychiatry* **56**, 649–654.

Rushworth MF, Walton ME, Kennerley SW, Bannerman DM (2004). Action sets and decisions in the medial frontal cortex. *Trends in Cognitive Science* **8**, 410–417.

Rypma B, Prabhakaran V, Desmond JE, Glover GH, Gabrieli JDE (1999). Load-dependent roles of frontal brain regions in the maintenance of working memory. *NeuroImage* **9**, 216–226.

Saperstein AM, Fuller RL, Avila MT, Adami H, McMahon RP, Thaker GK, Gold JM (2006). Spatial working memory as a cognitive endophenotype of schizophrenia: assessing risk for pathophysiological dysfunction. *Schizophrenia Bulletin* **32**, 498–506.

Silver H, Feldman P, Bilker W, Gur RC (2003). Working memory deficit as a core neuropsychological dysfunction in schizophrenia. *American Journal of Psychiatry* **160**, 1809–1816.

Smith CW, Park S, Cornblatt B (2006). Spatial working memory deficits in adolescents at clinical high risk for schizophrenia. *Schizophrenia Research* **81**, 211–215.

Stevens AA, Goldman-Rakic PS, Gore JC, Fulbright RK, Wexler BE (1998). Cortical dysfunction in schizophrenia during auditory word and tone working memory demonstrated by functional magnetic resonance imaging. *Archives of General Psychiatry* **55**, 1097–1103.

Suzuki M, Zhou SY, Takahashi T, Hagino H, Kawasaki Y, Niu L, Matsui M, Seto H, Kurachi M (2005). Differential contributions of prefrontal and temporolimbic pathology to mechanisms of psychosis. *Brain* **128**, 2109–2122.

Talairach J, Tournoux P (1988). *A Co-planar Stereotactic Atlas of the Human Brain*. Thieme Medical Publishers: New York.

Thirion B, Pinel P, Meriaux S, Roche A, Dehaene S, Poline J-B (2007). Analysis of a large fMRI cohort: statistical and methodological issues for group analysis. *NeuroImage* **35**, 105–120.

Valmaggia LR, McCrone P, Knapp M, Woolley JB, Broome MR, Tabraham P, Johns LC, Prescott C, Bramon E, Lappin J, Power P, McGuire PK (2009). Economic impact of early intervention in people at high risk of psychosis. *Psychological Medicine* **39**, 1617–1626.

Vance A, Hall N, Bellgrove MA, Casey M, Karsz F, Maruff P (2006). Visuospatial working memory deficits in adolescent onset schizophrenia. *Schizophrenia Research* **87**, 223–227.

Wagner AD, Shannon BJ, Kahn I, Buckner RL (2005). Parietal lobe contributions to episodic memory retrieval. *Trends in Cognitive Science* **9**, 445–453.

Wagner M, Frommann I, Jessen F, Pukrop R, Bechdolf A, Ruhrmann S, Klosterkotter J, Brinkmeyer J, Woelwer W, Decker P, Maier W (2006). Cognitive and neurobiological risk indicators in early and late prodromal stages. *Schizophrenia Research* **86**, S35–S36.

Wood SJ, Pantelis C, Proffitt T, Phillips LJ, Stuart GW, Buchanan JA, Mahony K, Brewer W, Smith DJ, McGorry PD (2003). Spatial working memory ability is a marker of risk-for-psychosis. *Psychological Medicine* **33**, 1239–1247.

Wood SJ, Proffitt T, Mahony K, Smith DJ, Buchanan JA, Brewer W, Stuart GW, Velakoulis D, McGorry PD, Pantelis C (2002). Visuospatial memory and learning in first-episode schizophreniform psychosis and established schizophrenia: a functional correlate of hippocampal pathology? *Psychological Medicine* **32**, 429–438.

Yung AR, Phillips LJ, McGorry PD, McFarlane CA, Francey S, Harrigan S, Patton GC, Jackson HJ (1998). Prediction of psychosis. A step towards indicated prevention of schizophrenia. *British Journal of Psychiatry* **172**, 14–20.

Yung AR, Phillips LJ, Yuen HP, Francey SM, McFarlane CA, Hallgren M, McGorry PD (2003). Psychosis prediction: 12-month follow up of a high-risk ('prodromal') group. *Schizophrenia Research* **60**, 21–32.

Yung AR, Yuen HP, Berger GE, Francey S, Hung T-C, McGorry P (2007). Declining transition rate in ultra high risk (prodromal) services: dilution or reduction of risk? *Schizophrenia Bulletin* **33**, 673–681.