Brain Advance Access published May 6, 2009

BRAIN
A JOURNAL OF NEUROLOGY

Functional integration between the posterior hippocampus and prefrontal cortex is impaired in both first episode schizophrenia and the at risk mental state

Stefania Benetti,[1] Andrea Mechelli,[1,2] Marco Picchioni,[1,5] Matthew Broome,[3] Steven Williams[4] and Philip McGuire[1]

1 Division of Psychological Medicine and Psychiatry, Section of Neuroimaging, Institute of Psychiatry, King's College London, London, UK
2 King's College London, Department of Psychology, London, UK
3 Psychosis Research Group, Health Science Research Institute, Medical School, University of Warwick, Coventry, UK
4 Department of Clinical Neuroscience, Neuroimaging Research Group, Institute of Psychiatry, King's College London, London, UK
5 St Andrew's Academic Centre, King's College London, Institute of Psychiatry, Northampton, NN1 5BW

Correspondence to: Stefania Benetti,
Division of Psychological Medicine and Psychiatry,
Box P067, Institute of Psychiatry,
De Crespigny Park, SE5 8AF,
London, UK
E-mail: stefania.benetti@iop.kcl.ac.uk

Recent neuroimaging studies have reported deficits in functional integration between prefrontal cortex and the hippocampal formation in schizophrenia. It is unclear whether these alterations are a consequence of chronic illness or its treatment, and whether they are also evident in non-psychotic subjects at increased risk of the disorder. We addressed these issues by investigating prefrontal–hippocampal interactions in patients with first episode schizophrenia and subjects with an At Risk Mental State (ARMS). Using functional Magnetic Resonance Imaging, we measured brain responses from 16 individuals with an ARMS, 10 patients with first episode schizophrenia and 14 healthy controls during a delayed matching to sample task. Dynamic causal modelling was used to estimate the effective connectivity between prefrontal cortex and anterior and posterior hippocampal regions. The normal pattern of effective connectivity from the right posterior hippocampus to the right inferior frontal gyrus was significantly decreased in both first episode patients and subjects with an ARMS (ANOVA; $F = 8.16$, $P = 0.01$). Interactions between the inferior frontal gyrus and the anterior part of the hippocampus did not differ across the three groups. Perturbed hippocampal–prefrontal interactions are evident in individuals at high risk of developing psychosis and in patients who have just developed schizophrenia. This suggests that it may be a correlate of increased vulnerability to psychosis and that it is not attributable to an effect of chronic illness or its treatment.

Keywords: schizophrenia; at risk mental state; object working memory; functional neuroimaging; dynamic casual modelling

Abbreviations: ARMS = At Risk Mental State; DCM = Dynamic Causal Modelling; DMTS = Delayed matching to sample; FE = First Episode; fMRI = functional Magnetic Resonance Imaging; HF = Hippocampal Formation

Received November 14, 2008. Revised March 9, 2009. Accepted March 10, 2009

Introduction

Neuropathological (Arnold and Trojanowski, 1996; Harrison and Eastwood, 2001), structural (Borgets, 1990) and functional (Carter *et al*., 1998; Heckers *et al*., 1998) neuroimaging studies provide converging evidence for localized anatomical and functional abnormalities in both the prefrontal cortex and hippocampal formation in schizophrenia. In addition, cognitive models of schizophrenia propose that a disturbance of the normal interaction between these two regions might underlie many of the associated symptoms and cognitive deficits (Weinberger *et al*., 1992; Fletcher, 1998). Consistent with this notion, several neuroimaging studies have reported altered functional integration between prefrontal and hippocampal regions in schizophrenia (Weinberger *et al*., 1992; Heckers *et al*., 1999; Meyer-Lindenberg *et al*., 2005; Zhou *et al*., 2007, 2008). For instance, Meyer-Lindenber and colleagues (2005) reported a regionally specific alteration in the functional coupling between the dorsolateral prefrontal cortex and hippocampal formation in the context of a working memory task (Meyer-Lindenberg, *et al*., 2005), while reduced functional connectivity between the medial prefrontal cortex and the hippocampi has been described in patients studied in the resting state (Zhou *et al*., 2008).

As these studies have largely been conducted in patients with chronic schizophrenia, the extent to which alterations in functional integration between regions are secondary to psychotic illness or its treatment is unclear. Some neuroimaging abnormalities in schizophrenia appear to change progressively over the course of the disorder, although to date these data have mainly been derived from volumetric rather than functional studies (Lieberman, 1999; Lieberman *et al*., 2001; Cahn *et al*., 2006). There is also evidence that antipsychotic treatment can alter both the structure and function of cortical and subcortical regions (for a review see Scherk and Falkai, 2006). The influence of these potential confounds may be reduced by studying patients at the onset of schizophrenia, who have had minimal exposure to treatment. A second issue is whether alterations in functional integration are specific to schizophrenia *per se* or are also evident in individuals at high risk of the disorder. Individuals with an At Risk Mental State (ARMS) have a 25–40% risk of developing a psychotic disorder in the next 24 months (Miller *et al*., 2003; Yung *et al*. 2003; Mason *et al*., 2004). Structural and functional imaging studies have revealed that the ARMS is associated with regional volumetric and functional abnormalities that are qualitatively similar to those in patients with schizophrenia but are less severe (Phillips *et al*. 2002; Pantelis *et al*., 2003; Morey *et al*., 2005; Borgwardt *et al*., 2007; Broome *et al*., 2009). In particular, these studies indicate that the prefrontal cortex and the hippocampal region are affected, as in schizophrenia. However, to our knowledge, the functional relationship between these regions has yet to be investigated in the ARMS, or in other high-risk groups.

The first aim of the present study was to examine prefronto-hippocampal connectivity in patients with first episode schizophrenia and individuals with an ARMS. We used functional MRI (fMRI) to measure brain responses while subjects performed a delayed matching to sample (DMTS) task which engages both the prefrontal cortex and hippocampal region (Picchioni *et al*., 2007). We then used dynamic casual modelling (Friston *et al*., 2003; Mechelli *et al*., 2003) to estimate the influence that these regions exerted on each other (Friston *et al*., 1993*b*). Effective connectivity is distinct from functional connectivity, which reflects temporal correlations between activation in different regions (Friston *et al*., 1993a) without providing information about the direction of influence between them. Our principal hypothesis, based on evidence of prefrontal and hippocampal abnormalities in both patients with schizophrenia and subjects at high risk of psychosis, was that alterations in prefronto-hippocampal connectivity would be evident in both patients with first episode schizophrenia and subjects with an ARMS.

The hippocampal formation is structurally and functionally heterogeneous. Its anterior and posterior parts have different afferent and efferent connections and are implicated in different cognitive functions. With respect to the anatomical prefronto-hippocampal connectivity, comparative studies have shown that the rostral CA1′ and CA1 fields of the hippocampal formation project directly to medial prefrontal cortices while lateral prefrontal areas receive indirect projections from the caudal subicular and presubicular fields through the fornix via the entorihnal cortex (Gaffan, 1974; Ferino *et al*., 1987; Barbas and Blatt, 1995). Although most of these indirect projections are ipsilateral, some appear to cross in the body of the fornix (Carr and Sesack 1996; Kuroki *et al*., 2006). With respect to prefrontal projections to the hippocampal region, the hippocampus appears to receive projections only indirectly from the ispsilateral medial prefrontal cortex through the thalamic nucleus reuniens, whereas lateral prefrontal cortices project mainly to the posterior parahippocampal region (Roberts *et al*., 2006; Vertes *et al*., 2007). Functional neuroimaging studies of memory processing have found that anterior hippocampal regions are preferentially involved in encoding, while posterior hippocampal regions show familiarity effects and seem to be more involved in retrieval (Maguire *et al*., 1996; Lepage *et al*., 1998; Schacter and Wagner, 1999; Strange and Dolan, 1999). However, most structural and functional studies of hippocampal abnormalities in schizophrenia have not distinguished between the anterior and posterior parts of hippocampus (Wright *et al*., 2000; Meyer-Lindenberg *et al*., 2005; Glahn *et al*., 2008). A secondary aim of the present study was to assess whether the connectivity of the hippocampal region would vary between its putative functional subdivisions. We therefore examined the effective connectivity of the anterior and posterior portions of the hippocampus separately.

Materials and Methods

Participants

The study was approved by the Institute of Psychiatry Ethical Committee. All subjects gave written informed consent after a full description of the study aims and design.

ARMS group ($n = 16$)

Individuals meeting the Personal Assessment and Crisis Evaluation (PACE) criteria for the ARMS (Yung *et al*., 1998) were recruited from Outreach and Support in South London (OASIS). Individuals met the criteria for the ARMS if they presented with one or more of the following: (i) 'attenuated' positive symptoms; (ii) a brief psychotic episode of <1 week duration and that resolves without antipsychotic medication; or (iii) either they have a first degree relative with psychosis or they have a personal history of schizotypal personality disorder. Any of these trait factors has to be coupled with a recent decline in social and occupational functioning. The diagnosis was based on assessment by two experienced clinicians using the Comprehensive Assessment for the ARMS (CAARMS; Yung *et al*., 2003). All the participants were right-handed and none of them had ever received antipsychotic medication.

First Episode group ($n = 10$)

Patients who had recently presented with a first episode of psychosis were recruited from Lambeth Early Onset (LEO) Services (http://www.slam.nhs.uk/services/). All met ICD-10 criteria (WHO, 1992) for a 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 patients were medication naive. The other seven had been treated with either oral risperidone or quetiapine for a mean of 15 days (95% CI 11.6–18.4) at chlorpromazine equivalent mean dose of 121 mg/day. All the patients included in this study were right-handed.

Controls ($n = 14$)

Healthy volunteers without any current or lifetime evidence of psychiatric disorder were recruited by advertisement from the local community. All healthy participants were right handed.

General Intellectual function was estimated using the National Adult Reading Test (NART). The severity of symptoms in the clinical groups on the day of scanning was assessed with the Positive and Negative Symptom Scales (PANSS) (Kay *et al*., 1987) by a psychiatrist trained in its use. The groups were matched on socio-demographic variables (Table 1) and subjects were excluded if there was a history of neurological disorder or if they met (DSM-IV) criteria for a substance misuse disorder.

Neuroimaging experiment

The cognitive task we employed has been detailed elsewhere (Picchioni *et al*., 2007). In brief, fMRI data were acquired while subjects performed a modified version of the DMTS test from the Cambridge Neuropsychological Test Automated Battery (CANTAB). During the first 'encoding' phase, subjects were presented with a complex abstract pattern (the sample) for 5000 ms in the centre of the screen and instructed to remember it, as they would be asked to identify it later. The following 'maintenance' phase involved a delay during which subjects had to hold the sample in memory while maintaining visual fixation on a central cross. In the final 'recognition' phase, subjects were shown four patterns in a North, South, East and West distribution around a central location for 6000 ms and asked to identify the original sample via a joystick press in the corresponding direction. The duration of the maintenance delay varied across trials, resulting in three maintenance conditions: simultaneous, 4000 and 12 000 ms. Simultaneous trials involved no delay; here the sample and choice patterns were shown together at recognition. In the other trials, there was a delay of either 4000 or 12 000 ms between encoding and recognition; here only the choice patterns were displayed at recognition. At the end of each trial subjects were asked to maintain visual fixation on a central cross in order to equalize the inter-trial (encoding) interval to 27 000 ms while randomly varying the inter-stimulus (recognition) interval.

Data acquisition

The imaging procedures have been detailed elsewhere (Picchioni *et al*., 2007). In brief, images were acquired in a 1.5 T system (Signa LX-GE, Milwaukee, USA) at the Maudsley Hospital with TR of 2 s, TE 40 ms, slice thickness 7 mm and interslice gap of 0.7 mm. A total of 648 images volumes were acquired in two runs of 10 min, with each whole brain volume consisting of 22 near-axial slices parallel to the intercommissural (AC-PC) line. The first four images were discarded to allow the magnetization to reach equilibrium amplitude.

Data analysis

Pre-processing

Pre-processing of the functional volumes was performed using SPM5 (http://www.fil.ion.ucl.ac.uk/spm), running in Matlab 6.5 (Mathworks Inc. Sherbon MA, USA). All volumes from each subject were realigned using the first as reference and resliced with sync interpolation. The functional images were spatially normalized (Friston *et al*., 1995*a, b*) to a standard MNI-305 template using non-linear-basis functions. Functional data were spatially smoothened with a 6-mm full width at half maximum isotropic Gaussian kernel, to compensate for residual variability in functional anatomy after spatial normalization and

Table 1 Demographics and clinical characteristics of the three experimental groups

Variable	Controls, $n = 14$	ARMS, $n = 16$	First episode, $n = 10$	Group comparisons
Age (years)	26.04 (4.64)	24.13 (3.97)	25.50 (5.89)	$F = 0.65$, $P = 0.53$
N, Male/Female	9/5	10/6	7/3	$\chi^2 = 0.16$, df = 2, $P = 0.92$
Premorbid IQ (NART)	114.0 (8.6)	100.3 (11.8)	105.4 (10.5)	$F = 6.75$, $P = 0.003$
PANSS Total	NA	44.2 (10.9)	58.1 (9.5)	$F = 9.43$, $P = 0.058$
PANSS Positive	NA	11.3 (3.6)	18.5 (4.6)	$F = 20.48$, $P < 0.001$
PANSS Negative	NA	9.3 (2.3)	10.0 (2.3)	$F = 0.21$, $P = 0.65$
Typical: Atypical	NA	NA	0:7 (3 NA)	NA
CPZ equivalents	NA	NA	121.43 (26.73)	NA

Data reflect mean (SD) unless otherwise stated.
CPZ = chlorpromazine; NA = not applicable.

to permit application of Gaussian random field theory for adjusted statistical inference.

Statistical parametric mapping

We performed a standard statistical analysis of regional responses to identify regional activations in each subject independently. To remove low-frequency drifts, the data were high-pass filtered using a set of discrete cosine basis functions with a cut off period of 128 s. Each of the five conditions (i.e. encoding; 0 ms maintenance; 4000 ms maintenance; 12 000 ms maintenance; recognition) was modelled independently by convolving the onset times with a canonical haemodynamic response function. In addition, incorrect responses were modelled separately in each subject and then excluded from the second level analysis. The parameter estimates were calculated for all brain voxels using the general linear model and contrasts were computed for each experimental condition. The subject-specific contrast images were then entered into a second level ANOVA to make inferences at the second level (Penny and Holmes, 2004). This allowed us to identify areas of the prefrontal cortex that expressed differential activation across the first episode, ARMS and control groups during task performance relative to fixation. These prefrontal areas were then entered into our dynamic causal modelling (DCM) analysis in order to test the hypothesis that abnormal prefrontal function was associated with altered functional integration with anterior and posterior hippocampal regions.

Dynamic casual modelling

We used DCM (Friston *et al*., 2003; Mechelli *et al*., 2003) as implemented in SPM5 software. The aim of dynamic casual modelling is to estimate, and make inferences about, the influence that one neural system exerts over another and how this is affected by the experimental context. In dynamic casual modelling, a reasonably realistic but simple neuronal model of interacting neural regions is constructed. Dynamic casual modelling uses a previously validated biophysical model of fMRI measurements to predict the underling neuronal activity from the observed haemodynamic response (Friston *et al*., 2000). The estimated underlying neural responses are then used to derive the connectivity parameters, as described elsewhere (Friston *et al*., 2003; Mechelli *et al*., 2003). In order to test whether the interaction between prefrontal cortex and anterior or posterior hippocampal regions is disturbed in first episode schizophrenia and in the ARMS, for each subject four dynamic causal models were constructed (Fig. 1). Each model included two areas: an inferior frontal region and an anterior or posterior hippocampal region. The inferior frontal region [mean coordinates (x, y, z): –32, 22, 6 (left); (x, y, z): 32, 22, 6 (right)] was selected on the basis that it showed increased activation in the first episode group relative to healthy controls during recognition relative to fixation in the standard SPM analysis. The coordinates of the anterior and posterior hippocampal regions were derived from previous two voxel-based morphometry studies (Maguire *et al*., 2000, 2003) of grey matter volume, which provided evidence suggesting a functional segregation within the hippocampus and from [left anterior hippocampus (x, y, z): –30, –10, –20; left posterior hippocampus (x, y, z): –30, –30, –10; right anterior hippocampus (x, y, z): 30, –10, –20; right posterior hippocampus (x, y, z): 30, –30, –10]. The first dynamic casual modelling model (Fig. 1A) included the left inferior frontal region and the left anterior hippocampus and allowed us to test whether abnormal prefrontal function in the left hemisphere was associated with abnormal functional integration with the anterior hippocampus of the same hemisphere. The second dynamic casual modelling model (Fig. 1B) included the left inferior frontal region and the left posterior hippocampus; this model allowed us to test whether abnormal left prefrontal function could be explained by abnormal functional integration with the posterior part of the left hippocampus. The third (Fig. 1C) and fourth (Fig. 1D) models were identical to the first two except that the inferior frontal and the hippocampal regions were localized to the right instead of the left hemisphere. Principal eigenvariates were extracted to summarize regional responses in 9 mm spheres centred on the regions included in the dynamic casual modelling models. To account for individual differences, the location of these regions was based upon the local maxima of the subject-specific statistical parametric maps, defined as the nearest maxima (within 4 mm) of the group maxima. The network comprised forward and backward connections (i.e. endogenous

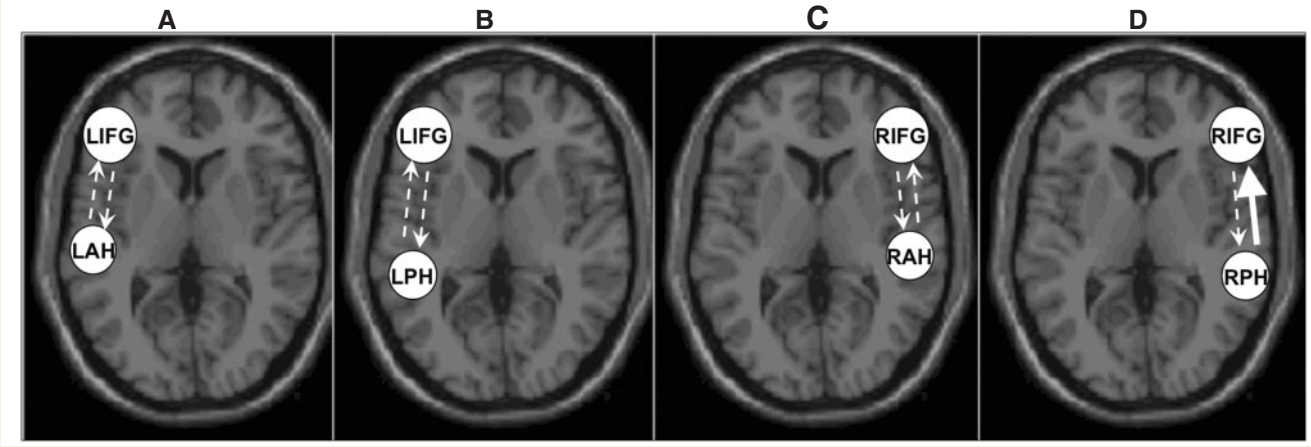

Figure 1 Four dynamic casual models that were used to investigate the regional prefrontal–hippocampal coupling in first episode, ARMS and control groups. Each model included a prefrontal region and the ipsilateral anterior or posterior hippocampal region. LIFG = left inferior frontal gyrus; LAH = left anterior hippocampus; LPH = left posterior hippocampus; RIFG = right inferior frontal gyrus; RAH = right anterior hippocampus; RPH = right posterior hippocampus. The solid arrow in (**D**) indicates that there was significant decreased right-sided effective connectivity between the RPH and the RIFG, irrespective of the maintenance delay during the task in FE patients and ARMS subjects relative to controls (statistical threshold of $P = 0.01$).

connections) characterizing the coupling between prefrontal and hippocampal regions throughout the whole experiment, regardless of different components of the task (i.e. encoding, maintenance and recognition; Fig. 1). The stimulus function, which encoded the presentation of the sample, its maintenance and its recognition at each of the three maintenance delays, entered the dynamic causal model through the hippocampal region. The resulting perturbation was then allowed to propagate throughout the model via the interconnections between hippocampal and prefrontal regions.

The forward and backward 'endogenous connections' were estimated for each subject independently. In dynamic casual modelling, the parameters describe the rate of change (units of 1/s) in the 'target' region as a linear function of the activity in the 'source' region. Positive (or negative) intrinsic connection strengths indicate that the rate of change (i.e. an increase in activity) in the target region is positively (or negatively) proportional with activity in the source region.

The subject-specific estimates were then entered into an ANOVA in SPSS in order to identify significant differences amongst the three experimental groups. Our four dynamic casual models resulted in a total of eight intrinsic connection comparisons. A Bonferroni correction for multiple comparisons would have resulted in a corrected threshold of $P \leqslant 0.006$ (0.05/8). However, this correction would have been inappropriate since it assumes comparisons to be independent, whereas statistical inferences about intrinsic connections are likely to be highly correlated. In the absence of any established procedure, as in previous dynamic casual modelling studies (Mechelli *et al*., 2007), we controlled for false positive rate using a relatively conservative statistical threshold of $P<0.025$, which yields an expected false positive rate of 2.5%. Once significant differences amongst the three experimental groups were identified using the ANOVA, *post hoc* two-tailed *t*-tests in SPSS (SPSS version 13.0, Chicago) were used to better characterize the intrinsic endogenous.

Results

Behavioural data

The proportion of correct responses and the response latencies are displayed in Table 2.

Correct responses

There was a trend for a significant interaction between group and delay maintenance ($\chi^2=9.26$, df = 4, $P=0.055$). A series of pair-wise *t*-tests revealed that in the First Episode group the proportion of correct responses was significantly lower than in the control group at any maintenance condition. Although in the ARMS group the proportion of correct responses was lower than in the control group, the difference did not reach statistical significance (Table 2).

Response latencies

There was a main effect of maintenance delay ($\chi^2=19.42$, df = 2, $P=0.001$) while the main effect of group ($\chi^2=0.68$, df = 2, $P=0.71$) and the interaction between group and delay of maintenance ($\chi^2=4.12$, df = 4, $P=0.39$) did not reach significance (Table 2).

fMRI

Encoding was associated with greater, bilateral activation across the three groups in the superior parietal gyrus extending through the intraparietal sulcus to the supramarginal gyrus (BA7 & BA40), the inferior and middle occipital gyrus (BA18), the middle extending to the superior frontal gyrus (BA6/8), the insula and the anterior cingulate. Repeated measures ANOVA did not reveal a significant interaction between group and encoding (Fig. 2).

The main effect of maintenance across groups was associated with greater bilateral activation in the anterior part of the insula (BA13), the superior parietal gyrus extending to the inferior (BA7/40), and the superior frontal gyrus (BA6). A greater activation was also observed in the left dorsal precentral gyrus and the right anterior cingulate. No significant interaction was found between group and maintenance (Fig. 2).

Increased BOLD response at correct recognition common to the three maintenance delays (0, 4000 and 12 000 mm) across the three groups compared with rest was associated with right-sided activation in the inferior frontal gyrus and insula, and bilateral activation in the middle frontal gyrus, superior parietal lobule, precuneus, cuneus, inferior occipital gyrus and cerebellar cortex ($P<0.05$, FEW corrected; Fig. 2).

Analysis of the group × recognition task interaction (Fig. 3) showed significant differences in the inferior frontal gyrus and the superior temporal gyrus bilaterally, as well as in the right insula and middle temporal gyrus. In all these areas, first episode patients showed greater activation than both the control and ARMS groups (Fig. 3).

Table 2 Performance data during DMTS task by groups

	Mnemonic delay	Group		
		First episode psychosis	ARMS	Control
Proportion correct responses	Simultaneous	**0.79** ($P=0.018$)	0.92	0.92
	4000	**0.71** ($P=0.021$)	0.77	0.86
	12 000	**0.64** ($P=0.010$)	0.71	0.81
Response latency (s) for correct responses Mean (SD)	Simultaneous	2.38 (1.34)	2.24 (0.98)	2.32 (1.02)
	4000	2.30 (1.30)	2.48 (1.24)	2.50 (1.12)
	12 000	2.47 (1.54)	2.65 (1.31)	2.66 (1.16)

Data reflect mean (SD). We report the *P*-values of the FE and Control groups differences (in brackets) with the significantly lower proportions of correct responses in FE highlighted in bold.

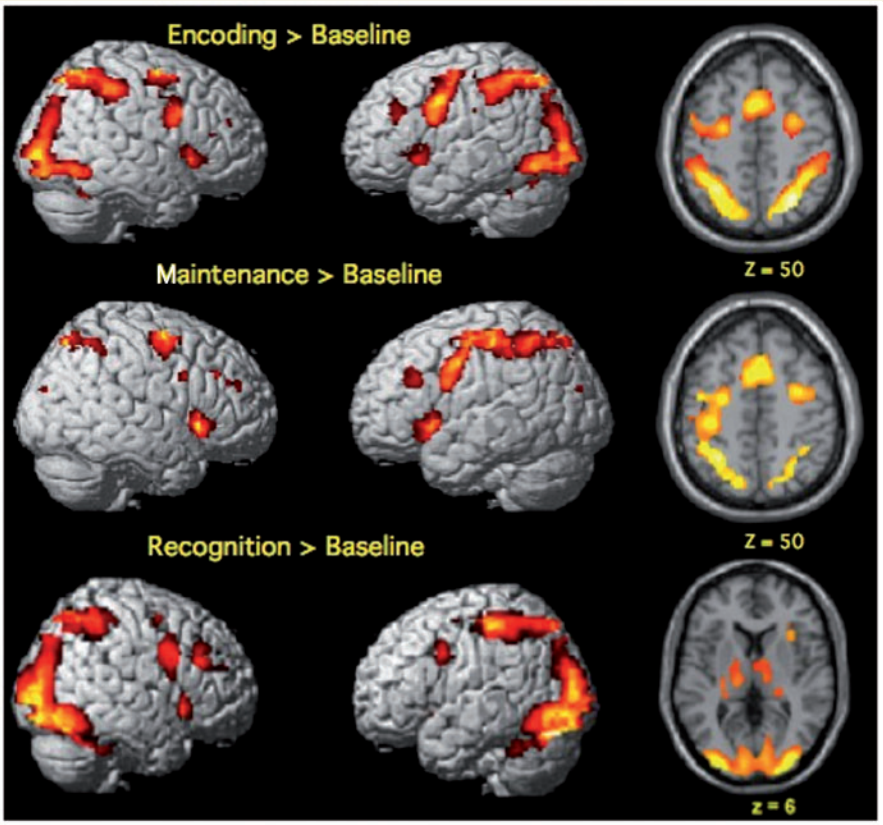

Figure 2 Main effect of encoding, maintenance and recognition tasks showing regions with significant activations across the three groups. Highlighted voxels are significant at $P \leqslant 0.05$, FWE corrected.

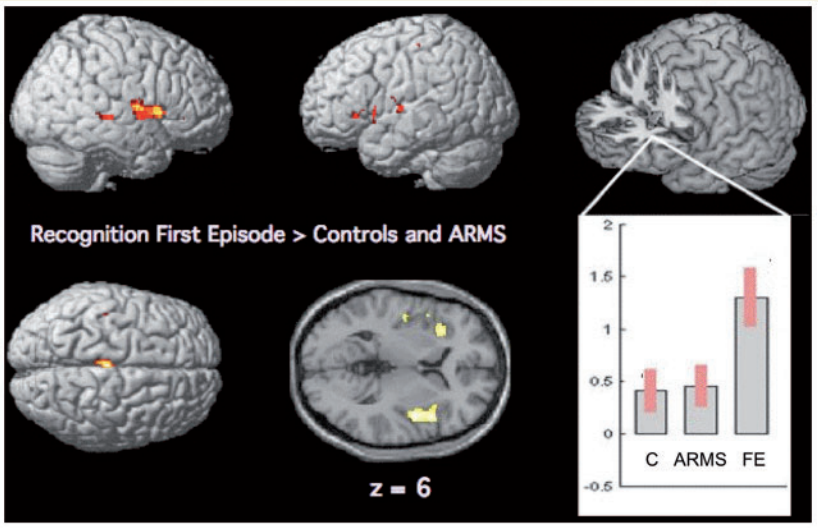

Figure 3 (Upper left and middle) Group × task interaction. In regions shown in yellow, activation in First Episode patients was significantly greater than in both Control and ARMS subjects ($P \leqslant 0.05$ FWE corrected). (Upper right) Render cut-out showing the left Inferior Frontal Gyrus (IFG), where the interaction was most significant. The parameter estimates in the IFG in the three groups are shown below. Error bars indicate 90% CI.

Table 3 Endogenous connections in controls, 'ARMS' and first episode

Endogenous connections	Controls, $n=14$	ARMS, $n=16$	First episode, $n=10$	All groups combined (*P*-values)	Group comparisons (*P*-values)
				Endogenous connections	Endogenous connections
L inf front → L ant hipp	−0.00 (0.18)	0.08 (0.21)	0.04 (0.25)	0.20	0.54
R inf front → R ant hipp	−0.05 (0.28)	0.08 (0.22)	−0.02 (0.26)	0.84	0.32
L ant hipp → L inf front	−0.19 (1.23)	−0.22 (0.82)	0.63 (0.85)	0.69	0.11
R ant hipp → R inf front	−0.12 (1.23)	−0.01 (0.98)	−0.13 (1.04)	0.64	0.95
L inf front → L post hipp	**0.07 (0.14)**	**0.12 (0.20)**	**0.11 (0.29)**	**<0.01**	0.77
R inf front →R post hipp	**0.09 (0.24)**	**0.07 (0.22)**	**0.12 (0.76)**	**0.02**	0.85
L post hipp → L inf front	**0.72 (0.85)**	**0.20 (0.82)**	**0.77 (0.65)**	**<0.01**	0.12
R post hipp →R inf front	**1.11 (0.33)**	**0.32 (0.89)**	**0.65 (0.71)**	**<0.01**	**0.01**

Group mean estimates and SD (in brackets) are reported for endogenous connections, with those that were significantly greater than zero across the three groups highlighted in bold. We also report the *P*-values of group differences, which were identified using a series of ANOVAs with significant effects highlighted in bold (statistical threshold $P<0.025$).
L = left; R = Right; inf = inferior; front = frontal; ant = anterior; post = posterior; hipp = hippocampus.

Dynamic casual modelling: endogenous connections

Based on the fMRI results, we constructed four DCM models estimating the functional coupling between inferior frontal and hippocampal regions in the left and right hemispheres (Fig. 1). We were interested in the strength of the endogenous connections which refer to the impact that one region exerted over another (regardless of the length of the maintenance delay) during the task.

When all subjects were combined, the forward and backward endogenous connections between the posterior hippocampus and the inferior frontal cortex were significantly greater than zero, indicating strong functional integration during task performance (Table 3). Group comparisons revealed that the intrinsic connection from right posterior hippocampus to the right inferior frontal gyrus differed across the three groups (ANOVA; $F=8.16$, df = 2, $P=0.01$). *Post hoc*, two-tailed *t*-tests showed that this connection was stronger in controls than both first episode patients (two-sample *t*-test; $P=0.007$) and ARMS subjects (two-sample *t*-test; $P=0.004$), but did not differ between with the first episode and ARMS groups (Table 3 and Fig. 1D). The parameters for the reverse connection from the right inferior frontal gyrus to the posterior hippocampus, the connections between the right inferior frontal gyrus and the anterior hippocampus, and the connections between the left inferior frontal gyrus and both the anterior and posterior hippocampus did not differ significantly between the groups, even at a liberal statistical threshold (ANOVA; $P>0.1$).

Discussion

The aim of the present investigation was to examine prefronto-hippocampal interactions in the 'ARMS' and in first episode schizophrenia using fMRI in conjunction with DCM (Friston *et al*., 2003; Mechelli *et al*., 2003).

During correct recognition, first episode patients expressed significantly increased activation in the inferior frontal gyrus bilaterally, relative to both controls and individuals with an ARMS. However, there was no significant difference in activation between individuals with an ARMS and healthy controls in this region. Functional neuroimaging studies of working memory in individuals with psychosis have repeatedly reported both reduced and increased engagement of neuronal resources within the prefrontal cortex (Callicot *et al*., 2000; Perlstein *et al*., 2001; Glhan *et al*., 2005). One possible explanation for this inconsistency is that there may be a difference in the relationship between prefrontal activation and working memory capacity and behavioural performance (Manoach *et al*., 2003; Bertolino *et al*., 2006). In our study, the increased activation in the inferior frontal gyrus in first episode patients may be interpreted as reflecting 'inefficient' cortical function and support the hypothesis of compromised neural strategies for handling information, as proposed when this has previously been observed in the context of other working memory tasks in schizophrenia (Callicot *et al*., 2003). The possibility that this increased activation was related to an effect of antipsychotic medication cannot be excluded either (Mendrek, *et al*., 2005; Tan *et al*., 2005; Fusar-Poli *et al*., 2007), although the first episode patients we studied had only briefly been exposed to low doses of medication. Further, and more speculatively, increased prefrontal activation during this WM task could be in part related to the genetic modulation of dopamine in patients with schizophrenia (Egan *et al*., 2001; Matsumoto *et al*., 2003; Bertolino *et al*., 2004; Bertolino *et al*., 2006*a, b*).

The focus of the present investigation was to examine functional integration between this inferior frontal region and the anterior and posterior segments of the hippocampal formation. Interestingly, the bilateral anterior and posterior regions of the hippocampus did not show strong regional activation in the standard SPM analysis and yet the posterior regions expressed strong functional integration with the inferior prefrontal cortex, as revealed by our dynamic casual modelling analysis. This dissociation illustrates that inferences about functional integration

between regions are independent of inferences about regional activation in the same regions (Stephan *et al*., 2007). Furthermore, this finding indicates that the posterior hippocampus was indeed engaged during task performance, despite the loss of strong regional activation. We found that the intrinsic connection from the right posterior hippocampus to the right inferior frontal gyrus was impaired in first episode patients and individuals with ARMS, relative to controls during a DMTS task (Fig. 1D). The intrinsic connection strength refers to the influence that one area exerts over another, regardless of task conditions. As a difference in intrinsic connection strength might reflect differences in IQ between groups, and the controls had higher NART scores than the other groups, we tested whether the strength of this intrinsic connection was related to IQ within each group. However, no significant correlation was found in the first episode ($r = 0.57$, $P = 0.14$), ARMS ($r = –0.31$, $P = 0.24$) or control groups ($r = 0.27$, $P = 0.93$). Second, the difference in intrinsic connection strength may reflect neuropsychological changes associated with antipsychotic medication (Honey and Bullmore, 2004). The groups also differed with respect to exposure to antipsychotic medication, with only the first episode group having had antipsychotic treatment. We explored the possibility that medication could have accounted for the difference in connection strength by examining the correlation between the strength of the intrinsic connection and exposure to antipsychotic medication within the first episode group. There was no significant correlation with either the cumulative dose ($r = –0.10$, $P = 0.83$) or the duration of treatment ($r = –0.357$, $P = 0.31$) within the first episode group. We also note that, so far, no studies have demonstrated a significant influence of IQ or antipsychotic medication on the functional coupling between the hippocampus and the inferior frontal gyrus.

Our result is consistent with previous reports of an impairment of functional integration in schizophrenia (Fletcher *et al*., 1999; Schlosser *et al*., 2003; Shergill *et al*., 2003; Honey *et al*., 2005; Meyer-Linden *et al*., 2005; Mechelli *et al*., 2006) and in particular, adds to the evidence for a specific disturbance of the functional coupling between prefrontal and hippocampal regions (Weinberger *et al*., 1992; Heckers *et al*., 1999; Meyer-Lindenberg *et al*., 2005; Zhou *et al*., 2007, 2008). However, our data extend these previous findings with respect to three main aspects.

First, previous studies investigated the coupling between prefrontal cortex and hippocampal formation in terms of temporal correlations, that is 'functional connectivity' (Friston *et al*., 1993a), and could not therefore indicate the direction of the impaired connection. By using dynamic casual modelling (Friston *et al*., 1993*b*), we were able to show that the altered connectivity was from the right posterior hippocampal formation to the right inferior frontal gyrus. Although this result needs to be replicated, it appears to be inconsistent with cognitive models of schizophrenia in which a top–down context-processing disturbance is thought to be responsible for cognitive deficits and to bias the selection of behavioural responses (Frith and Done, 1988; Cohen and Servan-Schreiber, 1992; Braver *et al*., 1999). Our finding seems to support the notion that a disruption of bottom–up neural mechanisms might sustain at least some of the neurocognitive features of schizophrenia (Broome *et al*., 2005), and is consistent with data from a previous study in which a disruption of bottom–up effective connectivity was evident in chronic schizophrenic patients with auditory verbal hallucinations (Mechelli *et al*., 2007).

Second, we investigated the interaction between hippocampal and prefrontal cortex function in patients who had just developed schizophrenia, as opposed to chronic patients, and in ARMS subjects who were not psychotic but have a high risk of becoming psychotic. This minimized the risk that the findings were secondary to an effect of chronic illness or its treatment. Both functional and structural abnormalities in schizophrenia may change over the course of psychotic disorders (for a review see Fusar-Poli *et al*., 2007) and antipsychotic medication can modify activation during cognitive tasks (Mendrek *et al*., 2005; Tan *et al*., 2005). We found a significant decrease in the strength of the intrinsic connection from the right posterior hippocampal formation and right inferior frontal gyrus in both first episode patients and subjects at high risk. An anecdotal examination of the group specific endogenous connections suggested that subjects at high risk expressed an even greater decrease of functional connectivity than first episode patients; nevertheless a direct comparison indicated that the difference between the two groups was not significant (two-sample *t*-test; $P = 0.33$). This observation of decreased intrinsic connectivity in both first episode patients and subjects at high risk is consistent with a recent report of abnormal functional connectivity between prefrontal regions and more posterior cortical and subcortical regions in the relatives of patients with schizophrenia (Whalley *et al*., 2005), and with evidence that the ARMS is associated with focal neuroimaging abnormalities in prefrontal and medial temporal cortex (Pantelis *et al*., 2003; Morey *et al*., 2005; Borgwardt *et al*., 2007; Broome *et al*., 2009). Our findings suggest that a disruption of hippocampal–prefrontal connectivity is evident at the onset of schizophrenia and also in subjects who are not psychotic but are at high risk of developing the disorder. This suggests that the disruption of connectivity represents a correlate of increased vulnerability to psychosis.

Third, we found that the alteration in intrinsic connectivity with the inferior frontal gyrus was specific to the posterior part of the right hippocampus. Although the functional parcellation of hippocampal sub-regions is still unclear, a number of previous neuroimaging studies of memory in healthy subjects (Maguire *et al*., 1996; Lepage *et al*., 1998; Strange *et al*., 1999) have reported that the retrieval of previously seen objects, pictures and complex visual scenes is often associated with activation in the caudal portion of the hippocampal formation, suggesting an involvement of posterior hippocampus in the retrieval of familiar stimuli. This is consistent with evidence that posterior hippocampal volume was significantly increased in taxi drivers, and was correlated with the time they had spent in the job (Maguire *et al*., 2000). In contrast, the encoding of previously unseen object and pictures has been associated with activation in the anterior hippocampal region (Tulving, 1996; Lepage *et al*., 1998; Rombouts *et al*., 1999, 2000; Strange *et al*., 1999; Weiss *et al*., 2004). In the present study, we analysed activation associated with the correct recognition of previously presented stimuli, consistent with

greater involvement of posterior than anterior hippocampus. With respect to the laterality of the hippocampus (as opposed to its anterior/posterior division), right-sided activation has been repeatedly associated with the encoding and retrieval of objects, pictures and abstract visual patterns (Martine *et al*., 1997; Kelley *et al*., 1998; Golby *et al*., 2001), whereas left-sided hippocampal activation has been associated with encoding and retrieval of meaningful and verbal stimuli (Martin *et al*., 1997; Kelly *et al*., 1998; Weiss *et al*., 2004; Rametti *et al*., 2007). Our findings of impaired connectivity between the right hippocampal region and the prefrontal cortex may thus reflect the nature of the experimental task, which involved the visual processing of complex abstract patterns. In addition, the disruption of right-sided prefronto-hippocampal connectivity in both first episode patients and individuals with an ARMS is consistent with previous finding of impaired performance in visual but not verbal memory tests in individual at high risk of psychosis prior to the onset of psychosis (Brewer *et al*., 2005).

Whether the anterior and posterior parts of the hippocampus are differentially affected in schizophrenia is unclear, with some studies suggesting that the anterior part is more susceptible and other studies implicating posterior regions (Bilder *et al*., 1995; Narr *et al*., 2001; Narr *et al*., 2002; Szeszko *et al*., 2002, 2003; Pegues *et al*., 2003). However, to our knowledge, the regional specificity of abnormal connectivity between the hippocampal formation and the prefrontal cortex has not yet been investigated. We might suggest that a disturbance of neural interactions between posterior hippocampus and prefrontal cortex may be detected early in the neuropathological course of schizophrenia and be more evident in the right than in the left hemisphere during an object working memory task. A limitation of the present study is that our characterization of prefronto-hippocampal coupling was based on all components of the object working memory task combined; future investigations could examine how prefronto-hippocampal coupling is differentially modulated during encoding, maintenance and recognition.

Interestingly, our analysis of regional responses showed that the anterior and posterior hippocampus did not show different regional activation across our experimental groups and maintenance delays. This finding seems to be consistent with a previous behavioural study, which has not shown long delay-dependent effects for object working memory in first episode schizophreniform psychosis and established schizophrenia (Mathes *et al*., 2005). Nevertheless, our analysis of effective connectivity revealed that the functional coupling between right posterior hippocampus and the prefrontal cortex was altered in patients and ARMS subjects, relative to controls. These results are consistent with the idea that the neural correlates of schizophrenia are best characterized in terms of abnormal interactions within a distributed network of regions rather than localized deficits (Friston and Frith, 1995; Gold and Weinberger, 1995; Stephan *et al*., 2006).

In summary, using fMRI and dynamic casual modelling, in association with a DMTS task, we found that the intrinsic connection from the right posterior hippocampus to the right inferior frontal gyrus was impaired in both first episode patients and individuals with an ARMS, relative to controls. This suggests that a disruption of bottom–up hippocampal–prefrontal integration is evident not only at the onset of schizophrenia but also in subjects at high-risk of psychosis, and may therefore represent a correlate of increased vulnerability to psychosis rather than the disorder itself.

Funding

Glaxo SmithKline grant.

References

Arnold S, Trojanowski J. Recent advances in defining the neuropathology of schizophrenia. Acta Neuropathol 1996; 92: 217–31.

Barbas H, Blatt G. Topographically specific hippocampal projections target functionally distinct prefrontal areas in the rhesus monkey. Hippocampus 1995; 5: 511–33.

Bertolino A, Blasi G, Latorre V, Rubino V, Rampino A, Sinibaldi L, et al. Text Additive effects of genetic variation in dopamine regulating genes on working memory cortical activity in human brain. J Neurosci 2006a; 26: 3918–22.

Bertolino A, Caforio G, Blasi G, De Candia M, Latorre V, Petruzzella V, et al. Interaction of COMT (Val(108/158)Met) genotype and olanzapine treatment on prefrontal cortical function in patients with schizophrenia. Am J Psychiatry 2004; 161: 1798–805.

Bertolino A, Rubino V, Sambataro F, Blasi G, Latorre V, Fazio L, et al. Prefrontal-hippocampal coupling during memory processing is modulated by COMT val158met genotype. Biol Psychiatry 2006b; 60: 1259–8.

Bilder R, Bogerts B, Ashtari M, Wu H, Alvir J, Jody D, et al. Anterior hippocampal volume reductions predict frontal lobe dysfunction in first episode schizophrenia. Schizophr Res 1995; 17: 47–58.

Bogerts B, Ashtari M, Degreef G, Alvir J, Bilder R, Lieberman J. Reduced temporal limbic structure volumes on magnetic resonance images in first episode schizophrenia. Psychiatry Res 1990; 35: 1–13.

Borgwardt S, McGuire P, Aston J, Berger G, Dazzan P, Gschwandtner U, et al. Structural brain abnormalities in individuals with an at-risk mental state who later develop psychosis. Biol Psychiatry 2007; 61: 1148–56.

Brewer WJ, Francey SM, Wood SJ, Jackson HJ, Pantelis C, et al. Memory impairments identified in people at ultra-high risk for psychosis who later develop first-episode psychosis. Am J Psychiatry 2005; 162: 71–8.

Broome M, Matthiasson P, Fusar-Poli P, Wolley JB, Johns LC, Tabraham P, *et al*. Neural correlates of executive function and working memory in the 'at-risk mental state'. Br J Psychiatry 2009; 194: 25–33.

Broome M, Woolley JB, Tabraham P, Johns LC, Bramon E, Murray GK, et al. What causes the onset of psychosis? Schizophrenia Research 2005; 79: 23–4.

Cahn W, van Haren N, Hulshoff Pol H, Schnack H, Caspers E, Laponder D, et al. Brain volume changes in the first year of illness and 5-year outcome of schizophrenia. Br J Psychiatry 2006; 189: 381–2.

Callicott J, Mattay V, Verchinski B, Marenco S, Egan M, Weinberger D. Complexity of prefrontal cortical dysfunction in schizophrenia: more than up or down. Am J Psychiatry 2003; 160: 2209–15.

Carr DB, Sesack SR. Hippocampal afferents to the rat prefrontal cortex: synaptic targets and relation to dopamine terminals. J Comp Neurol 1996; 369: 1–15.

Carter C, Perlstein W, Ganguli R, Brar J, Mintun M, Cohen J. Functional hypofrontality and working memory dysfunction in schizophrenia. Am J Psychiatry 1998; 155: 1285–7.

Egan M, Goldberg T, Kolachana B, Callicott J, Mazzanti CM, Straub RE. Effect of COMT Val108/158 Met genotype on frontal lobe function and risk for schizophrenia. Proc Natl Acad Sci USA 2001; 98: 6917–22.

Ferino F, Thierry AM, Glowinki J. Anatomical and electrophysiological evidence for a direct projection from Ammon's horn to the medial prefrontal cortex in the rat. Exp Brain Res 1987; 65: 421–6.

Fletcher P. The missing link: a failure of fronto-hippocampal integration in schizophrenia. Nat Neurosci 1998; 1: 266–7.

Friston K, Ashburner J, Frith C, Poline JB, Heather J, Frackowiak R. Spatial registration and normalization of images. Hum Brain Mapp 1995b; 2: 1–25.

Friston K, Frith C. Schizophrenia: a disconnection syndrome? Clin Neurosci 1995a; 3: 89–97.

Friston K, Frith C, Frackowiak R. Time-dependent changes in effective connectivity measured with PET. Hum Brain Map 1993b; 1: 69.

Friston K, Frith C, Liddle P, Frackowiak R. Functional connectivity: the principal component analysis of large (PET) data sets. J Cereb Blood Flow Metab 1993a; 13: 5–14.

Friston K, Harrison L, Penny W. Dynamic casual modelling. Neuroimage 2003; 19: 1273–302.

Friston K, Mechelli A, Turner R, Price C. Nonlinear responses in fMRI: the Balloon model, Volterra kernels, and other hemodynamics. Neuroimage 2000; 12: 466–77.

Fusar-Poli P, Broome M, Matthiasson P, Williams S, Brammer M, McGuire P. Effects of acute antipsychotic treatment on brain activation in first episode psychosis: an fMRI study. Eur Neuropsychopharmacol 2007; 17: 492–500.

Fusar-Poli P, Perez J, Broome M, Borgwardt S, Placentino A, Cavarzasi E, et al. Neurofunctional correlates of vulnerability to psychosis: a systematic review and meta-analysis. [Review]. Neurosci Biobehav Rev 2007; 31: 465–84.

Gaffan D. Recognition impaired and association intact in the memory of monkeys after transection of the fornix. J Comp Physiol Psychol 1974; 86: 1100–9.

Glahn DC, Ragland J, Abramoff A, Barrett J, Laird A, Bearden C, et al. Beyond hypofrontality: a quantitative meta-analysis of functional neuroimaging studies of working memory in schizophrenia. Hum Brain Mapp 2005; 25: 60–9.

Golby A, Poldrack R, Brewer J, Spencer D, Desmond J, Aron A, et al. Material-specific lateralization in the medial temporal lobe and prefrontal cortex during memory encoding. Brain 2001; 124: 1841–54.

Gold J, Weinberger D. Cognitive deficits and the neurobiology of schizophrenia. Curr Opin Neurobiol 1995; 5: 225–30.

Harrison P, Eastwood SL. Neuropathological studies of synaptic connectivity in the hippocampal formation in schizophrenia. Hippocampus 2001; 11: 508–19.

Heckers S, Goff D, Schacter D, Savage C, Fischman A, Alpert N, et al. Functional imaging of memory retrieval in deficit vs nondeficit schizophrenia. Arch Gen Psychiatry 1999; 56: 1117–23.

Heckers S, Rauch S, Goff D, Savage C, Schacter D, Fischman A, et al. Impaired recruitment of the hippocampus during conscious recollection in schizophrenia. Nat Neurosci 1998; 1: 318–23.

Honey G, Bullmore E. Human pharmacological MRI. Trends Pharmacol Sci 2004; 25: 366–74.

Kay S, Fiszbein A, Opler L. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull 1987; 13: 261–76.

Kelley W, Miezin F, McDermott K, Buckner R, Raichle M, Cohen N, et al. Hemispheric specialization in human dorsal frontal cortex and medial temporal lobe for verbal and nonverbal memory encoding. Neuron 1998; 20: 927–36.

Kuroki N, Kubicki M, Nestor PG, Salisbury DF, Park HJ, Levitt JJ, et al. Fornix integrity and hippocampal volume in male schizophrenic patients. Biol Psychiatry 2006; 60: 22–31.

Lepage M, Habib R, Tulving E. Hippocampal PET activations of memory encoding and retrieval: the HIPER model. Hippocampus 1998; 8: 313–22.

Lieberman J. Searching for the neuropathology of schizophrenia: neuroimaging strategies and findings. [Review]. Am J Psychiatry 1999; 156: 1133–6.

Lieberman J, Chakos M, Wu H, Alvir JH, Hoffman E, Robinson D, et al. Abstract Longitudinal study of brain morphology in first episode schizophrenia. Biol Psychiatry 2001; 49: 487–99.

Maguire E, Frackowiak R, Frith C. Learning to find your way: a role for the human hippocampal formation. Proc Biol Sci 1996; 263: 1745–50.

Maguire E, Gadian D, Johnsrude I, Good C, Ashburner J, Frackowiak R, et al. Navigation-related structural change in the hippocampi of taxi drivers. Proc Natl Acad Sci USA 2000; 97: 4398–403.

Maguire E, Spiers H, Good C, Hartley T, Frackowiak R, Burgess N. Navigation expertise and the human hippocampus: a structural brain imaging analysis. Hippocampus 2003; 13: 250–9.

Manoach D. Prefrontal cortex dysfunction during working memory performance in schizophrenia: reconciling discrepant findings. Schizophr Res 2003; 60: 285–98.

Martin A, Wiggs C, Weisberg J. Modulation of human medial temporal lobe activity by form, meaning, and experience. Hippocampus 1997; 7: 587–93.

Mason O, Startup M, Halpin S, Schall U, Conrad A, Carr V. Risk factors for transition to first episode psychosis among individuals. Schizophr Res 2004; 71: 227–37.

Mathes B, Wood S, Proffitt T, Stuart G, Buchanan J, Velakoulis D, et al. Early processing deficits in object working memory in first-episode schizophreniform psychosis and established schizophrenia. Psychol Med 2005; 35: 1053–62.

Matsumoto M, Weickert C, Akil M, Lipska B, Hyde T, Herman M, et al. Catechol O-methyltransferase mRNA expression in human and rat brain: evidence for a role in cortical neuronal function. Neuroscience 2003; 116: 127–37.

McGuffin P, Farmer A, Harvey I. A polydiagnostic application of operational criteria in studies of psychotic illness. Development and reliability of the OPCRIT system. Arch Gen Psychiatry 1991; 48: 764–70.

Mechelli A, Price J, Noppeney U, Friston K. A dynamic causal modeling study on category effects: bottom-up or top-down mediation? J Cogn Neurosci 2003; 15: 925–34.

Mendrek A, Kiehl K, Smith A, Irwin D, Forster B, Liddle P. Dysfunction of a distributed neural circuitry in schizophrenia patients during a working-memory performance. Psychol Med 2005; 35: 187–96.

Meyer-Lindenberg A, Olsen R, Kohn P, Brown T, Egan M, Weinberger D. Regionally specific disturbance of dorsolateral prefrontal-hippocampal functional connectivity in schizophrenia. Arch Gen Psychiatry 2005; 62: 379–86.

Miller T, MCGlashan T, Rosen J, Cadenhead K, Cannon T, Ventura J, et al. Prodromal assessment with the structured interview for prodromal syndromes and the scale of prodromal symptoms: predictive validity, interrater reliability, and training to reliability. Schizophr Bull 2003; 29: 703–15.

Morey R, Inan S, Mitchell T, Perkins D, Lieberman J, Belger A. Imaging frontostriatal function in high-risk, early, and chronic schizophrenia during executive processing. Arch Gen Psychiatry 2005; 62: 167–76.

Narr KT, Moussai J, Blanton RA, Edris A, Krupp R, Rayman J, et al. Three-dimensional mapping of temporo-limbic regions and the lateral ventricles in schizophrenia: gender effects. Biol Psychiatry 2001; 50: 84–97.

Narr K, van Erp TC, Woods RT, Jang SB, Standerksjöld-Nordenstam C, Kaprio J, et al. A twin study of genetic contributions to hippocampal morphology in schizophrenia. Neurobiol Dis 2002; 11: 83–95.

Pantelis C, Velakoulis D, McGorry P, Wood S, Suckling J, Phillips L, et al. Neuroanatomical abnormalities before and after onset of psychosis: a cross-sectional and longitudinal MRI comparison. Lancet 2003; 361: 281–8.

Pegues M, Rogers L, Amend D, Vinogradov S, Deicken R. Anterior hippocampal volume reduction in male patients with schizophrenia. Schizophr Res 2003; 60: 105–15.

Penny W, Holmes A. Random effects analysis. In: Frackowiak RS, Friston K, Frith C, Dolan R, Price CJ, Zeki J, et al. editors. Human brain function. 2nd edn., London: Elsevier; 2004. p. 843–50.

Perlstein WM, Carte CS, Noll DC, Cohen JD. Relation of prefrontal cortex dysfunction to working memory and symptoms in schizophrenia. Am J Psychiatry 2001; 158: 1105–13.

Phillips L, Velakoulis D, Pantelis C, Wood S, Yuen H, Yung A, et al. Non-reduction in hippocampal volume is associated with higher risk of psychosis. Schizophr Res 2002; 58: 145–58.

Picchioni M, Matthiasson P, Broome M, Giampietro V, Brammer M, Mathes B, et al. Medial temporal lobe activity at recognition increases with the duration of mnemonic delay during an object working memory task. Human Brain Mapping 2007; 28: 1235–50.

Rametti G, Segarra N, Junqué C, Bargalló N, Caldú X, Ibarretxe N, et al. Left posterior hippocampal density reduction using VBM and stereological MRI procedures in schizophrenia. Schizophr Res 2007; 96: 62–71.

Roberts AC, Tomic DL, Parkinson CH, Roeling TA, Cutter DJ, Robbins TW, *et al*. Forebrain Connectivity of the Prefrontal Cortex in the Marmoset Monkey (*Callithirix jacchus*): an Anterograde and Retrograde Tract-Tracing Study. J Comp Neurol 2006; 502: 86–112.

Rombouts S, Scheltens P, Machielson W, Barkhof F, Hoogenraad F, Veltman D, et al. Parametric fMRI analysis of visual encoding in the human medial temporal lobe. Hippocampus 1999; 9: 637–43.

Schacter D, Wagner D. Medial temporal lobe activations in fMRI and PET studies of episodic encoding and retrieval. Hippocampus 1999; 9: 7–24.

Scherk H, Falkai P. Effects of antipsychotics on brain structure. [Review]. Curr Opin Psychiatry 2006; 19: 145–50.

Stephan K, Baldeweg T, Friston K. Synaptic plasticity and dysconnection in schizophrenia. Biol Psychiatry 2006; 59: 929–39.

Stephan K, Marshall J, Penny W, Friston K, Fink GR. Interhemispheric integration of visual processing during task-driven lateralization. J Neurosci 2007; 27: 3512–22.

Strange B, Dolan R. Functional segregation within the human hippocampus. Mol Psychiatry 1999; 4: 508–11.

Szeszko P, Goldberg E, Gunduz-Bruce H, Ashtari M, Robinson D, Malhotra A, et al. Smaller anterior hippocampal formation volume in antipsychotic-naive patients with first-episode schizophrenia. Am J Psychiatry 2003; 160: 2190–7.

Szeszko P, Strous R, Goldman R, Ashtari M, Knuth K, Lieberman J, et al. Neuropsychological correlates of hippocampal volumes in patients experiencing a first episode of schizophrenia. Am J Psychiatry 2002; 159: 217–26.

Tan H, Choo W, Fones C, Chee M. fMRI study of maintenance and manipulation processes within working memory in first-episode schizophrenia. Am J Psychiatry 2005; 162: 1849–58.

Tulving E, Markowitsch H, Craik F, Habib RH. Novelty and familiarity activations in PET studies of memory encoding and retrieval. Cereb Cortex 1996; 6: 71–9.

Vertes RP, Hoover WB, Szigeti-Buck K, Leranth C. Nucleus reuniens of the midline thalamus: Link between the medial prefrontal cortex and the hippocampus. Brain Res Bull 2007; 71: 601–9.

Weinberger D, Berman K, Suddath R, Torrey E. Evidence of dysfunction of prefrontal-limbic network in schizophrenia: a magnetic resonance imaging and regional cerebral blood flow study of discordant monozygotic twins. Am J Psychiatry 1992; 149: 890–97.

Weiss A, Zalesak M, DeWitt I, Goff D, Kunkel L, Heckers S. Impaired hippocampal function during the detection of novel words in schizophrenia. Biol Psychiatry 2004; 55: 668–75.

Whalley H, Simonotto E, Marshall I, Owens D, Goddard N, Johnstone E, et al. Functional disconnectivity in subjects at high genetic risk of schizophrenia. Brain 2005; 128: 2097–108.

Wright I, Rabe-Hesketh S, Woodruff P, David A, Murray R, Bullmore E. Meta-analysis of regional brain volumes in schizophrenia. Am J Psychiatry 2000; 157: 16–25.

Yung A, Phillips L, McGorry P, McFarlane C, Francey S, Harrigan SPG, et al. Prediction of psychosis. A step towards indicated prevention of schizophrenia. Br J Psychiatry Suppl 1998; 172: 14–20.

Yung A, Phillips L, Yuen H, Francey S, McFarlane C, Hallgren M, et al. Psychosis prediction: 12-month follow up of a high-risk (''prodromal'') group. Schizophr Res 2003; 60: 21–32.

Zhou Y, Shu N, Liu Y, Song M, Hao Y, Liu H, et al. Altered resting-state functional connectivity and anatomical connectivity of hippocampus in schizophrenia. Schizophr Res 2008; 100: 120–32.