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Event-related fMRI of word classification and successful word recognition in subjects at genetically enhanced risk of schizophrenia

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ABSTRACT

Background. Verbal declarative memory is a core deficit in schizophrenia patients, seen to a lesser extent in unaffected biological relatives. Neuroimaging studies suggest volumetric differences and aberrant function in prefrontal and temporal regions in schizophrenia patients compared to controls. These deficits are also reflected in the small number of similar investigations in unaffected biological relatives. However, it is unclear the extent to which dysfunction is genetically mediated or a feature of the established illness.

Method. Event-related blood-oxygen-level-dependent (BOLD) functional magnetic resonance imaging (fMRI) was used to measure brain activation in 68 biological relatives of schizophrenia patients (of whom 27 experienced transient or isolated psychotic symptoms) and 21 controls during verbal classification and recognition.

Results. During word classification, the high-risk group showed a greater response relative to controls in the right inferior frontal gyrus. During correct recognition (relative to correct rejection), the high-risk group showed significantly greater response relative to controls in the right cerebellum. When the high-risk group was split into those with (HR+) and without (HR−) psychotic symptoms, the increased response in the right inferior frontal gyrus was only seen when the HR+ were compared to controls. The greater cerebellar response was seen when both HR groups were compared to controls.

Conclusions. Activation increases in the right inferior frontal gyrus and cerebellum in high-risk subjects compared to controls during a relatively low-load memory task are likely to represent compensation for genetically mediated abnormalities. This is consistent with a leftward shift of the inverted 'U' load–response model of cognitive function in schizophrenia.

INTRODUCTION

Schizophrenia is a complex psychiatric disorder with a lifetime risk of approximately 1% in the general population. This risk increases with the number and proximity of affected biological relatives, making it a highly heritable disorder (Gottesman, 1991). This debilitating condition is characterized by disordered thought, language, behaviour and social function, and is associated with deficits in a range of cognitive domains (Bilder, 1996; Heinrichs & Zakzanis, 1998), some of which are apparent, to a lesser extent, in the unaffected biological relatives of

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schizophrenia patients (Heinrichs & Zakzanis, 1998; Aleman *et al*. 1999; Sitskoorn *et al*. 2004*a*; Whyte *et al*. 2005, 2006). However, it is unclear the extent to which general functional deficits are genetically mediated or features of the established illness.

The Edinburgh High-Risk Study (EHRS) has attempted to address these issues through the prospective investigation of a large sample of young people at genetic risk of schizophrenia and matched controls using repeated clinical and neuropsychological assessment and structural and functional magnetic resonance imaging (MRI) (Johnstone *et al*. 2000). As predicted, based on the known frequency of schizophrenia in relatives and the incidence of the disorder in individuals under the age of 30 years, approximately 10–15% of the high-risk group developed the condition by the end of 2002. However, isolated psychotic symptoms, which preceded schizophrenia in most of those who developed psychosis, occurred in two to three times the number of subjects as were expected to develop schizophrenia (Johnstone *et al*. 2000, 2005). A number of high-risk individuals participating in the functional MRI (fMRI) investigations reported transient and/or isolated psychotic symptoms at psychiatric interview, close to or on the day of scanning. In a previous study these individuals showed increased activation of the left inferior parietal lobule while performing a sentence completion paradigm (Whalley *et al*. 2004, 2005). Although it is possible that some may still go on to develop a psychiatric disorder, or indeed have since done so, none met diagnostic criteria for any psychiatric disorder at the time of investigation, and all were functioning normally at the time of the scan.

Memory deficits are considered integral to the cognitive profile of schizophrenia (Heinrichs & Zakzanis, 1998; Aleman *et al*. 1999). However, the nature of these deficits is unclear. A number of studies have shown impaired verbal list and story recall, with poor but less impaired verbal recognition memory in patients relative to controls (Nathaniel-James *et al*. 1996; Kenny *et al*. 1997; Rushe *et al*. 1999; Bilder *et al*. 2000; Moritz *et al*. 2001; Holthausen *et al*. 2003), suggesting an access rather than a storage problem, also possibly an artefact of task difficulty. Other studies have revealed verbal information acquisition deficits in patients relative to controls attributed to poor spontaneous usage of semantic cues, context and organization during encoding (Brebion *et al*. 1997; Holthausen *et al*. 2003; Van Oostrom *et al*. 2003; Hill *et al*. 2004). Some, but not all, studies have reported normal performance when cues and strategies are provided overtly (Manschrek *et al*. 1997; Chan *et al*. 2000). A similar, but less severe, memory performance profile has also been reported in unaffected close biological relatives of patients with schizophrenia, suggesting a genetically mediated deficit (Saykin *et al*. 1991, 1994; Toulopoulou *et al*. 2003; Sitskoorn *et al*. 2004*a*, *b*; Wittorf *et al*. 2004; Whyte *et al*. 2005).

Word recognition memory tests are often used in functional brain imaging studies to examine declarative verbal memory performance. Abnormal activation patterns have been demonstrated in a number of regions in patients with schizophrenia, including the bilateral dorsolateral prefrontal cortex (Fletcher *et al*. 1998; Crespo-Facorro *et al*. 1999; Barch & Al, 2002; Ragland *et al*. 2004), right anterior prefrontal cortex (Heckers *et al*. 1998; Jennings *et al*. 1998; Hofer *et al*. 2003), left inferior prefrontal cortex (Ragland *et al*. 2001; Kubicki *et al*. 2003), bilateral superior temporal gyrus (Fletcher *et al*. 1998; Jennings *et al*. 1998), and middle temporal gyrus (Barch & Al, 2002; Jessen *et al*. 2003). It is suggested that these functional deficits may be linked to aberrant frontotemporal functioning (Curtis *et al*. 1998; Ragland *et al*. 2004).

Given the evidence for memory dysfunction in schizophrenia patients and close biological relatives, we aimed to further characterize this profile using an event-related fMRI verbal classification and recognition paradigm in the EHRS group. The verbal semantic classification (living *versus* non-living words) and recognition (old *versus* new words) tasks have previously been used in healthy volunteers (Kapur *et al*. 1994), older adults with Alzheimer's disease (Lustig *et al*. 2003), and in participants with schizophrenia (Jennings *et al*. 1998; Ragland *et al*. 2004). The word classification task was used in the current study to facilitate semantic processing of words subsequently presented in the recognition task, and to enable characterization of brain responses associated with

verbal processing. The recognition task allowed comparison of events associated with successful identification of studied and unstudied words, or the 'old–new effect', often used to explore successful recognition processes (Henson, 2005). The demands of both tasks (adapted for the current investigation) were not excessive, with the aim of ensuring that any activation differences were unlikely to be attributable to task difficulty. From the literature described above, we expected abnormal activation patterns in prefrontal and temporal regions. We were specifically interested in any differences in biological brain response during verbal processing and successful retrieval between genetically at-risk participants and controls (i.e. 'trait' effects) and between those at risk who were and were not experiencing transient psychotic symptoms (i.e. early 'state' effects), without the confounds of medication and chronicity effects.

METHOD

Participants

All EHRS participants were recruited between the ages of 16 and 25 years. High-risk participants were selected based on having at least two second- or first-degree biological relatives with schizophrenia. Controls were closely matched and had no history of schizophrenia. In order to remain consistent with previously reported results of an fMRI executive function task (Whalley *et al.* 2004, 2005), this report concerns the first 100 participants to attend for an fMRI scan between 1999 and 2002. Of this number, five declined a scan and a further six were excluded (two due to loss of behavioural data, two due to minor vascular abnormalities and two due to excessive movement). Data are presented for a total of 89 participants (68 high-risk participants and 21 controls). All provided written informed consent. A standard psychiatric interview, the Present State Examination (Wing *et al.* 1974), was conducted on all participants on the same day or as close as possible to the day of the scan, within an average of 19.2 (S.D. = 52) days. The majority (75 subjects) had the assessments within 1 month. Five subjects (one control, three high-risk without symptoms, and one high-risk with symptoms) had the assessments performed with a time interval greater than 3 months due to scanner malfunction at the time of their original visit. Based on this examination, high-risk participants were classified according to the presence (HR+) or absence (HR−) of psychotic symptoms (i.e. isolated transient delusions and/or hallucinations, or attenuated/partial psychotic symptoms or perceptual distortions). No participants met criteria for a psychiatric disorder, were seeking medical treatment or were on antipsychotic medication, and all considered themselves well. The Psychiatry and Clinical Psychology subcommittee of the Lothian Research Ethics Committee approved the study.

Tasks

Stimuli used were 83 words of high imageability (at least 5·9 on a scale of 1–7) matched across categories for word length, concreteness, syntactic category and frequency in the English language (Celex written frequency) and could be classified as either living (e.g. dog) or non-living (e.g. table) objects (MRC Psycholinguistic database available at: www.psy.uwa.edu.au/uwa_mrc.htm). No ambiguous word categories, such as fruit or body parts, were included. The tasks were generated and presented using the Integrated Functional Imaging System (IFIS) program (IFIS-SA, Invivo, Orlando, FL, USA). Stimuli were presented for 2 s (36 pt Times New Roman font black on white screen), followed by a variable fixation period of 2–10 s. Responses could be made at any time during presentation and subsequent fixation period by pressing a button on a keypad strapped to the participants' dominant hand. Trials were randomized across participants. Both tasks were preceded by practice task instructions, a short practice session with feedback, followed by instructions for the actual task. Participants were aware that a semantic word classification task would be followed by a test of memory for that material. During the 200-s word classification task, participants were randomly presented with 36 words (18 words referring to living things and 18 to non-living things) and asked to identify them as either living or non-living. During the 400-s retrieval task, 72 words were presented; the same 36 words presented previously (old) intermixed with another 36 matched lures (new). Participants were required to make an old/new recognition, that is a yes or no decision based on whether or not they had previously viewed that

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word. An additional verbal paradigm was also presented during the same scanning session, details of which have been presented elsewhere (Whalley *et al*. 2004, 2005).

Image acquisition

MRI data were acquired on a 1·5 Tesla Magnetom Signa General Electric (GE) scanner at the SHEFC Brain Imaging Research Centre for Scotland (SBIRCS) at the Western General Hospital in Edinburgh. Structural data were also acquired using the Magnetization Prepared Rapid Acquisition Gradient Echo (MPRAGE) sequence, consisting of a 180° inversion pulse with a Fast Low Angle Shot (FLASH) collection (flip angle = 15°, TR = 10 ms, TE = 4 ms, TI = 600 ms, relaxation delay = 200 ms, field of view = 22 cm, matrix = 256 × 192). The ensuing 128 contiguous coronal slices were three-dimensional with a slice thickness of 1·7 mm and an in-plane resolution of 1 mm. The gradients had a maximum strength of 23 mT/m, and a slew rate of 120 T/m . s. Functional images were then collected using a gradient Echo Planar Imaging (EPI) sequence (flip angle = 90°, TR = 2 s, TE = 40 ms, field of view = 22 × 22 cm, matrix = 64 × 64 pixels, pixel size = 3·4 × 3·4 mm, slice thickness = 5 mm with no gap between slices, single shot). Twenty-four contiguous axial (horizontal) slices were collected at an oblique angle aligned with the anterior and posterior commissure, moving from the bottom of the brain and up (ascending) (per volume/image). Data were acquired during two sessions, consisting of 100 volumes for the first (word classification) and 200 volumes for the second session (word recognition).

Data analysis

Behavioural responses and associated parameters were logged in a data file using the E-Data Aid (Edat) function within the E-prime suite of programs (E-Prime, 2000). Behavioural data were analysed using SPSS version 11 (SPSS Inc., Chicago, IL, USA). Mean response scores and reaction times were compared between groups using one-way analyses of variance (ANOVAs).

Raw functional data were reconstructed to ANALYZE format (Mayo Foundation, Rochester, MN, USA). Functional images were pre-processed and analysed using the software package Statistical Parametric Mapping (SPM99 and SPM2, Wellcome Department of Cognitive Neurology, London, UK; http://www.fil.ion.ucl.ac.uk/spm), implemented in MATLAB (The Math Works, Natick, MA, USA). Pre-processing was performed using SPM99. All volumes were realigned to the first scan in the series to correct for participant movement during acquisition. Each volume was normalized to a standard SPM EPI template using linear affine transformations followed by non-linear deformations and spatially smoothed with a 6 × 6 × 6 cubic mm full-width half-maximum gaussian filter.

Statistical analysis was performed using the general linear model in SPM2. For the word classification condition, all items were treated as equal and entered into a single regressor model, with the regressor obtained by convolving a canonical haemodynamic response function with a vector of the onset times. For the retrieval condition, incorrect responses were not considered because the number of incorrect old (misses) and incorrect new (false positives) events was not substantial enough to enable analysis (i.e. less than 12 events in each discrete category). This also ruled out a contrast of subsequent hits *versus* subsequent misses (i.e. items in the study phase that were later remembered *versus* those later forgotten). Instead, three event classes were entered into a three regressor model: correct old, correct new, and errors (comprising incorrect responses and null responses). This permitted a comparison of correct old events (hits) *versus* correct new events (correct rejections), also known as the old–new effect, and typically used to investigate successful recognition (Henson, 2005). In both cases estimates of head movement from the realignment stage of pre-processing were included as additional regressors in the analysis to model movement-related residual variance. First-level contrast parameter estimate images for each individual participant were computed and entered into second-level one-sample *t* tests to calculate within-group effects and a one-way ANOVA, followed by *post hoc* two-sample *t* tests to examine between-group effects. Contrasts were therefore computed for the controls *versus* the high-risk group as a whole (i.e. to examine trait effects), as well as *versus* those with and without transient psychotic

Table 1. *Participant demographic characteristics*

	Controls ($n=21$)	High-risk without psychotic symptoms ($n=41$)	High-risk with psychotic symptoms ($n=27$)	Test statistic	p
Mean age, years (S.D.)	26·8 (2·7)	26·6 (3·3)	25·1 (3·1)	$F=2·5$[a]	0·09
Gender (male : female)	13 : 8	18 : 23	13 : 14	$\chi^2=2·3$[b]	0·30
AHI left : right : mixed	2 : 17 : 1	3 : 37 : 1	3 : 22 : 2	$\chi^2=1·30$[c]	0·85
WAIS-R FS-IQ (S.D.)	107·5 (12·5)	103·5 (14·5)	99·4 (12·7)	$F=2·0$[a]	0·14
NART FS-IQ (S.D.)	102·8 (9·4)	102·1 (8·4)	97·9 (10·8)	$F=1·9$[a]	0·19

S.D., Standard deviation; AHI, Annett Handedness Inventory; WAIS-R, Wechsler Adult Intelligence Scale – Revised; NART, National Adult Reading Test; FS, full-scale.

[a] One-way analysis of variance (ANOVA).

[b] Pearson's χ^2.

[c] Kruskal–Wallis.

symptoms. Contrasts were also made between the latter two groups (i.e. to examine early 'state' effects).

For the between-group results statistical thresholds were set at a significance level of $p<0·001$ (uncorrected for multiple comparisons) cluster extent ($k_E>20$ voxels, and regions were considered significant at $p<0·05$ cluster level corrected for multiple comparisons. Where corrected p values in hypothesized regions did not achieve significance, p values uncorrected for multiple comparisons are also presented. Coordinates were converted from MNI (Montreal Neurological Institute) to Talairach coordinates using a nonlinear transformation (http://www.mrc-cbu.cam.ac.uk/Imaging).

RESULTS

Participants

Participant details are presented in Table 1. Twenty-seven high-risk participants presented with isolated or transient psychotic symptoms at the time of the scan. The high-risk and control groups were initially matched for age, gender and handedness on entry to the study. In this subsample, participant groups were suitably balanced for age, handedness, gender, Wechsler Adult Intelligence Scale – Revised (WAIS-R) full-scale IQ and National Adult Reading Test (NART) – estimated full-scale IQ (Table 1).

Behaviour

For all participant groups more than 97% of responses given during word classification [controls (C) 98·3%, HR− 97·7%, HR+ 97·2%] and more than 70% of responses given during retrieval (C 71·3%, HR− 74%, HR+ 71·6%) were correct. The mean recognition accuracy (proportion of true positives – proportion of false positives) for each group was C 0·49 (S.D. = 0·19), HR− 0·55 (S.D. = 0·15), HR+ 0·49 (S.D. = 0·19). A series of one-way ANOVAs revealed no significant main effects of group in the number of correct classification responses [$F(2, 88)=0·5$, $p=0·6$] or reaction times [$F(2, 88)=0·3$, $p=0·8$]. Similarly, there were no significant differences between groups in the number of correct responses [$F(2, 88)=0·4$, $p=0·6$], reaction times [$F(2, 88)=0·3$, $p=0·7$] or recognition accuracy [$F(2, 88)=1·09$, $p=0·4$] during the recognition task. All groups therefore performed well above chance and were equivalent in both accuracy and speed.

Functional MRI

Word classification

Within-group results for word classification relative to the baseline experimental activation are shown in Fig. 1. In general, all groups presented activation in the bilateral cerebellum, bilateral superior/medial frontal gyrus (BA 6), inferior frontal gyrus (BA 47/44) and left parietal lobe (with peak maxima in postcentral gyrus in controls and HR−, and in the inferior parietal lobule in HR+). For the reverse contrast (baseline activation relative to the word classification condition), areas of activation were predominantly seen in posterior brain regions across all groups, including the cuneus, precuneus, posterior cingulate and fusiform gyri.

Between-group results for the word classification task (Table 2) showed no areas of

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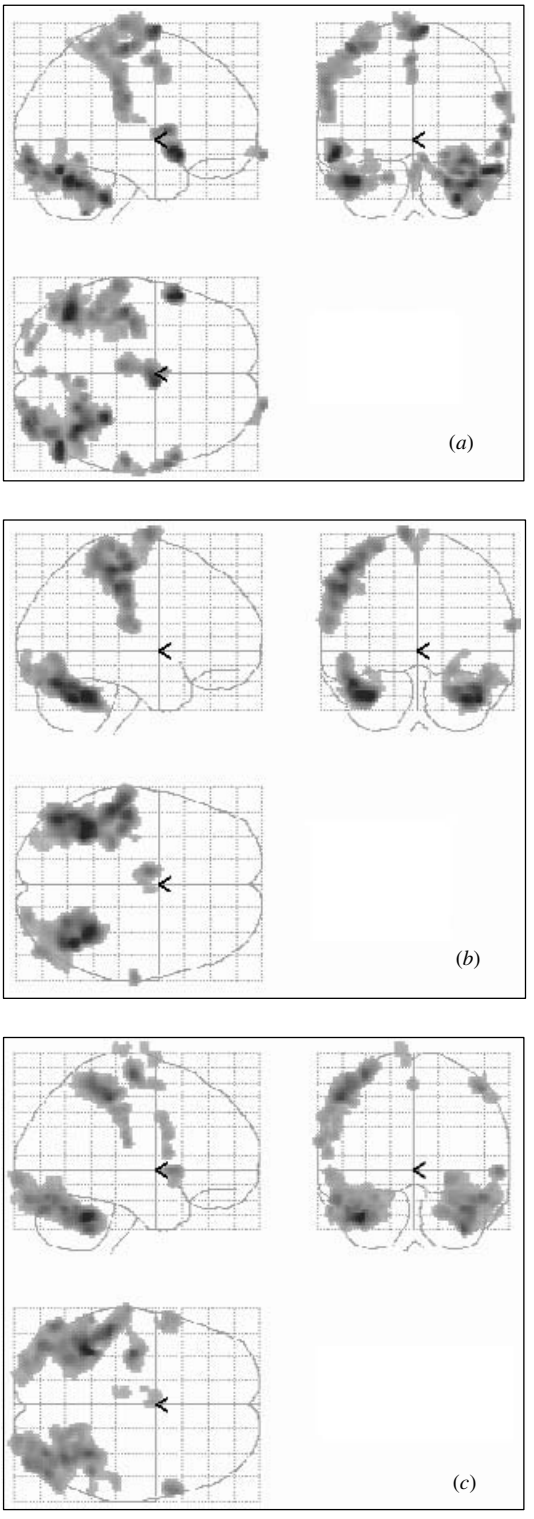

significantly greater activation in the controls relative to the high-risk group as a whole. The high-risk group, however, showed a larger blood-oxygen-level-dependent (BOLD) fMRI response in the right inferior frontal gyrus relative to the control group (p corrected = 0·14, p uncorrected = 0·006, see Table 2 and Fig. 2). The HR+ also showed a trend for a significantly increased response relative to controls in the same region (p corrected = 0·095, p uncorrected = 0·004). Finally, the HR+ relative to the HR− showed a greater response in the left inferior parietal lobule, although this was not significant at the corrected level.

Correct recognition

For the contrast correct old *versus* correct new responding, the three groups demonstrated different patterns of activation (Fig. 3). Both the controls and the HR− demonstrated activation in subcortical structures including the lentiform and thalamus. The controls and HR+ also demonstrated similar areas of activation in the left inferior/middle frontal gyrus (BA 10/46); however, the controls presented additional activation in the left postcentral gyrus, and the HR+ in the right superior parietal lobule and right cerebellum. Similarly, for the reverse contrast the three groups also demonstrated different patterns of activation. The controls presented greater activation for correct new *versus* correct old responding in the bilateral medial frontal gyrus, cerebellum, right temporal regions and right parietal lobe. The HR− demonstrated activation in the bilateral occipital regions and left pre/postcentral gyrus, and the HR+ demonstrated activation in the right cerebellum and left posterior temporal/occipital region.

Between-group results (Table 2) showed that during correct old relative to correct new responding, controls showed no significant areas of greater response relative to the high-risk group as a whole, or those with or without transient psychotic symptoms. The high-risk

FIG. 1. Within-group maps for word classification relative to baseline experimental activation: (*a*) controls, (*b*) high-risk without psychotic symptoms, (*c*) high-risk with psychotic symptoms. Statistical maps are thresholded to account for differences in group size [threshold t value scaled by $\sqrt{(n-1)}$], where for controls the t threshold = 3·55, for all groups $k_E = 50$.

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Table 2. *Between-group results*

	p value	Extent	*z* score	Peak height coordinates x	y	z	Region
Word classification *versus* baseline							
Controls > high-risk	N.S.						
Controls > high-risk without psychotic symptoms	N.S.						
Controls > high-risk with psychotic symptoms	N.S.						
Controls < high-risk	0·14	137	3·81	51	26	6	R inferior frontal gyrus, BA9/45
	(0·006)			51	26	3	R inferior frontal gyrus, BA45
				54	19	13	R inferior frontal gyrus, BA45
Controls < high-risk without psychotic symptoms	N.S.						
Controls < high-risk with psychotic symptoms	0·095	154	4·04	51	26	6	R inferior frontal gyrus, BA45
	(0·004)			62	22	14	R inferior frontal gyrus, BA45
				43	21	18	R inferior frontal gyrus, BA45
High-risk without > high-risk with psychotic symptoms	N.S.						
High-risk without < high-risk with psychotic symptoms	0·069	168	3·90	−46	−58	49	L inferior parietal lobule, BA40
				−42	−60	42	L inferior parietal lobule, BA40
Correct old *versus* correct new responses							
Controls > high-risk	N.S.						
Controls > high-risk without psychotic symptoms	N.S.						
Controls > high-risk with psychotic symptoms	N.S.						
Controls < high-risk	< 0·001	388	4·44	40	−60	−27	R cerebellum, posterior lobe, tuber
				30	−55	−16	R cerebellum, posterior lobe, declive
Controls < high-risk without psychotic symptoms	0·053	183	3·92	−2	−48	−10	L cerebellum, anterior lobe, culmen
				12	−46	−6	R cerebellum/lingual gyrus
				3	−28	−3	R brainstem
	0·035	202	3·89	28	−53	−18	R cerebellum, anterior lobe, culmen
				40	−60	−26	R cerebellum, posterior lobe, tuber
Controls < high-risk with psychotic symptoms	0·005	300	4·39	40	−59	−38	R cerebellum, posterior lobe, cerebellar tonsil
				34	−62	−22	
				24	−42	−12	R cerebellum, posterior lobe, uvula
							R cerebellum, anterior lobe, culmen
High-risk without > high-risk with psychotic symptoms	0·046	190	3·89	14	−5	15	R thalamus
				−4	−5	11	L thalamus
High-risk without < high-risk with psychotic symptoms	N.S.						

Thresholded 0·001 uncorrected $k_E = 20$ voxels. *p* values in parentheses are at the uncorrected level, one *p* value per cluster reported.
N.S., Not significant; R, right; L, left.

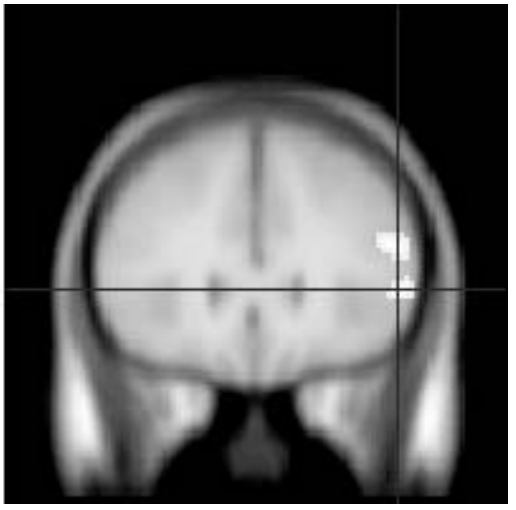

FIG. 2. Between-group maps for word classification relative to baseline experimental activation. Greater activation seen in right inferior frontal gyrus in all high-risk subjects *versus* controls (crosshair at $x=51$, $y=26$, $z=6$). For illustration, statistical maps are thresholded at 0·001 uncorrected $k_E=100$ voxels.

group as a whole, however, showed a significantly greater fMRI response relative to the controls in the right cerebellum (Fig. 4). This was also significant for both high-risk groups individually tested against the control group, but not between the two high-risk groups. The HR− group also demonstrated greater activation in the bilateral thalamus relative to the HR+ group.

DISCUSSION

This study is one of a small number of functional imaging studies in relatives of people with schizophrenia, and one of an even smaller number of studies in people at elevated risk as they were relatively young. Although a number of high-risk participants were experiencing transient psychotic symptoms, none met the diagnostic criteria for any psychiatric disorder, and none were medicated. The in-scanner

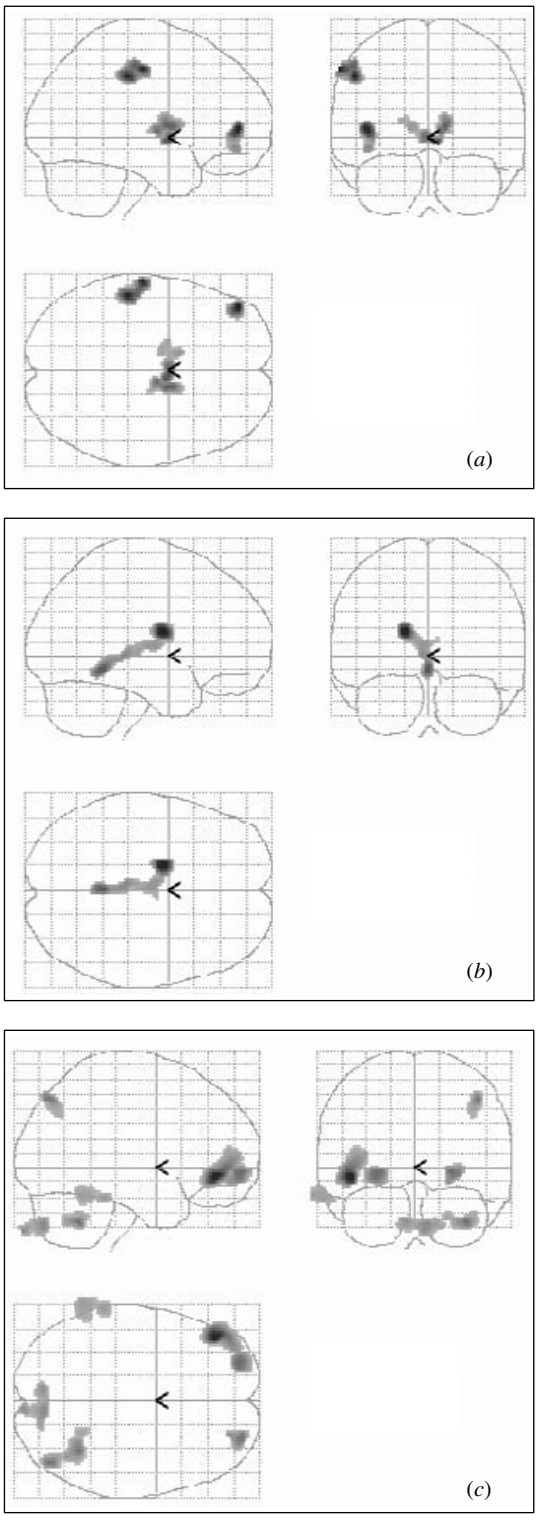

FIG. 3. Within-group maps for correct old relative to correct new responding: (*a*) controls, (*b*) high-risk without psychotic symptoms, (*c*) high-risk with psychotic symptoms. Statistical maps are thresholded to account for differences in group size [threshold t value scaled by $\sqrt{(n-1)}$], where for controls the t threshold = 2·53, for all groups $k_E=100$.

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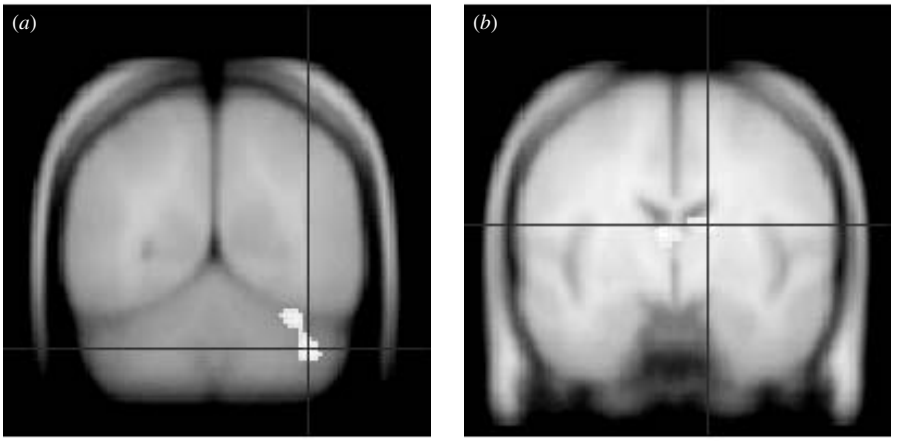

FIG. 4. Between-group maps for correct old relative to correct new responding. Greater activation seen in (*a*) right cerebellum in high-risk subjects *versus* controls (crosshair at $x=40$, $y=-60$, $z=-27$) and (*b*) bilateral thalamus in high-risk subjects without psychotic symptoms *versus* those with (crosshair at $x=14$, $y=-5$, $z=15$). For illustration, statistical maps are thresholded at 0·001 uncorrected $k_E=100$ voxels.

performance measure demonstrated that both tasks were performed well by all participants.

For word classification relative to baseline, the within-group maps showed increased response in areas previously shown to be activated during similar tasks in normal adults. These included the left medial frontal gyrus, left inferior frontal gyrus and left lateral parietal cortex, considered to reflect language processing, covert articulation and working memory operations (Cabeza & Nyberg, 2000; Leube *et al.* 2001; Pilgrim *et al.* 2002). The region of activation in the medial frontal gyrus in our study (BA 6) is more posterior and superior to regions commonly associated with semantic processing tasks (BA 8); however, other studies have also reported activation in supplementary motor areas during semantic tasks in healthy controls (see Gitelman *et al.* 2005), and this region has also been reported to be involved during tasks requiring verbal working memory (Fiez *et al.* 1996). For the reverse contrast, areas of 'deactivation' were also comparable to those regions showing reduced activation during word classification and semantic generation tasks, such as the superior temporal gyrus (Frith *et al.* 1991; Warburton *et al.* 1996), or those that are shown to be consistently 'deactivated' in various cognitive tasks, such as the medial parietal cortex (precuneus and cuneus) and medial frontal cortex (Shulman *et al.* 1997; McKiernan *et al.* 2003).

Previous fMRI studies in healthy adults investigating differences in brain activity between correctly recognized old previously studied items (hits) and correctly identified new previously unstudied items (correct rejections), or the 'old–new effect', have shown activations in varied regions including the anterior prefrontal cortex (Buckner & Koutstaal, 1998; Henson *et al.* 1999*a*, *b*; McDermott *et al.* 2000), lateral and medial parietal cortex (Konishi *et al.* 2000; Kahn *et al.* 2004) and left medial temporal lobes, including the hippocampus and parahippocampal gyrus (Donaldson *et al.* 2001). The within-group functional activation maps for the old–new effect contrast here revealed different patterns across the three groups. Activation in the controls, however, was seen in the anterior prefrontal cortex, as described in the above studies (see Fig. 3), with additional areas of activation in the left postcentral gyrus and subcortical structures, including the thalamus, which, although less common, have also been reported in other studies of healthy controls performing similar tasks (Konishi *et al.* 2000). In general, this contrast revealed less widespread activations than those seen in the previous word classification task. This is probably because of the overlap in brain areas recruited during the identification of both types of event, but could also be indicative of less neural effort required for successful recognition.

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Our paradigm also enabled the characterization of differences between groups in functional brain response. During word classification, the high-risk group as a whole showed a greater activation (before correction for multiple comparisons) in the right inferior frontal gyrus relative to controls. Further splitting of the groups revealed increased right inferior frontal gyrus activation only in those high-risk subjects with psychotic symptoms *versus* controls, not in those without symptoms (before correction for multiple comparisons). This continuum of hyperfrontality in the high-risk groups may therefore indicate that this is not purely a trait-related finding. Findings of both hypo- and hyperfrontality on verbal memory tasks have been extensively reported in the established illness, where the direction of abnormality is considered to be associated with task difficulty and performance (e.g. Heckers *et al*. 1998; Ragland *et al*. 2004). Overactivation in the right dorsolateral prefrontal cortex (BA 9/46) has also been previously reported in unaffected relatives performing a working memory task in the absence of detrimental performance and was interpreted as representing inefficient processing in this region (Callicott *et al*. 2003). This could be the case here, although this region was not apparently active in the word classification *versus* baseline contrast at the thresholds chosen. It could therefore represent subtle additional compensatory recruitment of right-sided regions to supplement left-sided activity normally involved in semantic processing in order to enhance performance in the high-risk subjects, consistent with other studies of patients with schizophrenia (Bonner-Jackson *et al*. 2005) and high-risk individuals (see Sommer *et al*. 2004).

During successful recognition of old relative to new words, the high-risk group showed greater activation relative to controls in the right cerebellum. In this case further splitting of the high-risk group revealed significant differences in both high-risk groups *versus* the controls, indicating the presence of a robust trait effect. Performance was not significantly worse in the high-risk group, making it likely that this hyperactivation is compensatory to assist in the recognition of previous semantically processed information. During a covert word generation task in the same group, however, controls showed a greater task-related increase in the left posterior lobe of the cerebellum relative to the high-risk group (Whalley *et al*. 2004). This is somewhat at odds with our current finding. However, it is plausible that aspects of the current task required greater effort for the high-risk group than the controls, thus resulting in an increased recruitment of this area. A task of increasing levels of difficulty may result in high-risk participants reaching their peak capacity of activation earlier than controls, resulting in the eventual ineffective recruitment of this area (Fletcher & Henson, 2001).

Structural deficits in the cerebellum have previously been demonstrated in schizophrenia (Levitt *et al*. 1999; Nopoulos *et al*. 1999), and have been linked to dysfunctions in motor control and coordination in first-episode and chronic schizophrenics, and motor developmental abnormalities in biological relatives at high-risk of the disorder (Andreasen *et al*. 1999; Niemi *et al*. 2003). The cerebellum is increasingly viewed as a crucial component in the network supporting verbal episodic retrieval, and both anterior and posterior cerebellar areas have been demonstrated as significantly correlated with aspects of cognitive function, including story recall and visual recall (MacLullich *et al*. 2004). There is some evidence for impaired cerebellar function in schizophrenia during tasks of verbal memory and language, attributed to a dysfunctional fronto-thalamic-cerebellar network, and resulting in a failure in the process of monitoring and coordination of cognition or 'cognitive dysmetria' (Andreasen *et al*. 1996, 1999; Crespo-Facorro *et al*. 1999). These findings are consistent with evidence from neuroimaging studies in healthy volunteers implicating the cerebellum not only in tasks of verbal working memory (Paulesu *et al*. 1993; Awh *et al*. 1995; Desmond *et al*. 1998; Li *et al*. 2004) but also in tasks of attention (Allen *et al*. 1997; Desmond *et al*. 1997; Desmond & Fiez, 1998) and memory retrieval (Andreasen *et al*. 1996; Schacter *et al*. 1996).

We have therefore shown differences in BOLD response between groups during a basic verbal memory paradigm. Although we reported no performance differences between the groups on either of the tasks, dual process theories of episodic memory posit that there are two separate processes underlying recognition memory judgements, recollection and familiarity, such

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that familiarity in the absence of recollection would be sufficient to support recognition memory (see Yonelinas, 2001). As we only recorded 'yes/no' responses, we cannot discriminate between these two components. This therefore limits the confidence with which we can state that the groups are truly matched on performance. Future investigations might benefit from paradigm modifications allowing responses with differing levels of confidence. Similarly, any inferences about the nature of the verbal processes during the classification task (i.e. probably a mixture of both semantic and phonological coding) are limited without an additional task controlling for phonological or perceptual judgement.

An additional limitation to this analysis is the moderate number of events included (i.e. 36 targets and 36 lures), chosen principally to limit the amount of time participants were required to spend in the scanner. In total, there were on average approximately 50 correct events per participant. For our correct old *versus* correct new comparison, this most probably reduced statistical power to detect significant responses both within and between groups, while a comparison of incorrect old and incorrect new events was precluded because of too few incorrect response events.

In summary, these results provide an insight into putative trait effects in biological relatives of schizophrenics within the period of maximum risk for the disorder during an fMRI investigation. Prefrontal and cerebellar hyperactivation in well relatives is likely to be compensatory for the neural network aberrations underlying more serious verbal memory deficits seen in patients, and is consistent with a leftward shift of the inverted 'U' load–response model of cognitive function in schizophrenia.

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DECLARATION OF INTEREST

None.

REFERENCES

Aleman, A., Hijman, R., De Haan, E. H. & Kahn, R. S. (1999). Memory impairment in schizophrenia: a meta-analysis. *American Journal of Psychiatry* **156**, 1358–1366.

Allen, G., Buxton, R., Wong, E. & Courchesne, E. (1997). Attentional activation of the cerebellum independent of motor involvement. *Science* **275**, 1940–1943.

Andreasen, N. C., Nopoulos, P., O'Leary, D. S., Miller, D. D., Wassink, T. & Flaum, M. (1999). Defining the phenotype of schizophrenia: cognitive dysmetria and its neural mechanisms. *Biological Psychiatry* **46**, 908–920.

Andreasen, N. C., O'Leary, D. S., Cizadlo, T., Arndt, S., Rezai, K., Ponto, L. L., Watkins, G. L. & Hichwa, R. D. (1996). Schizophrenia and cognitive dysmetria: a positron-emission tomography study of dysfunctional prefrontal-thalamic-cerebellar circuitry. *Proceedings of the National Academy of Sciences USA* **93**, 9985–9990.

Awh, E., Smith, E. & Jonides, J. (1995). Human rehearsal processes and the frontal lobes: PET evidence. *Annals of the New York Academy of Sciences* **769**, 97–117.

Barch, D. & Al, E. (2002). Working and long term memory deficits in schizophrenia: is there a common prefrontal mechanism? *Journal of Abnormal Psychology* **111**, 478–494.

Bilder, R. M. (1996). Neuropsychology and neurophysiology in schizophrenia. *Current Opinion in Psychiatry* **9**, 57–62.

Bilder, R. M., Goldman, R. S., Robinson, D., Reiter, G., Bell, L., Bates, J. A., Pappadopulos, E., Willson, D. F., Alvir, J. M. J., Woerner, M. G., Geisler, S., Kane, J. M. & Lieberman, J. A. (2000). Neuropsychology of first-episode schizophrenia: initial characterization and clinical correlates. *American Journal of Psychiatry* **157**, 549–559.

Bonner-Jackson, A., Haut, K., Csernansky, J. G. & Barch, D. M. (2005). The influence of encoding strategy on episodic memory and cortical activity in schizophrenia. *Biological Psychiatry* **58**, 47–55.

Brebion, G., Amador, X., Smith, M. & Gorman, J. (1997). Mechanisms underlying memory impairment in schizophrenia. *Psychological Medicine* **27**, 383–393.

Buckner, R. L. & Koutstaal, W. (1998). Functional neuroimaging studies of encoding, priming, and explicit memory retrieval. *Proceedings of the National Academy of Sciences USA* **95**, 891–898.

Cabeza, R. & Nyberg, L. (2000). Imaging cognition II: an empirical review of 275 PET and fMRI studies. *Journal of Cognitive Neuroscience* **12**, 1–47.

Callicott, J. H., Egan, M. F., Mattay, V. S., Bertolino, A., Bone, A. D., Verchinksi, B. & Weinberger, D. R. (2003). Abnormal fMRI response of the dorsolateral prefrontal cortex in cognitively intact siblings of patients with schizophrenia. *American Journal of Psychiatry* **160**, 709–719.

Chan, A. S., Kwok, I. C., Chiu, H., Lam, L., Pang, A. & Chow, L. (2000). Memory and organizational strategies in chronic and acute schizophrenic patients. *Schizophrenia Research* **42**, 431–445.

Crespo-Facorro, B., Paradiso, S., Andreasen, N. C., O'Leary, D. S., Watkins, G. L., Boles Ponto, L. L. & Hichwa, R. D. (1999). Recalling word lists reveals 'cognitive dysmetria' in schizophrenia: a positron emission tomography study. *American Journal of Psychiatry* **156**, 386–392.

Curtis, V. A., Bullmore, E. T., Brammer, M. J., Wright, I. C., Williams, S. C., Morris, R. G., Sharma, T. S., Murray, R. M. & McGuire, P. K. (1998). Attenuated frontal activation during a verbal fluency task in patients with schizophrenia. *American Journal of Psychiatry* **155**, 1056–1063.

Desmond, J. E. & Fiez, J. A. (1998). Neuroimaging studies of the cerebellum: language, learning and memory. *Trends in Cognitive Sciences* **2**, 355–362.

Desmond, J. E., Gabrieli, J. D. E. & Glover, G. H. (1998). Dissociation of frontal and cerebellar activity in a cognitive task: evidence for a distinction between selection and search. *NeuroImage* **7**, 368–376.

Desmond, J. E., Gabrieli, J. D. E., Wagner, A. D., Ginier, B. L. & Glover, G. H. (1997). Lobular patterns of cerebellar activation in verbal working-memory and finger-tapping tasks as revealed by functional MRI. *Journal of Neuroscience* **17**, 9675–9685.

Donaldson, D. I., Peterson, S. E. & Buckner, R. L. (2001). Dissociating memory retrieval processes using fMRI: evidence that priming does not support recognition memory. *Neuron* **31**, 1047–1059.

E-Prime (2000). E-prime 1.0.15.10, E-Prime 1.0 (Beta 5.0) (1.0.15.0). Psychology Software Tools, Pittsburgh, PA, USA.

Fiez, J. A., Raife, E. A., Balota, D. A., Schwarz, J. P., Raichle, M. E. & Petersen, S. E. (1996). A positron emission tomography study of the short-term maintenance of verbal information. *Journal of Neuroscience* **15**, 808–822.

Fletcher, P. C. & Henson, R. (2001). Frontal lobes and human memory. *Brain* **124**, 849–881.

Fletcher, P. C., McKenna, P. J., Frith, C. D., Grasby, P. M., Friston, K. J. & Dolan, R. J. (1998). Brain activations in schizophrenia during a graded memory task studied with functional neuroimaging. *Archives of General Psychiatry* **55**, 1001–1008.

Frith, C. D., Friston, K. J., Liddle, P. F. & Frackowiak, R. S. J. (1991). A PET study of word finding. *Neuropsychologia* **29**, 1137–1148.

Gitelman, D. R., Nobre, A. C., Sonty, S., Parrish, T. B. & Mesulam, M. (2005). Language network specializations. An analysis with parallel task designs and functional magnetic resonance imaging. *NeuroImage* **26**, 975–985.

Gottesman, I. I. (1991). *Schizophrenia Genesis: The Origins of Madness*. W. H. Freeman and Company: New York.

Heckers, S., Rauch, S. L., Goff, D., Savage, C. R., Schacter, D. L., Fischman, A. J. & Alpert, N. M. (1998). Impaired recruitment of the hippocampus during conscious recollection in schizophrenia. *Nature Neuroscience* **1**, 318–323.

Heinrichs, R. W. & Zakzanis, K. K. (1998). Neurocognitive deficit in schizophrenia: a quantitative review of the evidence. *Neuropsychology* **12**, 426–445.

Henson, R. N. (2005). A mini-review of fMRI studies of human medial temporal lobe activity associated with recognition memory. *Quarterly Journal of Experimental Psychology. B, Comparative and Physiological Psychology* **58**, 340–360.

Henson, R. N. A., Rugg, M. D., Shallice, T., Josephs, O. & Dolan, R. J. (1999*a*). Recollection and familiarity in recognition memory: an event-related functional magnetic resonance imaging study. *Journal of Neuroscience* **19**, 3962–3972.

Henson, R. N. A., Shallice, T. & Dolan, R. J. (1999*b*). Right prefrontal cortex and episodic memory retrieval: a functional MRI test of the monitoring hypothesis. *Brain* **122**, 1367–1381.

Hill, K., Beers, S. R., Kmiec, J. A., Keshavan, M. S. & Sweeney, J. A. (2004). Impairment of verbal memory and learning in antipsychotic-naive patients with first-episode schizophrenia. *Schizophrenia Research* **68**, 127–136.

Hofer, A., Weiss, E. M., Golaszewski, S. M., Brinkhoff, C., Kremser, C., Felber, S. & Fleischhacker, W. (2003). An fMRI study of episodic encoding and recognition of words in patients with schizophrenia in remission. *American Journal of Psychiatry* **160**, 911–918.

Holthausen, E. A. E., Wiersma, D., Sitskoorn, M. M., Dingemans, P. M., Schene, A. H. & Van Den Bosch, R. J. (2003). Long-term memory deficits in schizophrenia: primary or secondary dysfunction? *Neuropsychology* **17**, 539–547.

Jennings, J. M., McIntosh, A. R., Kapur, S., Zipursky, R. B. & Houle, S. (1998). Functional network differences in schizophrenia: a rCBF study of semantic processing. *Neuroreport* **9**, 1697–1700.

Jessen, F., Scheef, L., Germeshausen, L., Tawo, Y., Kockler, M., Kuhn, K.-U., Maier, W., Schild, H. H. & Heun, R. (2003). Reduced hippocampal activation during encoding and recognition of words in schizophrenia patients. *American Journal of Psychiatry* **160**, 1305–1312.

Johnstone, E. C., Abukmeil, S., Byrne, M., Clafferty, R., Grant, E., Hodges, A., Lawrie, S. M. & Owens, G. C. (2000). Edinburgh high-risk study-findings after four years: demographic, attainment and psychopathological issues. *Schizophrenia Research* **46**, 1–15.

Johnstone, E. C., Ebmeier, K. P., Miller, P., Owens, D. G. C. & Lawrie, S. M. (2005). Predicting schizophrenia: findings from the Edinburgh High-Risk Study. *British Journal of Psychiatry* **186**, 18–25.

Kahn, I., Davachi, L. & Wagner, A. D. (2004). Functional-neuroanatomic correlates of recollection: implications for models of recognition memory. *Journal of Neuroscience* **24**, 4172–4180.

Kapur, S., Craik, F., Tulving, E., Wilson, A., Houle, S. & Brown, G. M. (1994). Neuroanatomical correlates of encoding in episodic memory: levels of processing effect. *Proceedings of the National Academy of Sciences USA* **91**, 2008–2011.

Kenny, J. T., Friedman, L., Findling, R. L., Swales, T. P., Strauss, M. E., Jesberger, J. A. & Schulz, S. C. (1997). Cognitive impairment in adolescents with schizophrenia. *American Journal of Psychiatry* **154**, 1613–1615.

Konishi, S., Wheeler, M. E., Donaldson, D. I. & Buckner, R. L. (2000). Neural correlates of episodic retrieval success. *NeuroImage* **12**, 276–286.

Kubicki, M., McCarley, R. W., Nestor, P. G., Huh, T., Kikinis, R., Shenton, M. E. & Wible, C. G. (2003). An fMRI study of semantic processing in men with schizophrenia. *NeuroImage* **20**, 1923–1933.

Leube, D. T., Erb, M., Grodd, W., Bartels, M. & Kircher, T. T. J. (2001). Activation of right fronto-temporal cortex characterizes the 'living' category in semantic processing. *Cognitive Brain Research* **12**, 425–430.

Levitt, J. J., McCarley, R. W., Nestor, P. G., Petrescu, C., Donnino, R., Hirayasu, Y., Kikinis, R., Jolesz, F. A. & Shenton, M. E. (1999). Quantitative volumetric MRI study of the cerebellum and vermis in schizophrenia: clinical and cognitive correlates. *American Journal of Psychiatry* **156**, 1105–1107.

Li, D. X. W., Gandour, J. C. A., Dzemidzic, M., Tong, Y., Talavage, T. & Lowe, M. (2004). Neural network for encoding immediate memory in phonological processing. *Neuroreport* **15**, 2459–2462.

Lustig, C., Snyder, A. Z., Bhakta, M., O'Brien, K. C., McAvoy, M., Raichle, M. E., Morris, J. C. & Buckner, R. L. (2003). Functional deactivations: change with age and dementia of the Alzheimer type. *Proceedings of the National Academy of Sciences USA* **100**, 14504–14509.

MacLullich, A. M. J., Edmond, C. L., Ferguson, K. J., Wardlaw, J. M., Starr, J. M., Seckl, J. R. & Deary, I. J. (2004). Size of the neocerebellar vermis is associated with cognition in healthy elderly men. *Brain and Cognition* **56**, 344–348.

Manschrek, T. C., Maher, B. A., Beaudette, S. M. & Redmond, D. A. (1997). Context memory in schizoaffective and schizophrenic disorders. *Schizophrenia Research* **26**, 153–161.

McDermott, K. B., Jones, T. C., Petersen, S. E., Lageman, S. K. & Roediger, H. L., 3rd (2000). Retrieval success is accompanied by enhanced activation in anterior prefrontal cortex during recognition memory: an event-related fMRI study. *Journal of Cognitive Neuroscience* **12**, 965–976.

McKiernan, K. A., Kaufman, J. N., Kucera-Thompson, J. & Binder, J. R. (2003). A parametric manipulation of factors affecting task-induced deactivation in functional neuroimaging. *Journal of Cognitive Neuroscience* **15**, 394–408.

Moritz, S., Heeren, D., Andresen, B. & Krausz, M. (2001). An analysis of the specificity and syndromal correlates of verbal memory impairments in schizophrenia. *Psychiatry Research* **101**, 23–31.

Nathaniel-James, D. A., Brown, R. & Ron, M. A. (1996). Memory impairment in schizophrenia: its relationship to executive function. *Schizophrenia Research* **21**, 85–96.

Niemi, L. T., Suvisaari, J. M., Tuulio-Henriksson, A. & Lonnqvist, J. K. (2003). Childhood developmental abnormalities in schizophrenia: evidence from high-risk studies. *Schizophrenia Research* **60**, 239–258.

Nopoulos, P. C., Ceilley, J. W., Gailis, E. A. & Andreasen, N. C. (1999). An MRI study of cerebellar vermis morphology in patients with schizophrenia: evidence in support of the cognitive dysmetria concept. *Biological Psychiatry* **46**, 703–711.

Paulesu, E., Frith, C. & Frackowiak, R. (1993). The neural correlates of the verbal component of working memory. *Nature* **362**, 342–345.

Pilgrim, L. K., Fadili, J., Fletcher, P. & Tyler, L. K. (2002). Overcoming confounds of stimulus blocking: an event-related fMRI design of semantic processing. *NeuroImage* **16**, 713–723.

Ragland, J. D., Gur, R. C., Raz, J., Schroeder, L., Kohler, C. G., Smith, R. J., Alavi, A. & Gur, R. E. (2001). Effect of schizophrenia on frontotemporal activity during word encoding and recognition: a PET cerebral blood flow study. *American Journal of Psychiatry* **158**, 1114–1125.

Ragland, J. D., Gur, R. C., Valdez, J., Turetsky, B. I., Elliott, M., Kohler, C., Siegel, S., Kanes, S. & Gur, R. E. (2004). Event-related fMRI of frontotemporal activity during word encoding and recognition in schizophrenia. *American Journal Psychiatry* **161**, 1004–1015.

Rushe, T. M., Woodruff, P. W. R., Murray, R. M. & Morris, R. G. (1999). Episodic memory and learning in patients with chronic schizophrenia. *Schizophrenia Research* **35**, 85–96.

Saykin, A. J., Gur, R., Gur, R. E., Mozley, D. P., Mozley, L. H., Resnick, S. M., Kester, B. & Stafiniak, P. (1991). Neuropsychological function in schizophrenia. *Archives of General Psychiatry* **48**, 618–624.

Saykin, A. J., Schtasel, D. L., Gur, R. E., Kester, D. B., Mozley, L. H., Stafinaik, P. & Gur, R. (1994). Neuropsychological deficits in neuroleptic naive patients with first episode schizophrenia. *Archives of General Psychiatry* **51**, 124–131.

Schacter, D. L., Reiman, E., Curran, T., Sheng Yun, L., Bandy, D., McDermott, K. B. & Roediger, H. L. (1996). Neuroanatomical correlates of veridical and illusory recognition memory: evidence from positron emission tomography. *Neuron* **17**, 267–274.

Shulman, G. L., Fiez, J. A., Corbetta, M., Buckner, R. L., Miezin, F. M., Raichle, M. E. & Petersen, A. S. E. (1997). Common blood flow changes across visual tasks: II. Decreases in cerebral cortex. *Journal of Cognitive Neuroscience* **9**, 648–663.

Sitskoorn, M. M., Aleman, A., Ebisch, S. J. H., Appels, M. C. M. & Kahn, R. S. (2004*a*). Cognitive deficits in relatives of patients with schizophrenia: a meta-analysis. *Schizophrenia Research* **71**, 285–295.

Sitskoorn, M. M., Ebisch, S. J. H., Appels, M., Nuyen, J. & Kahn, R. S. (2004*b*). Memory profiles in parents of patients with schizophrenia. *Psychiatry Research* **128**, 27–37.

Sommer, I. C., Ramsey, N. F., Mandl, R. C. W., van Oel, C. J. & Kahn, R. S. (2004). Language activation in monozygotic twins discordant for schizophrenia. *British Journal of Psychiatry* **184**, 128–135.

Toulopoulou, T., Rabe-Hesketh, S., King, H., Murray, R. M. & Morris, R. G. (2003). Episodic memory in schizophrenic patients and their relatives. *Schizophrenia Research* **63**, 261–271.

Van Oostrom, I., Dollfus, S., Brazo, P., Abadie, P., Halbecq, I., Thery, S. & Marie, R. M. (2003). Verbal learning and memory in schizophrenic and Parkinson's disease patients. *Psychiatry Research* **117**, 25–34.

Warburton, E., Wise, R., Price, C., Weiller, C., Hadar, U., Ramsay, S. & Frackowiak, R. (1996). Noun and verb retrieval by normal subjects. Studies with PET. *Brain* **119**, 159–179.

Whalley, H. C., Simonotto, E., Flett, S., Marshall, I., Ebmeier, K. P., Owens, D. G. C., Goddard, N. H., Johnstone, E. C. & Lawrie, S. M. (2004). fMRI correlates of state and trait effects in subjects at genetically enhanced risk of schizophrenia. *Brain* **127**, 478–490.

Whalley, H. C., Simonotto, E., Marshall, I., Owens, D. G. C., Goddard, N. H., Johnstone, E. C. & Lawrie, S. M. (2005). Functional disconnectivity in subjects at high genetic risk of schizophrenia. *Brain* **128**, 2097–2108.

Whyte, M.-C., McIntosh, A. M., Johnstone, E. C. & Lawrie, S. M. (2005). Declarative memory in unaffected adult relatives of patients with schizophrenia: a systematic review and meta-analysis. *Schizophrenia Research* **78**, 13–26.

Whyte, M.-C., Brett, C., Harrison, L. K., Byrne, M., Miller, P., Lawrie, S. M. & Johnstone, E. C. (2006). Neuropsychological performance changes over time in people at high-risk of developing schizophrenia and controls. *Biological Psychiatry* **59**, 730–739.

Wing, J. K., Cooper, J. E. & Sartorius, N. (1974). *The Description and Classification of Psychiatric Symptoms: An Instruction Manual for the PSE and CATEGO Systems*. Cambridge University Press: Cambridge.

Wittorf, A., Klingberg, S. & Wiedemann, G. (2004). Secondary verbal memory: a potential endophenotype of schizophrenia. *Journal of Psychiatric Research* **38**, 601–612.

Yonelinas, A. P. (2001). Components of episodic memory: the contribution of recollection and familiarity. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences* **356**, 1363–1374.