Preservation and compensation: The functional neuroanatomy of insight and working memory in schizophrenia

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ARTICLE INFO

ABSTRACT

Background: Poor insight in schizophrenia has been theorised to reflect a cognitive deficit that is secondary to brain abnormalities, localized in the brain regions that are implicated in higher order cognitive functions, including working memory (WM). This study investigated WM-related neural substrates of preserved and poor insight in schizophrenia.
Method: Forty stable schizophrenia outpatients, 20 with preserved and 20 with poor insight (usable data obtained from 18 preserved and 14 poor insight patients), and 20 healthy participants underwent functional magnetic resonance imaging (fMRI) during a parametric 'n-back' task. The three groups were preselected to match on age, education and predicted IQ, and the two patient groups to have distinct insight levels. Performance and fMRI data were analysed to determine how groups of patients with preserved and poor insight differed from each other, and from healthy participants.
Results: Poor insight patients showed lower performance accuracy, relative to healthy participants (p = 0.01) and preserved insight patients (p = 0.08); the two patient groups were comparable on symptoms and medication. Preserved insight patients, relative to poor insight patients, showed greater activity most consistently in the precuneus and cerebellum (both bilateral) during WM; they also showed greater activity than healthy participants in the inferior–superior frontal gyrus and cerebellum (bilateral). Group differences in brain activity did not co-vary significantly with performance accuracy.
Conclusions: The precuneus and cerebellum function contribute to preserved insight in schizophrenia. Preserved insight as well as normal-range WM capacity in schizophrenia sub-groups may be achieved via compensatory neural activity in the frontal cortex and cerebellum.

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1. Introduction

Poor insight is one of the most frequently reported symptoms of schizophrenia (Amador and David, 2004), with studies estimating that about 50–80% of patients do not believe that they have a disorder (Saeedi et al., 2007; Charkraborty and Basu, 2010). Much less is known about the neurobiology of poor insight, relative to its clinical consequences, in psychosis (Shad et al., 2007). At the neuropsychological level, many, though not all, studies have shown executive functioning deficits detected using the Wisconsin Card Sorting Test in patients

with poor insight, somewhat similar to those observed in patients with frontal lesions (Cooke et al., 2005). At the neural level, recent studies link poor insight with grey matter alterations, mainly reductions, not only in the frontal cortex (PFC), but also in the temporal and parietal cortices, anterior and posterior cingulate, insula and the cerebellum (Shad et al., 2007; Morgan et al., 2010; Palaniyappan et al., 2010; Bergé et al., 2011; Raij et al., 2012), and with white matter deficits in frontal, temporal and parietal regions (Antonius et al., 2011).

According to the model proposed by Shad et al. (2007), poor insight in schizophrenia reflects a cognitive deficit that is secondary to brain abnormalities, localized in the frontal and other brain regions that are implicated in higher order cognitive functions, including WM. WM, the process of actively holding information "on-line" in the mind's eye and manipulating it for guiding behaviour (Baddeley, 1992), is considered important for good insight in schizophrenia via its role in self-monitoring and awareness of symptoms (Shad et al., 2007). In general, schizophrenia patients show deficient WM and aberrant brain activity

during WM performance (Manoach, 2003) but no published study, to our knowledge, has yet investigated the activation of the WM neural network in relation to preserved or poor insight in this population.

In this study, we aimed to investigate whether and how the groups of patients with schizophrenia with preserved and poor insight differ from each other, and from healthy participants, in brain activity elicited by a parametric (n-back) working memory (WM) task, and detected with functional magnetic resonance imaging (fMRI). The n-back task, one of the most popular paradigms for functional neuroimaging studies of WM, consistently activates the frontal and parietal cortical regions, including the lateral premotor cortex, dorsal cingulate and medial premotor cortex, dorsolateral and ventrolateral PFC, and medial and lateral posterior parietal cortex (Owen et al., 2005). Here, we tested the hypothesis, derived from the neurobiological model of insight proposed by Shad et al. (2007), that patients with preserved insight, compared to those with poor insight, will have stronger WM capacity (Manoach, 2003) and this would be reflected as better performance and a greater increase in prefrontal and parietal activity from low to high WM load. The patients with preserved insight were expected to perform and show fMRI activity within normal range, or only subtly deficient, relative to the healthy group. Poor insight patients were expected to show poor WM and deficient neural activation, especially at the high WM load likely to exceed their WM capacity (Manoach, 2003).

2. Methods

2.1. Participants and design

This study included 60 right-handed participants. Of these, 40 were outpatients with schizophrenia, diagnosed using the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1995), and 20 were healthy participants. Of 40 patients, selected out of an initial pool of 70 patients, 20 met the criterion for preserved and 20 for poor insight (described further under 'Clinical Assessment' and 'Classification of Insight'). All included patients were required to be a) on stable doses of antipsychotic medication for ≥3 months, b) in the stable (chronic) phase of the illness, and c) not within two years of illness onset. The two patient groups were selected to be closely matched on age, sex and predicted IQ assessed using the National Adult Reading test (NART) (Nelson and Willison, 1991). Included healthy participants were screened to exclude neuropsychiatric conditions and matched for age, sex and predicted IQ of the patient sample. The study procedures had approval of the ethics committee of the Institute of Psychiatry and South London and Maudsley NHS Foundation Trust, London. All participants provided written informed consent and were compensated for their time and travel.

Of 20 patients with preserved insight, two patients had significant movement artefacts (i.e. rotations larger than 5° or translations greater than 5 mm) during fMRI and were excluded. Of 20 patients with poor insight, six patients were excluded because of movement artefacts (n = 2) or a failure to comply with given task instructions (n = 4). The final sample thus included 18 preserved insight and 14 poor insight patients, and 20 healthy participants. Table 1 shows demographic and clinical characteristics of the groups.

2.2. Clinical assessment

Insight in patients was assessed using a self-rated instrument, the Birchwood insight scale (BIS) (Birchwood et al., 1994). The BIS assesses David's (1990) three dimensions of insight, namely (i) the presence of a mental illness (items 2 and 7), (ii) the need for treatment (items 3–6), and (iii) the identification of symptoms as abnormal (items 1 and 8). As we did not include inpatients, item 4 "My stay in hospital is necessary" was excluded. Each item of the BIS is rated as 'agree', 'disagree' or 'unsure', giving an item score of 1 for unsure, and 0 or 2 for agree and disagree, depending on whether agreement with the statement indicates good insight; the items are counterbalanced for response valence. The BIS yields a maximum score of 16 (for this study, a maximum score of 14 after exclusion of item 4) with higher scores indicating better insight. The BIS has adequate internal consistency ($\alpha = 0.75$) and satisfactory test–retest reliability ($r = 0.90$ for the total insight score) (Birchwood et al., 1994). Insight assessed on the BIS correlates positively with other insight measures (Sapara et al., 2007). Patients completed the BIS under supervision. Symptoms were rated by a

Table 1
Demographics, clinical characteristics and task performance of study participants.

| Demographics | | Healthy participants n = 20 (15M:5F) | | Patients | | | |
| | | | | Preserved insight n = 18 (14M:4F) | | Poor insight n = 14; (9M = 5F) | |
		Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range
Age (years)		31.95 (7.6)	20–47	35.3 (9.92)	19–52	37.7	26–49
Education (years)		14.90 (3.06)	10–20	13.72 (2.89)	9–20	13.00 (1.35)	11–17
Predicted IQ (NART)[a]		113.22 (10.17)	91–128	108.66 (10.51)	86–122	106.76 (8.38)	90–119
Clinical characteristics							
BIS insight score				13.78 (0.43)	13–14	5.0 (2.04)	1–8
Age at illness onset (years)				24.95 (9.24)	12–48	22.36 (6.12)	10–33
Positive symptoms[b]				16.17 (5.07)	8–24	15.71 (4.75)	7–22
Negative symptoms[b]				16.83 (4.12)	7–25	19.29 (5.65)	8–27
General psychopathology[b]				33.50 (5.44)	24–42	32.29 (6.33)	21–40
Total symptoms[b]				66.50 (11.91)	43–83	67.29 (14.53)	37–86
Medication (chlorpromazine equivalents in mg)				459.93 (363.67)	100.00–1600.00	497.07 (348.63)	200–1367
Performance		Mean (SEM)		Mean (SEM)		Mean (SEM)	
Accuracy (%) (chance performance = 25%)	0-Back	88.42 (2.05)		89.85 (3.04)		84.10 (4.68)	
	1-Back	75.19 (5.03)		71.90 (6.99)		54.69 (7.46)	
	2-Back	52.47 (5.72)		51.37 (7.10)		34.73 (6.08)	
Reaction time (ms)	0-Back	187.57 (33.05)		215.05 (33.18)		242.70 (36.79)	
	1-Back	261.49 (34.34)		302.80 (36.68)		319.43 (53.36)	
	2-Back	394.38 (56.33)		532.99 (68.14)		482.58 (82.95)	

Duration of illness = current age minus age of illness onset.
[a] National Adult Reading Test.
[b] PANSS: Positive and Negative Symptom Scale.

psychiatrist (DF) using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987).

2.3. Classification of insight

Birchwood et al. (1994) suggested a BIS score of 9 as the cut off for good clinical insight. In this study, we defined scores ≥ 13 as preserved insight, and ≤ 8 as poor insight, to ensure that the two groups had clearly distinct insight levels.

2.4. fMRI: Paradigm and procedure

The task involved monitoring locations of dots (presentation time: 450 ms; inter-stimulus-interval: 1500 ms) within a diamond shaped box on the screen at a given delay from the original occurrence (0-back, 1-back, or 2-back) (Kumari et al., 2009). There were three 30-s active conditions (0-back, 1-back, 2-back), presented five times in pseudorandom order, controlling for order effect. Each active block had 15 stimulus presentations, starting with a 15 s rest block ('Rest' on the screen), and began with a 750 ms text delay to allow the participants to notice a change in task demand/condition. Participants viewed the paradigm projected onto a screen via a prismatic mirror whilst lying in the scanner. They were required to press the button on every trial, using the right thumb, corresponding to the correct location of the 0-back (current), 1-back (previous) or 2-back (previous but one) stimulus (chance performance = 25%; location of dots random).

Participants were requested to abstain from alcohol for at least 24 h prior to their scanning and given a chance to practice once on the task in advance of the scheduled scan to familiarize them with the procedures.

2.5. fMRI data acquisition

Echoplanar MR brain images were acquired using a 1.5 T GE Signa system (General Electric, Milwaukee WI, USA). In each of 16 near-axial non-contiguous planes parallel to the inter-commissural plane, T2*-weighted MR images depicting blood-oxygen-level-dependent contrast (Ogawa et al., 1990) were acquired over the experiment with echo time (TE) = 40 ms, repetition time (TR) = 3 s, in-plane resolution = 3.1 mm, slice thickness = 7.0 mm, and interslice gap = 0.7 mm. In the same session, a high-resolution 3-D inversion recovery prepared spoiled GRASS volume dataset was acquired with TE = 5.3 ms, TI = 300 ms, TR = 12.2 ms, in-plane resolution = 0.94 mm, and slice thickness = 1.5 mm.

2.6. Statistical analyses

2.6.1. Demographic, clinical and behavioural measures

Possible group differences in age, education and IQ (NART) were examined using a one-way analysis of variance (ANOVA) with Group as a between-subjects factor. Differences in clinical variables (insight, age at illness onset, symptoms) between the preserved and poor insight patient groups were examined using independent sample t-tests.

Group differences in performance were examined by a Group (preserved insight patients, poor insight patients, healthy participants) × Load (0-back, 1-back, 2-back) ANOVA [separately for accuracy (percentage correct responses) and latency (in ms) of correct responses] with Group as a between-subjects factor and Load as the within-subjects factor, followed by analysis of lower order effects as appropriate. Effect sizes for group differences in performance were estimated as partial eta^2 (the proportion of variance associated with a factor).

Data were analysed using SPSS 20.0 for Windows. The alpha level for significance (2-tailed) was set at p < 0.05 unless stated otherwise. Prior to conducting the analyses described above, the data were examined to ensure that statistical assumptions required were met.

2.6.2. Functional MRI

2.6.2.1. Image pre-processing. For each participant, the 225 volume functional time series were motion corrected (Friston et al., 1996), transformed into stereotactic space, spatially smoothed with a 8 mm FWHM Gaussian filter and band pass filtered using statistical parametric mapping software (SPM5; http://www.fil.ion.ucl.ac.uk/spm).

2.6.2.2. Models and statistical inferences. Data were analysed using a two-stage random effect procedure (Friston et al., 1999). The first stage identified subject-specific activations in all participants with a factorial model consisting of three active conditions (0-back, 1-back, 2-back) and rest as the implicit baseline. The boxcar for each 30-s epoch was convolved with the haemodynamic response function, global signal changes were removed and the time series were processed using a high-pass filter (128 s) to remove low-frequency artefacts. Generic task related activations in each group were identified (activation maps thresholded at p < 0.005; FWE-corrected at the cluster level, p < 0.05) for each of the active condition versus rest, 1-back and 2-back versus 0-back, and 2-back versus 1-back contrasts using one-sample t-tests. The second stage of analysis involved separate ANOVAs within SPM5, for each of the active condition versus rest, 1-back and 2-back versus 0-back, and 2-back versus 1-back contrasts, with Group as a between-subjects factor. These SPM ANOVAs were used to identify regions (height threshold p < 0.005, FWE-corrected at the cluster level p < 0.05) differentiating two or more groups using planned contrasts (each of the two patient groups vs the healthy group, poor and high insight patient group against each other). Analysis of some contrasts showed significant group differences only at the uncorrected level; these are also reported where the group difference occurred within regions linked to the WM network identified in previous studies.

Next, the subject-specific activation contrast image values were extracted (from one-sample tests including all participants) for the regions (peak voxel) differentiating the patient groups from each other, and from the healthy group, and examined for their possible relationships with performance (run within the SPSS) first using ANOVA with brain activity as the dependent variable and relevant Groups as the between-subjects variable, and then, in order to understand the contribution of (varying) performance to differences in brain activity of the three study groups, using analysis of co-variance (ANCOVA) with brain activity as the dependent variable, relevant Groups as the between-subjects variable, and performance accuracy over five blocks of 0-back (for 0-back > rest contrast), 1-back (for 1-back > 0-back/rest contrasts) or 2-back trials (for 2-back > 1back/0-back/rest contrasts) as the covariate.

3. Results

3.1. Demographic, clinical and behavioural measures

The final three study groups did not differ significantly in age [F(2,49) = 1.97, p = 0.15], education [F(2,49) = 2.527, p = 0.12], and NART IQ [F(2,49) = 1.99, p = 0.15] (Table 1).

The preserved and poor insight patient groups were comparable in age at illness onset [t(30) = 0.90, p = 0.37], positive symptoms [t(30) = 0.26, p = 0.80], negative symptoms [t(30) = 1.42, p = 0.17], general psychopathology [t(30) = 0.58, p = 0.56], and total PANSS symptoms [t(30) = 0.17, p = 0.87]. The groups were also taking similar doses of antipsychotic medication [t(30) = 0.31, p = 0.76]. By design, the two groups differed highly significantly in the level of insight [t(30) = 13.76, p < 0.001].

For performance accuracy, there was a highly significant effect of Load [F(2,98) = 79.44, p < 0.001; pta^2 = 0.62], indicating lower accuracy at higher memory load in all groups (Table 1). There was also a marginally significant main effect of Group [F(2,49) = 3.08,

$p = 0.055$, $pta^2 = 0.11$] indicating lower performance accuracy in poor insight patients, compared to preserved insight patients [$F(1,30) = 3.23$, $p = 0.08$, $pta^2 = 0.01$] and healthy participants [$F(1,32) = 6.70$, $p = 0.01$, $pta^2 = 0.17$]; preserved insight patients did not differ from healthy participants [$F(1,36) = 0.15$, $p = 0.70$]. The Group × Load interaction was not significant [$F(4,98) = 1.37$, $p = 0.25$].

For reaction time (to correct responses), there was only a significant main effect of Load [$F(2,98) = 30.66$, $p < 0.001$; $pta^2 = 0.39$], indicating longer reaction time at higher memory load in all three groups (Table 1). There was no effect of Group [$F(2,49) = 1.32$, $p = 0.28$] or Group × Load interaction [$F(4.98) = 0.74$, $p = 0.49$].

3.2. Functional MRI

3.2.1. Generic task related activations

Task related activations for each group are listed in Appendix 1 (supplementary materials) and displayed in Fig. 1. The activations, including fronto-parietal–cerebellar regions, in the healthy group were highly consistent with previous studies using this task (Kumari et al., 2006, 2009). The preserved insight group also showed significant activation of many of the same areas that were active in the healthy group. The poor insight group, however, showed activation in fewer clusters and did not show significant activation of any brain area during the 1-back and 2-back conditions, relative to the 0-back condition.
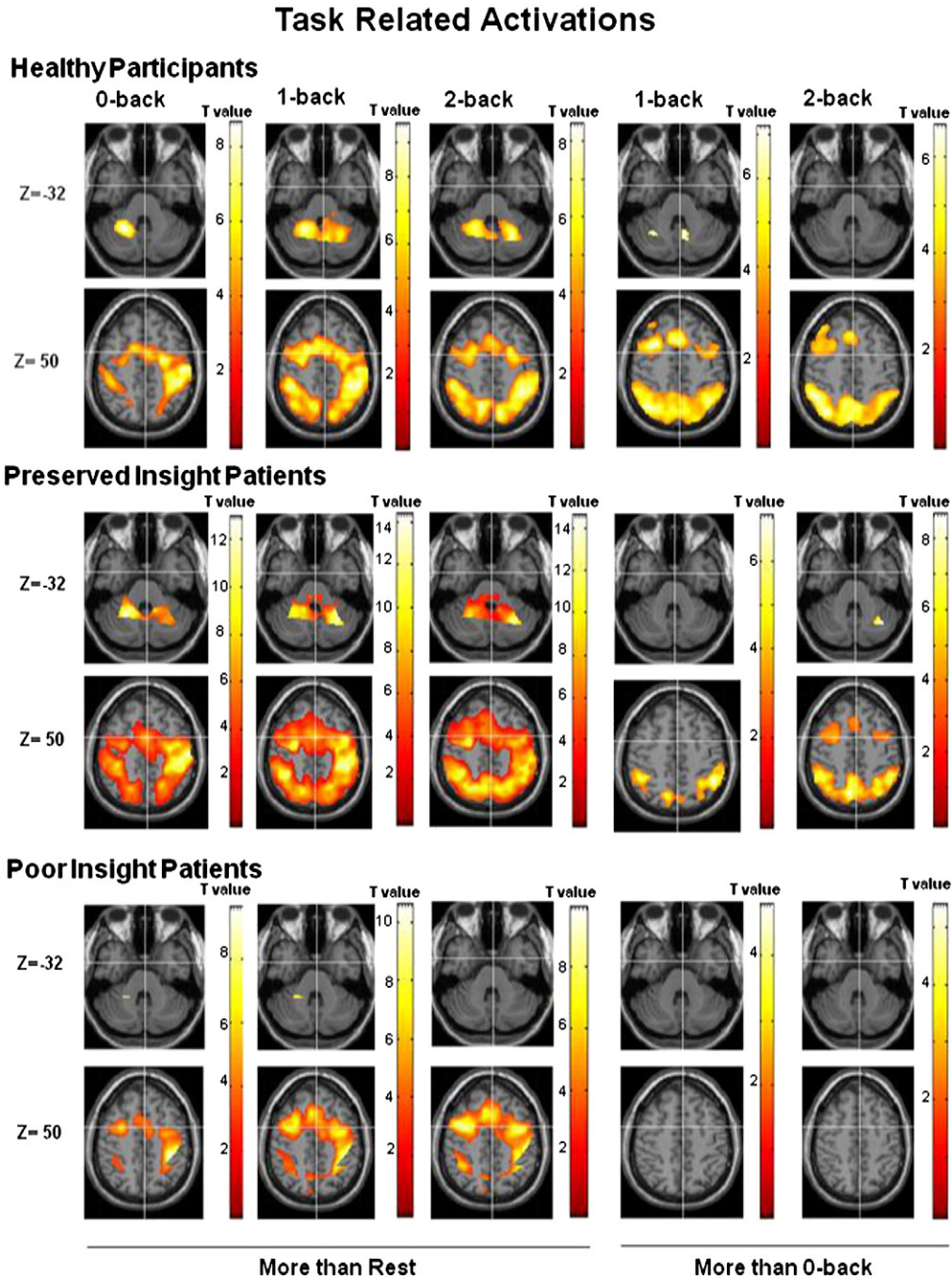

Fig. 1. Figure shows clusters of significant activity during active task conditions in the three study groups (height threshold p < 0.005; cluster p < 0.05 corrected). The MNI Z co-ordinate of each slice is given on the left of images. Right of image = left hemisphere.

Table 2
Areas showing group differences (height threshold p < 0.005) in activity to task demands.

	BA	Cluster size (voxels)	Side	X	Y	Z	Voxel T value	Cluster p (corrected unless shown in italics)
Preserved insight vs poor insight patients								
Preserved insight patients > poor insight patients								
2-Back > rest								
Precuneus	7	439	Right	6	−52	50	4.33	0.047
			Left	−8	−40	52	2.96	
Cerebellum	n/a	1489	Right	22	−42	−24	3.83	0.010
			Left	−10	−46	−24	3.73	
			Right	6	−48	−22	3.46	
2-Back > 1-back								
Cerebellum	n/a	821	Right	10	−42	−36	4.06	0.007
			Left	−10	−58	−30	3.89	
			Right	6	−56	−32	3.81	
Precuneus	7	949	Right	2	−52	50	3.94	0.044
			Left	−22	−70	60	3.72	
			Left	−4	−66	50	3.56	
Poor insight patients > preserved insight patients								
None significant in any contrasts								
Poor insight patients vs healthy participants								
Poor insight patients > healthy participants								
1-Back > rest								
Inferior frontal gyrus	45	389	Left	−38	26	12	3.96	0.030
			Left	−44	18	12	3.71	
			Left	−48	36	14	2.90	
Middle frontal gyrus	46	391	Right	48	18	20	3.46	0.030
Inferior frontal gyrus	45		Right	54	18	12	3.31	
			Right	44	32	16	2.88	
Healthy participants > poor insight patients								
2-Back > 0-back								
Cerebellum	n/a	686	Right	6	−48	−22	3.50	0.027
			Right	6	−64	−18	3.33	
			Left	−12	−46	−24	2.98	
Preserved insight patients vs healthy participants								
Preserved insight patients > healthy participants								
0-Back > rest								
Inferior frontal gyrus	45	4373	Right	48	20	18	5.09	<0.001
			Left	−22	38	30	4.56	
			Right	52	18	34	4.19	
Cerebellum		1098	Right	2	−50	2	4.56	0.025
Precuneus	31		Right	4	−44	38	3.62	
Posterior cingulate	23		Right	2	−40	24	3.05	
1-Back > rest								
Inferior frontal gyrus	46	356	Right	46	32	8	3.94	0.037
2-Back > rest								
Cerebellum	n/a	1039	Left	−38	−54	−22	4.22	0.042
			Left	−36	−62	−22	4.20	
Superior frontal gyrus	9	487	Right	16	56	24	3.55	0.038
			Right	16	32	30	3.28	
			Right	18	56	34	2.99	
2-Back > 1-back								
Superior frontal gyrus	10	450	Right	16	54	22	3.74	0.036
			Left	−16	50	22	3.58	
			Left	−2	42	26	3.25	
Healthy participants > preserved insight patients								
None significant in any contrasts.								

BA = Brodmann Area.

3.2.2. Group differences

Group differences in task related activations are noted in Table 2.

3.2.2.1. Preserved insight vs poor insight patients. Preserved insight patients, compared to those with poor insight, showed greater activity in the precuneus and cerebellum (both bilateral) during 2-back > rest and 2-back > 1-back contrasts (Table 2; Fig. 2). Poor insight patients, compared to preserved insight patients, did not show greater activity in any brain areas during any of task conditions.

3.2.2.2. Poor insight patients vs healthy participants. Compared to healthy participants, poor insight patients showed greater activations only during low WM load (1-back > rest), and these were observed in the inferior (bilateral) and middle (right) frontal gyri.

Healthy participants, in comparison with poor insight patients, showed greater cerebellar activations during the 2-back > 0-back (bilateral) contrast.

3.2.2.3. Preserved insight patients vs healthy participants. Many brain areas were activated to a greater extent in preserved insight patients, compared with healthy participants. For the 0-back > rest contrast, these included the inferior frontal gyrus (bilateral), cerebellum, precuneus and posterior cingulate (all right-sided). The preserved insight group also showed greater activation of the inferior frontal gyrus
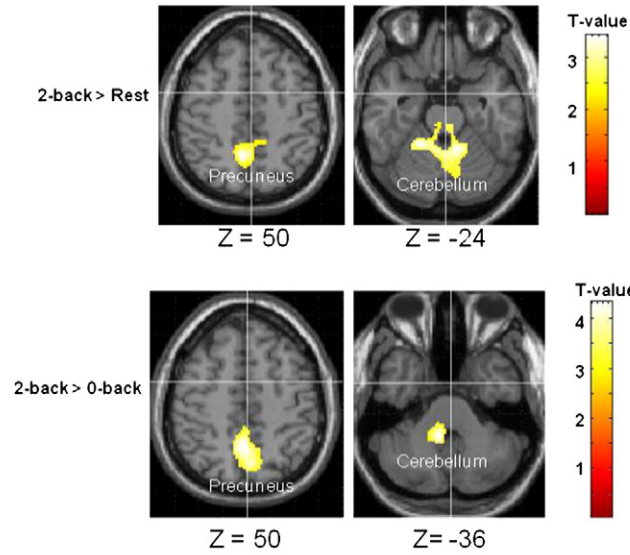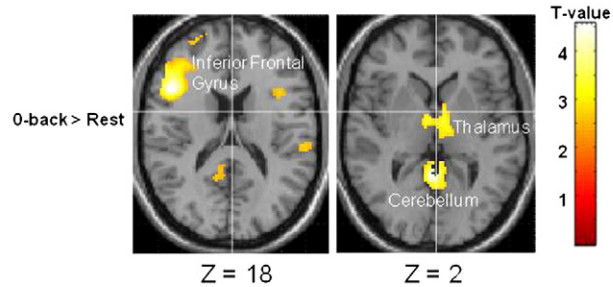
Greater Activation in Preserved Insight relative to Poor Insight Patients

Greater Activation in Preserved Insight Patients relative to Healthy Participants

Fig. 2. Axial sections of a standard brain with areas of greater activity in the preserved insight group, compared to the poor insight and healthy participant groups superimposed (height threshold p < 0.005, cluster p < 0.05 uncorrected). The MNI Z co-ordinate of each slice is given below each image. Right of image = left hemisphere.

Table 3
ANOVAs and ANCOVAs of group differences in cerebral activity for each working memory load with change in response accuracy as a covariate.

Group comparison	Contrast	Brain region	MNI					ANOVA		ANCOVA (with % correct as a covariate)	
			Side	X	Y	Z	BA	F(1,30)	p	F(1,29)	p
Preserved insight > poor insight patients	2-Back > rest	Precuneus	Right	6	−52	50	7	18.54	<0.001	13.75	0.001
		Cerebellum	Right	22	−42	−24	n/a	15.96	<0.001	13.24	0.001
	2-Back > 1-back	Cerebellum	Right	10	−42	−36	n/a	13.77	0.001	9.82	0.004
		Precuneus	Right	2	−52	50	7	11.00	0.002	7.24	0.012
								F(1,32)	p	F(1,31)	p
Poor insight patients > healthy participants	1-Back > rest	Inferior frontal gyrus	Left	−38	26	12	45	12.53	0.001	13.88	0.001
		Middle frontal gyrus	Right	48	18	20	46	13.82	0.001	16.07	<0.001
								F(1,32)	p	F(1,31)	p
Healthy participants > poor insight patients	2-Back > 0-back	Cerebellum	Right	6	−48	−22	n/a	11.27	0.002	7.93	0.008
								F(1,36)	p	F(1,35)	p
Preserved insight patients > healthy participants	0-Back > rest	Inferior frontal gyrus	Right	48	20	18	45	23.80	<0.001	23.07	<0.001
		Cerebellum	Right	2	−52	2	n/a	23.57	<0.001	22.88	<0.001
	1-Back > rest	Inferior frontal gyrus	Right	46	32	8	46	13.85	0.001	15.27	0.001
	2-Back > rest	Cerebellum	Left	−38	−54	−22	n/a	12.73	0.001	12.26	0.001
		Superior frontal gyrus	Right	16	56	24	9/10	14.82	0.001	14.07	0.001
	2-Back > 1-back	Superior frontal gyrus	Right	16	54	22	10	14.180	0.001	14.64	0.001

BA = Brodmann Area.

(right) for the 1-back > rest contrast; of the cerebellum (left) and superior frontal gyrus (right) for the 2-back > rest contrast; and of the superior frontal gyrus (bilateral) for the 2-back > 1-back contrast.

Healthy participants, compared to preserved insight patients, did not show greater activation in any area during any of the contrasts.

3.2.2.4. Group differences in brain activations co-varying for performance. As shown in Table 3, earlier-described group differences in task related activations did not co-vary with relevant performance accuracy measure. The strength of group difference was only minimally affected by co-varying for performance.

4. Discussion

Focussing on the neurobiology of preserved and poor insight in psychosis, we tested the hypothesis that patients with preserved insight, compared with those with poor insight, have stronger WM capacity and greater increases in fMRI activity in the prefrontal and parietal cortices from low to high WM load. Preserved insight patients were expected to perform and show fMRI activity broadly similar to those of the healthy group.

Behaviourally, performance declined with increasing WM load in all groups, as seen previously on this task (Kumari et al., 2006, 2009). Importantly, supporting the theorised association between a WM deficit and poor insight in schizophrenia (Shad et al., 2007), only poor insight patients, relative to healthy participants, showed significantly poor performance accuracy; preserved insight patients did not differ from healthy participants in performance accuracy. Impaired performance of poor insight patients most likely resulted from their low WM efficiency (as discussed later) though it may also reflect, at least to some extent, a lack of effort on their part. Poor WM is a common finding in schizophrenia (Reichenberg and Harvey, 2007). Our findings indicate that this may be particularly true for poor insight patients. The trend-level difference in performance of the low and high insight groups, despite them being comparable on premorbid IQ and symptoms (Table 1), may suggest a stronger association between WM and insight than between premorbid IQ and insight.

At the neural level, preserved insight patients, compared with poor insight patients, showed higher brain activity during the 2-back condition (relative to both the rest and 1-back condition) in the precuneus and cerebellum (bilateral). Poor insight patients, compared with preserved insight patients, did not show greater activity in any brain area. Since the differences observed in magnitude of brain activation between the two patient groups (i.e. higher activity in preserved insight patients) were not abolished after co-varying for performance (Table 3), and the two patients groups had comparable age, years of education and IQ scores (Table 1), they are most likely to be explained by differing insight levels of the two groups. We now discuss the meaning of these various brain-insight associations in turn.

Our finding of the precuneus–insight association has support from a previous structural MRI investigation which showed a direct positive correlation between insight and the left precuneus grey matter volume in psychosis (Cooke et al., 2008) and a recent single photon emission computed tomography study showing greater perfusion of the precuneus in patients with preserved insight (Faget-Agius et al., 2012). The observations of a number of recent studies in healthy people concerning precuneus function allow us to postulate how it might play a role in preservation of insight in psychosis. Specifically, a network involving this brain area has been put forward as the mechanism through which personal identity and past personal experiences are interlinked, allowing a person to move between representation and awareness of the self (Andreasen et al., 1995). Functional imaging studies have shown a) precuneus activity when comparing self to non-self representations (Kircher et al., 2000, 2002) and when participants reflect about their own personality traits and physical appearance (Kjaer et al., 2002), and b) a linear relationship between precuneus activity and the degree to which the retrieval of previous psychological traits was self-referential (Lou et al., 2004). These observations indicate that the precuneus is either involved in assigning first-person perspective (e.g. awareness of one's own mental states) (Vogeley and Fink, 2003), or more generally in internal representation through mental imagery and episodic/autobiographical memory retrieval (Cavanna and Trimble, 2006). An inability to access representations of his/her own mental states may prevent a patient from identifying that his/her mental states are problematic.

To our knowledge, ours is the first study to find an association between cerebellum activity and preserved insight but it is in line with finding of a recent study (Bergé et al., 2011) showing a positive relationship between cerebellum grey matter volume and insight in psychosis. The group differences we observed in cerebellum activity were somewhat reduced though not abolished after co-varying for performance, meaning that they probably arose from both insight and WM-related differences, the two themselves being related. Patients with cerebellar damage are reported to show intellectual and socio-emotional dysfunction (Schmahmann, 1991) and mild-to-moderate WM impairment (Timmann and Daum, 2007) whilst neuroimaging studies suggest cerebellum involvement in WM (Hayter et al., 2007) and the cerebellum is both clinically and cognitively implicated in schizophrenia (Picard et al., 2008). According to the model of Andreasen et al. (1999), disruption in the cortico–cerebellar–thalamo–cortical circuitry results in deficient processing, prioritising, retrieval, coordination, and responding to information, i.e. 'cognitive dysmetria', in schizophrenia. Our findings suggest that this circuitry may also have a role in insight in schizophrenia.

In addition to showing higher activity than the poor insight group (discussed above), the preserved insight group also showed greater brain activity in many areas including the PFC and cerebellum in comparison to the healthy group during all active conditions, including the 2-back. These observed activation patterns may suggest that preserved insight and normal-range WM capacity in this patient group may have been achieved via compensatory neural activity (Ettinger et al., 2011). Interestingly, the poor insight group, compared with the healthy group, also showed a trend towards greater activity (an uncorrected level of significance) in some regions but only during the 1-back condition, consistent with previous suggestions (Manoach, 2003) that individuals with lower WM capacity require much greater neuronal activity to maintain performance at a lower WM load. The poor insight group displayed no further increase from 0-back, and 1-back, to 2-back (higher load) condition (Appendix 1), further indicating a lower WM capacity in these patients. Additionally, the poor insight group showed a trend towards lower cerebellum activity compared with the healthy group during the 2-back condition, consistent with the earlier discussed role of cerebellum in schizophrenia.

The findings of the present study have clinical implications. For example, it may be possible to improve insight in schizophrenia by cognitive training to improve WM (McGurk et al., 2005) and functioning of the associated brain regions (Wykes et al., 2002). Insight is already known to predict treatment outcome and long-term prognosis (Amador and David, 2004; Charkraborty and Basu, 2010) and recent data indicate that PFC and cerebellum function is also predictive of clinical outcome following cognitive behaviour therapy for psychosis (Kumari et al., 2009).

The present study has a number of strengths. Firstly, the preserved and poor insight groups examined had clearly distinct levels of insight (although preselected on total BIS score, the preserved insight group had significantly higher scores on all three BIS dimensions) and the groups were closely matched for age, education and predicted IQ. Secondly, the study utilised a well-researched and well-established WM paradigm which has been used in many previous studies of schizophrenia patients and thus allows meaningful inferences to be drawn about the observed activation patterns in the preserved and poor insight groups.

The present study, however, was not without some limitations. Firstly, although 20 patients were initially recruited in each insight group, 6 poor insight patients had to be excluded resulting in a reduced sample size for this group, and the possibility of a Type-II error. In addition to the loss of 2/20 patients/group due to movement artefacts, 4 poor insight patients were excluded because of their poor compliance with task instructions during fMRI. As these procedural errors occurred in the poor insight group, they could possibly be due to their low WM capacity affecting their ability to execute the task. Interestingly, two of these poor insight patients persisted with initial set (0-back) of instructions throughout the entire task despite having practised with instructions provided prior to the fMRI scan. This could be viewed as a form of procedural perseveration in poor insight patients, impairing their capacity to perform successfully on the n-back task. Secondly, this study included outpatients maintained on antipsychotic medication which is known to impact on WM activations in schizophrenia (Ettinger et al., 2011). However, as the patient groups were largely comparable in medication use, age at illness onset and general symptomatology, the results observed should be interpreted in terms of difference in insight levels. Thirdly, this study utilised a block, rather than an event related, fMRI design, which does not allow us to examine group differences in neural activity in only correct trials. Lastly, since WM is not a direct measure of insight, activity differences between low and high insight groups seen in this study may include influences unrelated to insight differences.

5. Conclusion

This study provides direct empirical support for the theorised link between WM dysfunction and poor insight across the three dimensions measured with the BIS in schizophrenia. Furthermore, the findings demonstrate involvement of the WM neural network, in particular of the precuneus and cerebellum, as being involved in the preservation of insight in schizophrenia patients, and suggest that preserved insight as well as normal-range WM capacity in schizophrenia sub-groups may be achieved via compensatory neural activity in the frontal cortex and cerebellum.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.schres.2013.11.026.

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