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

Adegboyega Sapara [a], Dominic H. ffytche [b,d], Max Birchwood [c], Michael A. Cooke [a], Dominic Fannon [a], Steven C.R. Williams [d], Elizabeth Kuipers [a,e], Veena Kumari [a,e,*]

[a] Department of Psychology, Institute of Psychiatry, King's College London, London, UK
[b] Department of Old Age Psychiatry, Institute of Psychiatry, King's College London, London, UK
[c] School of Psychology, University of Birmingham, Birmingham, UK
[d] Department of Neuroimaging, Institute of Psychiatry, King's College London, London, UK
[e] NIHR Biomedical Research Centre for Mental Health, South London and Maudsley NHS Foundation Trust, London, UK

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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.

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

* Corresponding author at: Department of Psychology, P078, Institute of Psychiatry, King's College London, De Crespigny Park, London SE5 8AF, UK. Tel.: +44 207 848 0233.
E-mail address: veena.kumari@kcl.ac.uk (V. Kumari).

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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.

		Healthy participants n = 20 (15M:5F)		Patients			
				Preserved insight n = 18 (14M:4F)		Poor insight n = 14; (9M = 5F)	
Demographics		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.