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Pattern of activation during delayed matching to sample task predicts functional outcome in people at ultra high risk for psychosis

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ABSTRACT

Background: Clinical outcomes in people identified as at ultra-high risk (UHR) for psychosis are remarkably heterogeneous, and are difficult to predict on the basis of the presenting clinical features. Individuals at UHR are at risk of poor functional outcome regardless of development of psychotic disorder. The aim of the present study was to assess whether there is a relationship between functional neuroimaging measures at presentation and functional outcome as measured by the GAF three years after scanning.

Methods: Functional magnetic resonance imaging (fMRI) data were collected during an object working memory task in 34 ultra-high risk (UHR) subjects and 20 healthy controls. On the basis of their GAF scores at follow up, the UHR participants were divided into subgroups with good and poor functional outcomes, respectively.

Results: At baseline, the UHR group differed from controls in showing altered frontal and cuneus/posterior cingulate activation. Significant group x task interactions were found in the left cuneus and posterior cingulate gyrus, reflecting differential responses to the task conditions.

Within the UHR sample, the subgroup with a poor functional outcome exhibited altered activation in frontal, temporal and striatal regions, and reduced deactivation within default-mode network regions, relative to those with a good outcome. Within the whole UHR sample, in these regions the local task response was correlated with the GAF score at follow up.

Conclusions: The findings suggest a potential role of functional neuroimaging in the prediction of outcomes in people at high clinical risk of psychosis.

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1. Introduction

A substantial proportion of individuals at Ultra High Risk for psychosis (UHR) will develop a psychotic disorder within 3 years (Fusar-Poli et al., 2012c). The onset of psychosis has been the predominant outcome in prospective studies of UHR subjects, including those using neuroimaging. Transition to psychosis is operationally defined in terms of the severity of positive psychotic symptoms (Fusar-Poli et al., 2008). However, the threshold level for these symptoms is somewhat arbitrary (Lin et al., 2015), and other clinical features such as the severity of negative symptoms and the subject's level of functioning are not taken into account (Lin et al., 2015). As a result, individuals who have not met

criteria for transition (in terms of positive symptoms) can still have a very poor clinical outcome, because they have prominent negative symptoms and/or a low level of functioning (for example as measured by the GAF; Lin et al., 2015). Furthermore, data from studies in schizophrenia suggest that in terms of recovery, patients often regard their overall level of functioning as more important for their quality of life than the severity of their positive symptoms (Cichocki et al., 2015).

Working memory impairment is a cardinal cognitive feature of psychotic disorders (Forbes et al., 2009) and is evident in individuals at UHR (Fusar-Poli et al., 2012a). In both patients with schizophrenia and individuals at UHR, working memory impairments have been linked to poor functional outcome (Goghari et al., 2014; Vesterager et al., 2012). Functional MRI studies of tasks that engage working memory have identified differences in regional activation between UHR subjects and controls (e.g. Broome et al., 2010). Moreover, a follow up study suggested that longitudinal improvements in level of functioning were

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related to changes in activation during a working memory task, although the sample size was small (Fusar-Poli et al., 2010).

The aim of the present study was to determine whether functional neuroimaging data collected during a working memory task could predict functional outcome in people at UHR for psychosis, irrespective of transition to the full-blown disorder. Level of functioning was measured with the DSM-IV GAF-scale, a widely used instrument for assessing overall psychological, social and occupational functioning (Aas, 2010; Jones et al., 1995). The GAF is well-established, highly generalizable and has been used in many outcome studies including those of people at UHR (Brandizzi et al., n.d.; Kambeitz-Ilankovic et al., 2015; Lin et al., 2015). We used the delayed matching to sample (DMTS) task from the Cambridge Neuropsychological Test Automated Battery (CANTAB; Robbins et al., 1994), which permits the experimental manipulation of task demand. This is potentially useful in studies of UHR subjects, as there is some evidence that differential activation in this group becomes increasingly evident as the demands on working memory are increased (Broome et al., 2010; Fryer et al., 2013).

On the basis of data from previous neuroimaging studies of working memory in this group (Broome et al., 2010) we first predicted that UHR individuals would show altered prefrontal and parietal activation relative to controls, and that these differences would vary with increasing task demand. We then tested the hypothesis that within the UHR sample, the pattern of activation at baseline would be related to the level of functional outcome at follow up, as defined using the Global Assessment of Functioning (GAF) scale.

2. Methods and materials

2.1. Participants

The study was approved by the South London and Maudsley research ethics committee. All subjects gave written informed consent after a full description of the study. The sample consisted of 34 subjects at ultra-high risk (UHR) and 20 healthy controls (CTRL), all right handed and without any personal or family history of psychiatric disorders. Substance misuse disorder, an IQ < 70, history of another CNS disorder or head injury with documented cognitive sequelae, were exclusion criteria for all groups. Demographic and clinical details are provided in Table 1.

2.1.1. Ultra-high risk group (UHR)

Individuals meeting Personal Assessment and Crisis Evaluation (PACE) criteria for the UHR state of psychosis (Yung et al., 1998) were recruited from Outreach and Support in South London (OASIS; Broome et al., 2005) clinical service. The diagnosis was based on assessment by two experienced clinicians using the Comprehensive Assessment for the At-Risk-Mental State (CAARMS; Yung et al., 2005; Table

1) and a consensus meeting with the clinical team (see Supplementary Material).

2.1.2. Control group (CTRL)

Healthy participants were recruited via advertisements in local media. All individuals lived in the same London borough as the clinical participants. The groups differed in terms of age and IQ estimates (Table 1), so these were included as covariates in all subsequent analyses.

2.2. Clinical and neuropsychological/IQ assessment

Prior to scanning, all subjects were interviewed using the SCID-1 and SCID-2 interviews. Of 34 UHR subjects 9 (26%) had depression and/or anxiety. Family history was assessed using the Family Interview for Genetic Studies (FIGS). The Positive and Negative Syndrome Scale (PANSS) rated symptom severity (Table 1). Handedness was assessed with the Edinburgh Handedness Inventory and pre-morbid Wechsler Adult Intelligence Scale-Revised IQ (WAIS-R) using the National Adult Reading Test (NART) and standard tables.

2.3. Outcome measures

Based on the median GAF score of 70 at follow-up (cf. Kambeitz-Ilankovic et al., 2015), UHR participants were subdivided into good (UHRg; N = 10, GAF > 70) and poor functional outcome groups (UHRp; N = 9, GAF ≤ 70).

2.4. Task

Functional MRI data were acquired while subjects performed a modified version of the CANTAB delayed matching to sample (DMTS) task (Picchioni et al., 2007). The DMTS paradigm requires encoding and maintaining a complex visual pattern that, after a variable delay period, must be discriminated from a set with three additional distracters. Trials during which the recognition phase immediately follows the stimulus presentation are compared to trials testing recognition after a longer delay. Simultaneous and delayed task conditions are randomized, with all conditions being identical until after stimulus presentation. This design ensures comparable encoding for all task conditions, and restricts the difference between task conditions to the ability to hold information online. It is thus assumed that increased errors in the delayed compared to the immediate matching condition reflect processes that are not attentional or perceptual but more closely relate to WM maintenance. Stimuli, each subtending an angle of 5°, were presented using Visual Basic (Microsoft, Redmond) on a black screen, viewed through a mirror. Subjects initially focused on a central fixation cross. Each trial consisted of four phases (See Supplementary Material). During initial 'encoding', subjects were presented with a complex abstract pattern (the sample)

Table 1
Demographic and clinical participant characteristics at baseline. Figures represent mean and standard deviation unless stated.

	Group	Group comparison test
	Ultra high risk (N = 34)	Control (N = 20)
Age (Mdn. years)	22	25.5
Male/Female n	24/10	12/8
NART IQ	99.4 (12.27)	111.22 (11.37)
Ethnicity (% Caucasian)	64.7	75
PANSS pos	12.12 (3.98)	8.57 (3.31)
PANSS neg	9.79 (3.69)	7.14 (0.38)
PANSS gen (Mdn.)	23	16
PANSS tot (Mdn.)	43	30
GAF (SD; range)	57.5 (12.1; 35–75)	
Medication at baseline (no. of cases)		
No medication	24	
Antipsychotic	3	
Antidepressant	7	

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