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Semantic fluency deficits and reduced grey matter before transition to psychosis: A voxelwise correlational analysis

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ABSTRACT

Early identification of subjects with an increased risk of psychosis is necessary to develop interventions to delay or prevent disease onset. We recently reported that decreased semantic verbal fluency performance in ultra high risk (UHR) subjects predicts the development of psychosis (Becker et al., 2010). The present study investigated whether semantic and verbal fluency scores correlate with grey matter density in UHR subjects. Thirty-seven UHR subjects underwent structural MRI scanning and verbal fluency assessment after which they were followed up for 2 years. Using voxel-based morphometry, we investigated whether grey matter density correlated with verbal fluency scores in 10 UHR subjects who developed psychosis during follow-up and 27 UHR subjects who did not develop psychosis. In UHR subjects developing psychosis, lower semantic fluency scores correlated significantly with reduced grey matter density in the right superior and middle temporal gyrus, the right insula, and the left anterior cingulate cortex. This study shows that a correlation between semantic fluency performance and grey matter density in task-related areas can differentiate between UHR subjects who subsequently will develop psychosis and those who will not. Combining these two measures could improve psychosis prediction in UHR subjects.

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1. Introduction

Prospective identification and treatment of subjects in the putative prodromal phase of schizophrenia could ameliorate or delay psychosis onset, improve disease outcome or even prevent psychotic disorder (Falloon et al., 1996; Yung et al., 1996). Since 'prodromal phase' is a retrospective concept, sets of criteria have been developed to prospectively identify subjects at clinically increased risk of psychosis, also referred to as "ultra high risk" (UHR) subjects. A review of prospective investigations in UHR samples found that between 9% and 54% of UHR subjects develop psychosis within 1 year (Olsen and Rosenbaum, 2006). However, the high rate of false-positives lowers the benefit/risk ratio of possible prodromal interventions (de Koning et al., 2009) and increases the need for additional criteria to predict future transition to psychosis more accurately.

In schizophrenia cognitive impairments are a core feature of the disease. Because selected cognitive domains are already impaired before the development of psychosis (Fusar-Poli et al., 2007; Simon et al., 2007), cognitive deficits may index genetic liability for schizophrenia and could be candidate endophenotypes for the illness (Snitz et al., 2006). Verbal fluency is one of the most impaired cognitive domains in schizophrenia with a recent meta-analysis reporting large effect sizes (Mesholam-Gately et al., 2009). Typically, subjects are asked to generate as many words as possible from a category in a given time. This category can be semantic (e.g. words designating 'animals' or 'objects') or phonological (e.g. words beginning with the phoneme 'F' or 'S'). These measures are intended to make comparable demands on executive functioning, because both imply efficient organisation of verbal retrieval and recall, self-monitoring, effortful self-initiation and inhibition of inappropriate responses (Ruff et al., 1997). Conversely, while phonological verbal fluency (PVF) implies search strategies based mainly on lexical representations, semantic verbal fluency (SVF) depends intrinsically upon the integrity of semantic associations within the lexicon (Ojeda et al., 2010).

Two meta-analyses, including studies in which patients with schizophrenia and healthy controls completed both PVF and SVF tasks, concluded that patients with schizophrenia showed a larger deficit for SVF relative to PVF (Bokat and Goldberg, 2003; Henry and Crawford, 2004). The disproportionate SVF deficit in schizophrenia patients points towards a problem in semantic storage or retrieval, on top of general executive search and retrieval problems. The same pattern of disproportionate impairment in SVF over PVF is seen in UHR subjects (Magaud et al., 2010). Moreover, Szoke et al. (2008) suggested that SVF may be the best candidate cognitive endophenotype for schizophrenia because it is impaired in schizophrenia patients independent of disease or treatment

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state and in unaffected first-degree relatives of schizophrenia patients (Snitz et al., 2006).

We recently reported that SVF deficits in UHR subjects can predict development of psychosis (Becker et al., 2010). Becker et al. assessed SVF and PVF in 47 UHR subjects who were followed up for 2 years to assess transition to psychosis. Results showed that SVF scores were significantly lower in those UHR subjects who developed psychosis during follow-up (UHR—P) compared with UHR subjects who did not develop psychosis (UHR-NP) and healthy controls. The aetiology of these deficits in UHR subjects is, however, unclear.

In schizophrenia patients neuroimaging studies have linked SVF and PVF deficits to abnormalities in the frontal and temporal areas (Spence et al., 2000; Boksman et al., 2005; Kircher et al., 2008; Ragland et al., 2008). UHR subjects also show grey matter reductions in areas similar to those affected in schizophrenia (Pantelis et al., 2003; Borgwardt et al., 2007). Although other cognitive functions such as verbal learning have been successfully linked to grey matter reductions in subjects with a clinical high risk for psychosis (Hurlemann et al., 2008), for verbal fluency this association has not yet been investigated.

The aim of this study was to answer the following questions: 1) Is lower SVF and PVF performance correlated with reduced grey matter density (GMD) in UHR subjects? and 2) Is this correlation significantly different between UHR—P and UHR—NP subjects? Based on previous findings, we hypothesised that SVF and PVF scores would be correlated with GMD in frontotemporal areas in all UHR subjects. Secondly, we hypothesised that this correlation would be more prominent in UHR subjects that developed psychosis subsequent to scanning.

2. Material and methods

2.1. Study design

Between August 2002 and July 2009, UHR subjects were consecutively recruited at the Adolescent Clinic of the Academic Medical Center (AMC) in Amsterdam, the Netherlands. Recruitment took place within a naturalistic, longitudinal study programme (European Prediction of Psychosis Study (EPOS); Klosterkötter et al., 2005). Subjects were help-seeking individuals that had been referred by mental health services under suspicion of an increased risk for developing psychosis. Subjects were interviewed by a psychiatrist and a psychologist, while parents or caretakers were interviewed by a psychologist or a psychiatric nurse. The Semi-structured Interview for Prodromal Syndromes (SIPS; Miller et al., 2002) and the Bonn Scale for the Assessment of Basic Symptoms — Prediction List (BSABS—P; Klosterkötter et al., 2005) were used to assess whether or not subjects fulfilled the UHR criteria that were required for study participation.

This study was carried out in accordance with the latest version of the Declaration of Helsinki. The study design was approved by the Medical Ethical Committee of the AMC. Written informed consent of the participants was obtained after the nature of the procedures had been fully explained.

2.2. Subjects

Thirty-seven UHR subjects were recruited, of whom 10 developed a psychotic illness during a 2-year follow-up (UHR-P) against 27 who did not (UHR—NP). Subjects were considered to be at UHR if they met the criteria for one or more of the following groups: 1) Attenuated symptoms: psychotic-like symptoms that have not proceeded to frank psychosis, 2) Brief Limited Psychotic Symptoms (BLIPS): a frank psychotic period that subsided spontaneously in less than 1 week, 3) A decline in functioning over the past year (30% reduction in the Global Assessment of Functioning scale) plus a genetic risk (first-degree family member with a psychotic disorder or a schizotypal personality disorder in the identified patient) and/or 4) At least two "basic symptoms" which are cognitive, perceptual, emotional and social disturbances (Klosterkötter et al., 2005). Exclusion criteria were as follows: age <12 or >35 years, estimated premorbid verbal IQ<85 as assessed with the Dutch Adult Reading Test (Schmand et al., 1991), neurological or endocrine disease that may affect brain structure, use of illicit drugs other than cannabis during 3 months prior to the assessment as assessed with the Comprehensive International Diagnostic Interview sections J and L (CIDI; Andrews and Peters, 1998) and a previous psychotic episode for more than 1 week as assessed with the Structured Clinical Interview for Diagnosis Axis I (SCID-I; Spitzer et al., 1992).

2.3. Timeline

After inclusion into the study, subjects were assessed with two verbal fluency tests and structural magnetic resonance imaging (MRI) of the brain. Subsequently, subjects were followed up for 2 years to monitor their clinical development by assessment of the SIPS. After 9, 18 and 24 months, the SIPS was repeated to assess potential transition to psychosis during a face-to-face contact. If during follow-up it appeared that a subject had experienced a transition to psychosis, the SCID-I was used to establish a formal diagnosis.

2.4. Assessment of verbal fluency

To measure verbal fluency, subjects were asked to name as many words as possible within 1 min belonging to the semantic category "animals", or words beginning with the phoneme "F". The outcome variable for this task was the number of acceptable words produced in each condition.

2.5. Statistical analyses

Group differences in demographical and neuropsychological data were examined using SPSS 16.02 for Windows. Group differences in age, premorbid IQ estimates and verbal fluency scores were analysed using Mann Whitney *U* tests due to the small sample size of the UHR—P group. Group differences in gender, handedness, psychiatric medication use and lifetime/past month cannabis use were analysed with chi-square tests. Level of statistical significance was defined as $p<0.05$ (two-tailed).

2.6. Image acquisition and analyses

Whole brain images of the UHR subjects were acquired at baseline, on a Philips Intera 3 Tesla whole-body MRI scanner (Philips Intera, Philips Medical Systems, Best, the Netherlands). We used optimised voxel-based morphometry (VBM) (Good et al., 2001) implemented in SPM2 (Institute of Neurology, Queen's Square, London, UK, www.ion.fil.ac.uk) to identify regional GMD in all UHR subjects. Optimised VBM techniques, including customised template creation, spatial normalisation, tissue segmentation and smoothing were employed (Ashburner and Friston, 2000). A participant-based template was created, using all original 3D T1-weighted images of the complete sample. Next to the customised template, prior images of grey matter (GM), white matter (WM), and cerebrospinal fluid (CSF) were generated, based on the existing [Montreal Neurological Institute (MNI)] T1-weighted template in SPM2, and smoothed with a Gaussian kernel of 8-mm full width at half-maximum (FWHM).

Thereafter, automated optimizations (Department of Psychiatry, University of Jena, Germany) in SPM2 were used to spatially normalise and segment all T1-weighted images, based on the customised T1-weighted template. The prior images of GM, WM, and CSF were used for segmentation and stripping. All standard presets in SPM2 were maintained. For statistical comparison, GM segments were smoothed with a 10-mm FWHM isotropic Gaussian kernel, which rendered the data normally distributed to achieve optimal outcome in parametric statistical comparisons. In SPM2 the PVF and SVF scores were correlated with GMD. This analysis was performed in UHR—P and UHR—NP subjects separately.

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