Understanding cognitive heterogeneity in psychosis and high risk individuals

Meijer, J. H.

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SEMANTIC FLUENCY DEFICITS AND REDUCED GREY MATTER BEFORE TRANSITION TO PSYCHOSIS: A VOXELWISE CORRELATIONAL ANALYSIS

Julia H. Meijer, Nicole Schmitz, Dorien H. Nieman, Hiske E. Becker, Therese A.M.J. van Amelsvoort, Peter M. Dingemans, Don H. Linszen, Lieuwe de Haan

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ABSTRACT

**Background:** 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 phonological verbal fluency scores correlate with grey matter density in UHR subjects.

**Methods:** 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.

**Results:** 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.

**Conclusion:** This study shows that a correlation between semantic fluency performance and grey matter density in task-related areas may 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.
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 impairment is 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 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); Klosterkotter 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; Klosterkotter 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 (Klosterkotter
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 minute 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 16.0 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 were employed, including customised template creation, spatial normalisation, tissue segmentation and smoothing (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 optimisations (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. Results were localized using the Talairach and Tournoux atlas (Talairach and Tournoux, 1988).

3. RESULTS

In the 10 subjects that developed psychosis during follow-up, the median transition time to psychosis was 14 months. After transition to psychosis, the subjects received the following diagnoses: schizophrenia (n = 8), schizophreniform disorder (n = 1) and schizoaffective disorder (n = 1). As shown in Table 1, groups did not statistically differ with respect to age, premorbid IQ, gender, handedness, psychiatric medication or cannabis use. In the SVF test, UHR-P subjects generated 2.32 animal names less than UHR-NP subjects, a difference that was not significant (p = 0.38). In the PVF test UHR-P subjects generated 0.38 words more than UHR-NP subjects, a difference that was not significant (p = 0.76).

<table>
<thead>
<tr>
<th>Table 1. Demographic anc clinical characteristics of UHR-P subjects compared to UHR-NP subjects.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<tr>
<td>Age (Mean ± S.D.)</td>
</tr>
<tr>
<td>IQ (Mean ± S.D.)</td>
</tr>
<tr>
<td>Male/Female</td>
</tr>
<tr>
<td>Handedness (right/left/both/unknown)</td>
</tr>
<tr>
<td>N of subjects using antipsychotics in the past 3 months</td>
</tr>
<tr>
<td>Antipsychotic dose (chlorpromazine equivalents*, mean ± S.D.)</td>
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<tr>
<td>N of subjects using antidepressants in the past 3 months</td>
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<tr>
<td>N of subjects using benzodiazepines in the past 3 months</td>
</tr>
<tr>
<td>N of subjects using cannabis lifetime/in the past month</td>
</tr>
<tr>
<td>SVF score (Mean ± S.D.)</td>
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<tr>
<td>PVF score (Mean ± S.D.)</td>
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</tbody>
</table>

UHR-P; Ultra High Risk subjects who developed psychosis, UHR-NP; Ultra High Risk subjects who did not develop psychosis. * Chlorpromazine equivalents for the subjects that have been using antipsychotics were calculated according to Woods (2003).
As shown in Figure 1 and Table 2, in the UHR-P group lower SVF scores correlated significantly with reduced GMD in an area encompassing the right superior temporal gyrus (STG) and middle temporal gyrus (MTG) (Brodmann area (BA) 21) (p<0.001), the right posterior insula (BA 13) (p<0.001), and the left anterior cingulate cortex (ACC) (BA 32) (p< 0.036). In the UHR-NP subjects SVF scores did not correlate significantly with GMD. Also, PVF scores did not correlate significantly with areas of GMD in UHR-P or UHR-NP subjects. Table 2 also reports the results for three brain regions in the right ACC, the left cingulate gyrus and the right middle frontal gyrus that did not survive correction for multiple analyses.

Figure 1. Grey matter density of the left anterior cingulate cortex and right posterior insula correlating with semantic verbal fluency scores in UHR subjects that subsequently developed psychosis (n = 10).

Table 2. SPM Correlations between semantic verbal fluency scores and grey matter density in UHR subjects that subsequently developed psychosis.

<table>
<thead>
<tr>
<th>p value</th>
<th>Cl Cluster size</th>
<th>Brain region</th>
<th>BA</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>T value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.036</td>
<td>1433</td>
<td>Left anterior cingulate</td>
<td>32</td>
<td>-10</td>
<td>44</td>
<td>5</td>
<td>3.86</td>
</tr>
<tr>
<td>0.001</td>
<td>2908</td>
<td>Right middle temporal gyrus</td>
<td>21</td>
<td>43</td>
<td>-7</td>
<td>-10</td>
<td>4.07</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Right insula</td>
<td>13</td>
<td>40</td>
<td>-21</td>
<td>13</td>
<td>4.01</td>
</tr>
<tr>
<td>0.001</td>
<td>1261</td>
<td>Right anterior cingulate</td>
<td>32</td>
<td>9</td>
<td>42</td>
<td>7</td>
<td>5.15</td>
</tr>
<tr>
<td>0.001</td>
<td>1097</td>
<td>Left cingulate gyrus</td>
<td>31</td>
<td>-14</td>
<td>-24</td>
<td>40</td>
<td>4.25</td>
</tr>
<tr>
<td>0.001</td>
<td>1053</td>
<td>Right middle frontal gyrus</td>
<td>6</td>
<td>39</td>
<td>4</td>
<td>39</td>
<td>5.90</td>
</tr>
</tbody>
</table>

4. DISCUSSION

To our knowledge, this is the first study to examine UHR-P and UHR-NP subjects for GMD correlates with verbal fluency scores using optimised VBM. Our first prediction that verbal fluency scores would correlate with GMD in frontotemporal areas was true for semantic but not for phonological fluency. Moreover, in line with our second hypothesis, this correlation was only present in UHR subjects that developed psychosis subsequent to scanning. In UHR-P subjects, SVF performance was correlated with GMD reductions in the right STG and MTG (BA 21), right posterior insula (BA 13) and the left ACC (BA 32), areas that have been related to verbal fluency performance in previous functional and structural imaging studies in schizophrenia and healthy controls as discussed here. Findings indicate that the correlation between SVF, but not PVF, and GMD in frontotemporal and insular areas may be an additional risk marker for psychosis.

The MTG was one of the regions associated with semantic processing in a large-scale review of 120 functional neuroimaging studies of semantic memory (Binder et al., 2009). The STG has a role in the semantic representation of words (Frith et al., 1995). Access to, and decisions about, lexical-semantic information engage the STG and MTG in both hemispheres in healthy controls (Pugh et al., 1996). In schizophrenia patients performing a SVF task, activations in the STG and MTG have been reported to be stronger than in healthy controls, which may be reflecting an inefficient hemodynamic response (Ragland et al., 2008). Our finding that SVF correlated with GMD reductions in the right temporal region is surprising since linguistic functions of speech are normally primarily controlled by the left hemisphere (Gauthier et al., 2009). In schizophrenia however, a decreased or reversed language lateralization in the temporal lobes has been described (Weiss et al., 2006; Bleich-Cohen et al., 2009). Furthermore, a decreased lateralization is also present in non-psychotic monozygotic co-twins of schizophrenia patients (Sommer et al., 2004), which implies that decreased language lateralization may reflect a genetic risk factor for psychosis rather than a state-related trait.

The ACC is the structure typically known to be activated in word production tasks with increased demands like SVF compared to control tasks such as free verbal association (Whitney et al., 2009) or overlearned sequences (Gourovitch et al., 2000). Additionally, BA 32 of the ACC was activated in healthy controls during SVF performance compared to reading as a control task, while activation in schizophrenia patients was absent (Kircher et al., 2008). Kircher et al. suggested that the decreased performance on SVF in patients could have resulted from deficient control processes mediated by the ACC. On the contrary, an over-activation of the right ACC during SVF in schizophrenia patients compared to healthy controls has also been reported (Ragland et al., 2008), leading the researchers to suggest that an inefficient hemodynamic response in this area is associated with SVF deficits. In functional MRI (fMRI) studies assessing PVF, which is comparable to SVF in terms of the frontally controlled executive demands of the task (Whitney et al., 2009), first episode schizophrenia patients showed reduced activation of the right (Schaufelberger et al., 2005) and left (Boksman et al., 2005) ACC compared to control subjects. Similarly, in a study using positron emission tomography (PET), clinically stable schizophrenia patients were found to exhibit a functional disconnectivity between the ACC
and other prefrontal regions during PVF performance compared to healthy controls and first degree relatives (Spence et al., 2000).

Although involvement of the insular cortex is a common finding in neuroanatomical studies of schizophrenia, the correlation with SVF performance was less expected. While the anterior insula in humans is best known for the awareness of oneself, others and the environment, and thus a potential neural correlate of consciousness (Craig, 2009), the posterior insula is known to be involved in the subjective experience of body-ownership (Tsakiris, 2010). In schizophrenia patients, abnormalities in both activity and anatomy of the insula have been associated with experiencing hallucinations (Shergill et al., 2000). Failure of the insula in schizophrenia may lead to internally generated sensory information being attributed to an external source, contributing to hallucinations (Wylie and Tregellas, 2010). However, more in line with our findings, involvement of the insula in linguistic tasks such as phonological processing and the coordination of speech articulation has also been described (Ackermann and Riecker, 2010; Price, 2010). In schizophrenia, GM reduction and dysfunction of the insular cortex has been implicated in cognitive impairments (Curtis et al., 1998; Crespo-Facorro et al., 2000). Finally, in support of our findings, schizophrenia patients have been found to display stronger activation in the bilateral insula during SVF tasks compared with healthy controls (Ragland et al., 2008).

Our results suggest that worse SVF performance in UHR-P subjects is at least partly reflected in GMD reductions that are present well before the development of frank psychosis. Previous VBM studies have demonstrated that GM reductions in the right STG and right insular cortex predate the onset of frank symptoms and are more pronounced in UHR-P compared to UHR-NP subjects, making them potential markers of future transition to psychosis (Pantelis et al., 2003; Borgwardt et al., 2007). Moreover, Koutsouleris et al. (2009) found that subjects in a late UHR state showed more pronounced volume losses in the ACC, insula and MTG compared to subjects in an early UHR state, showing that GM loss in the same areas that we found is progressive towards transition to psychosis.

To our knowledge, SVF in UHR subjects has not been studied with structural or functional neuroimaging, but PVF has been assessed in an fMRI study (Broome et al., 2009). During PVF performance, UHR subjects showed activation in the ACC that was statistically intermediate compared with controls and psychotic patients. Also, in the left insula, UHR subjects showed intermediate patterns of activation during PVF that was highest in the psychosis group and weakest in the control group. The relatively greater engagement of the insula was hypothesised to reflect a compensatory response to compromised processing and attenuated activation of the inferior frontal gyrus. The absence of temporal involvement in the study by Broome et al. (2009) is in line with the view of PVF as a predominantly frontally based task (Henry and Crawford, 2004).

Our findings are further corroborated by recent evidence integrating genetic and neuroimaging techniques. Studies in healthy controls investigating the link between brain activation during SVF and three susceptibility genes for schizophrenia (neuregulin 1, dysbindin 1, D-amino acid oxidase activator G 72) found alterations of brain activation in the right MTG and ACC that correlated with the number of risk alleles (Kircher et al., 2009; Markov et al., 2009; Krug et al., 2010). In addition, schizophrenia susceptibility genes have been successfully
linked to SVF, but not to PVF. Kebir et al. (2009) found that SVF, as opposed to PVF, was associated with a polymorphism on the brain derived neurotrophic factor (BDNF) gene in schizophrenia patients. Patients homozygous for the VAL allele produced significantly more words on SVF with a medium effect size. Similar results were found in the study by Kircher et al. (2009), demonstrating a linear effect of Neuregulin 1 status on SVF but not PVF, with an inverse correlation between test performance and the number of risk alleles.

The following limitations should be acknowledged. Because we used a conservative analysis that was corrected for multiple comparisons in a limited study population, we might have missed structure-function correlations with smaller effect sizes. In addition, although the UHR-NP group was the most appropriate to control for potential influence of trait or state factors shared by the two cohorts (Sun et al., 2009), a healthy control group would have enabled us to draw conclusions regarding the specificity of the correlations found here. Furthermore, the assessment of just one semantic and phonological category may have limited the strength of the results due to potential bias of subjects for the specific category and adding one semantic (“objects”) and one phonemic category (“s”) would have increased generalisability. Finally, the correlation that we found does not allow us to make causal inferences, and future studies are needed to investigate the time sequence of GMD reductions and SVF deficits in UHR subjects.

In summary, this study demonstrates that frontotemporal and insular GMD reductions correlate with SVF performance in UHR individuals that subsequently develop psychosis. These regions have previously been related to SVF performance and to the neuroanatomy of schizophrenia. The correlation with GMD reductions was found in the absence of SVF performance differences between UHR-P and UHR-NP subjects, suggesting that combining structural and behavioural measures could be a more sensitive marker to identify future transition to psychosis than each of these measures separately.

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