Understanding cognitive heterogeneity in psychosis and high risk individuals
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Citation for published version (APA):
Meijer, J. H. (2012). Understanding cognitive heterogeneity in psychosis and high risk individuals
ASSOCIATION BETWEEN OLFATORY IDENTIFICATION DEFICITS AND PARKINSONISM IN PATIENTS WITH NON-AFFECTIVE PSYCHOSIS

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In progress
ABSTRACT

Background: Olfactory identification deficits (OIDs) are present in schizophrenia patients and individuals at increased risk for psychosis but its pathophysiology remains unclear. While dopaminergic imbalance is known to lie at the core of schizophrenia symptomatology, its role in the development of OIDs has not been elucidated yet. This study investigated the association between OIDs and symptoms of parkinsonism as a derivative of dopaminergic functioning.

Methods: In 320 patients diagnosed with non-affective psychosis, olfactory identification performance was assessed by means of the Sniffin’ Sticks task. Level of parkinsonian symptoms was assessed by means of the Unified Parkinson’s Disease Rating Scale (UPDRS-III). By means of linear regression, the association between UPDRS and Sniffin’ Sticks score was investigated while correcting for possible confounders.

Results: Higher UPDRS scores significantly predicted worse olfactory identification in patients with non-affective psychosis (beta -0.19; p<0.001). The other covariates significantly associated with olfactory identification were negative symptoms (beta -0.22; p<0.001) and estimated IQ (beta 0.14; p<0.012). Together, they accounted for 15% of the variance in olfactory identification.

Conclusion: Results provide preliminary evidence that the same dopaminergic vulnerability may underlie the development of motor symptoms and OIDs in patients with non-affective psychosis. Further investigation should evaluate the clinical value of OIDs as a marker of dopaminergic imbalance that may predict psychosis.
1. INTRODUCTION

Olfactory identification deficits (OIDs) are consistent features in patients with non-affective psychosis that already exhibit in first episode psychotic patients (Nguyen et al., 2010). The pathophysiological mechanism underlying OIDs in schizophrenia however remains unclear. What has been elucidated so far is that the variance in OIDs in schizophrenia patients may not be explained by a range of state-related factors such as level of positive symptomatology, neurocognitive functioning, the use of nicotine and cannabis, or illness duration (Nguyen et al., 2010; Moberg et al., 1999). The prevailing explanation for olfactory problems in patients with schizophrenia is that brain abnormalities in schizophrenia and olfactory processing involve overlapping neuroanatomic structures, including temporolimbic and prefrontal regions (Nguyen et al., 2010; Cohen et al., 2012; Turetsky et al., 2009).

Despite the variety of behavioural and biological research in the field of OIDs in patients with schizophrenia, the putative role of dopamine in its pathophysiology has received very little attention. This is surprising since a relationship between OIDs and dopamine seems plausible for various reasons. Disruptions in corticostriatal circuitry and dopamine neurotransmission are often regarded as central to the positive, negative, and cognitive symptoms observed in schizophrenia (Hows and Kapur, 2009; Hovingston and Lepage, 2012) and may also contribute to OIDs. Additionally, both human and animal studies have provided evidence that dopaminergic neurotransmission may play a central role in the synaptic organization, neural circuitry and biochemistry of the olfactory system (McLean and Shipley, 1988; Feron et al., 1999; Kamath et al., 2012). Finally, studies in non-psychotic populations, including patients with Parkinson’s disease, attention deficit hyperactivity disorder (ADHD), and drug-induced parkinsonism have indicated an association between olfactory performance and dopaminergic status (Kruger et al., 2008; Deeb et al., 2010; Schecklmann et al., 2011). Olfactory performance may therefore provide a unique model to investigate the effects of altered dopamine-mediated processes in patients with psychotic disorders.

Elucidating the putative dopaminergic contribution to OIDs in psychosis would not only shed light on pathophysiological mechanisms, but would also offer possible directions for early detection in at-risk subjects. For example, olfactory testing might be used to improve psychosis prediction similar to the prediction of Parkinson’s disease. Recent data indicate that more than 95% of patients with Parkinson’s disease present with significant olfactory loss that may precede clinical motor symptoms by years (Haehner et al., 2011). Likewise, several studies have demonstrated how a simple olfactory test was able to differentiate between asymptomatic subjects who would and would not develop Parkinson’s disease during follow-up (Landis et al., 2012).

Previous studies on the association between olfaction and dopaminergic functioning in different patient populations have used either Single Photon Emission Computed Tomography (SPECT) or motor abnormalities as a derivative of dopaminergic functioning (Ponsen et al., 2010; Berendse and Ponsen, 2009; Bovi et al., 2010). The aim of the current study was to assess the association between OIDs and parkinsonian symptoms in a cross-sectional sample of patients with non-affective psychosis. These motor abnormalities may have arisen either spontaneously (Pappa and Dazzan, 2009) or in response to antipsychotic treatment (Kruger et al., 2008; Bovi
et al., 2010) and are considered as a clinically relevant marker of dopaminergic imbalance. We hypothesized that the presence of OIDs would be associated with higher levels of parkinsonian symptoms.

2. METHODS

Study design and population
Data pertain to a subsample of the Genetic Risk and Outcome of Psychosis (GROUP) project, a longitudinal multicenter study in the Netherlands and Belgium (Korver et al., 2012). GROUP included patients with psychosis, their unaffected first-degree relatives, and control subjects. The present study investigated the association between OIDs and motor symptoms in the patient group exclusively.

Inclusion criteria were (1) age range of 16 to 50 years and (2) good command of the Dutch language. Patients had to meet DSM-IV-TR criteria for a non-affective psychotic disorder (APA, 2000) which was assessed with the Comprehensive Assessment of Symptoms and History interview (CASH; Andreasen et al., 1992) or the Schedules for Clinical Assessment in Neuropsychiatry version 2.1 (SCAN; Wing et al., 1990). The study protocol was approved centrally by the Ethical Review Board of the University Medical Centre Utrecht and subsequently by local review boards of each participating institute. All subjects gave written informed consent in accordance with the committee’s guidelines.

Olfactory Identification
Olfactory identification was assessed with a commercially available and comprehensively evaluated test battery called the Sniffin’ Sticks Test that is based on pen-like odour dispensing devices (Hummel et al., 2001). Participants had to identify 16 common odours by means of forced multiple choice from a list of four descriptors. Odour sticks were presented birhinally in a fixed order by a trained researcher. The interval between odour presentations was 30 seconds. Although tests of odour threshold and discrimination are also available, due to time constraints only odour identification was assessed as the olfactory domain most commonly affected in schizophrenia patients (Cohen et al., 2012). The Sniffin’ Sticks have been employed previously to assess olfactory identification in patients with psychosis and their unaffected twins (Ugur et al., 2005).

Parkinsonism and clinical variables
Parkinsonian symptoms such as bradykinesia, rigidity and tremor were assessed using the Unified Parkinson’s Disease Rating Scale (UPDRS-III; Ramaker et al., 2002). Severity of psychotic symptoms in patients was rated with the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987). Level of symptoms and disabilities was assessed with the Global Assessment of Functioning scale (GAF; APA, 2000). Substance use was assessed with a short version of the Composite International Diagnostic Interview (CIDI; World Health Organization 1990) sections B (tobacco use) and L (substance use). Current antipsychotic use was transferred into haloperidol dose equivalents (Kane et al., 2003). General IQ was estimated by means of the four-subtest short version of the Wechsler Adult Intelligence Scale (WAIS-III; Blyler et al., 2000).
Statistical analyses

Linear regression analysis was performed to determine whether level of parkinsonism (UPDRS score) predicted olfactory identification (Sniffin’ Sticks score) over and above other variables known to be associated with olfactory identification. In the first step, by means of Pearson’s correlations a range of potential confounders were tested separately for their association with Sniffin’ Sticks score. Age and gender were tested since older age and male gender are known to be associated with more OIDs (Hawkins and Pearlson, 2011; Malaspina et al., 2012). Estimated IQ score and highest level of education were tested since intellectual ability may have a positive influence on olfactory identification performance (Corcoran et al., 2005). PANSS positive, PANSS negative, PANSS general, GAF symptoms, GAF disabilities and illness duration in years were tested to exclude confounding by illness severity (Corcoran et al., 2005; Malaspina et al., 2012). The variable haloperidol dose equivalents was tested due to its association with parkinsonism (Seeman, 2010) and possibly OIDs. Past-year tobacco and cannabis use were tested since these may deteriorate peripheral odour sensitivity (Ishimaru and Fujii, 2007). In the second step, a multiple linear regression model was built using the stepwise procedure in SPSS 17.0 with UPDRS and significant covariates as predicting variables and Sniffin’ Sticks score as dependent variable. The significance level of α was set at <0.05.

3. RESULTS

Sample

The mean PANSS positive score was 11.2 (± 4.5), mean PANSS negative score was 12.4 (± 5.1), and mean PANSS general score was 24.5 (± 6.9). Mean age at psychosis onset was 22.2 years (± 6.2). Mean illness duration was 7.2 years (± 4.5). Daily nicotine use over the past year was present in 60.1% of patients and 25.0% had been using cannabis over the past year. Mean UPDRS score was 6.1 (± 7.4). The percentage of patients using antipsychotic medication at the time of testing was 79.7%, with a mean antipsychotic dosage in haloperidol dose equivalents of 4.1 (± 2.6).

Regression analysis

Pearson’s correlational analyses yielded significant associations between olfactory identification and PANSS negative (beta -0.32; p<0.001), UPDRS total (beta -0.30; p<0.001), WAIS IQ (beta 0.23; p<0.001), and haloperidol dose equivalents (beta -0.14; p<0.007). Hence, these variables were entered as predictor variables in the regression model by means of the stepwise procedure. Correlations with age, gender, highest educational level, PANSS positive and general score, GAF scores, illness duration, and past year tobacco and cannabis use were not significantly correlated with Sniffin’ Sticks score and therefore not entered into the model.

As presented in table 1, three variables in the final model significantly predicted olfactory identification performance: PANSS negative (R² change 0.10; p<0.001), UPDRS score (R² change 0.04; p<0.001) and WAIS estimated IQ (R² change 0.02; p<0.012). The variable haloperidol dose equivalents did not significantly predict olfactory identification over and above these three predictors and was excluded from the regression model.
4. DISCUSSION

The current study was the first to examine the association between OIDs and motor symptoms in a large sample of patients with non-affective psychosis. Two main findings arise from our cross-sectional study. First, we found that higher levels of parkinsonism were associated with lower olfactory identification scores. Second, higher level of negative—but not positive—symptomatology was also inversely associated with olfactory identification performance.

Our results are in line with a previous study that found a positive association between drug-induced parkinsonism and level of OIDs in patients diagnosed with depressive disorder (Kruger et al., 2008). In that study, patients were divided into three groups: one who had developed extrapyramidal symptoms (EPS) under antipsychotic treatment, one using antipsychotics without development of EPS, and one without use of antipsychotics. Patients in the EPS group exhibited significantly worse olfactory identification performance than those in the two other groups. The authors concluded that OIDs may be induced by antipsychotic treatment, but only in patients with a sensitivity toward developing EPS. In our study the association between parkinsonism and OIDs remained while correcting for antipsychotic dosage. It therefore appears that the sensitivity to develop parkinsonism and OIDs in patients with psychosis may be associated with an individual vulnerability of the dopaminergic system. This hypothesis is corroborated by a review and meta-analysis that did not find a relationship between OIDs and the use of antipsychotics per se (Rupp, 2010; Moberg et al., 1999).

In line with the literature, OIDs in our study were linked with more negative symptoms (Compton et al., 2006; Moberg et al., 1999; Rupp, 2010; Moberg et al., 2006). In a recent meta-analysis on the neuropsychology of deficit schizophrenia, which is characterized by idiopathic and enduring negative symptoms, olfactory functioning was mentioned as the task most affected in comparison to non-deficit patients with an effect size of 1.1 (Cohen et al., 2007). Moreover, both motor and negative symptoms have been linked to dopaminergic hypoactivity in specific brain regions. Parkinsonism, either drug-induced by blockade of the D2 receptor or spontaneous by a decrease in the production of dopamine, is believed to result from a relative shortage of dopaminergic signalling in the basal ganglia, especially the striatum (Caligiuri et al., 1993; Nord and Farde, 2011; Pappa and Dazzan, 2009). Negative symptoms on the other hand are known to correlate with lower dopaminergic activity in the frontal cortex (Hovington and Lepage, 2012; Semkovska et al., 2001).

Also with regard to OIDs there is evidence for an association with dopaminergic imbalance in subcortical and frontal brain regions. Dopaminergic involvement of the basal ganglia in OIDs

| Table 1. Regression results with olfactory identification as dependent variable |
|-----------------|-------|-------|-------|-------|-------|-------|
| b       | beta  | t     | ΔR²   | F ΔR² | p     |
| Constant | 12.73 | 19.67 |       |       |       |
| PANSS negative | -.07 | -.22  | -4.02 | .10   | 35.08 | <0.001 |
| UPDRS total | -.04 | -.19  | -3.30 | .04   | 15.37 | <0.001 |
| WAIS IQ | .01   | .14   | 2.53  | .02   | 6.40  | <0.012 |
was suggested in a recent SPECT study performed in psychiatric patients with drug-induced parkinsonism (Bovi et al., 2010). Worse olfactory performance was associated with lower dopamine uptake in the putamen. Moreover, evidence that the frontal cortex is involved in the development of OIDs was found already three decades ago in patients with orbitofrontal brain lesions that suffered from olfactory agnosia, i.e. inability to identify odours in the absence of olfactory sensitivity problems (Potter and Butters, 1980). Ever since, several imaging studies have shown a link between OIDs and hypoactivation of the frontal cortex in patients with schizophrenia (Schneider et al., 2007; Malaspina et al., 1998). Recent evidence furthermore indicates that the catechol-O-methyltransferase (COMT) val158met polymorphism, which is associated with dopamine levels mainly in the prefrontal cortex, may be linked with OIDs in patients with schizophrenia (Kamath et al., 2012).

Observations that OIDs are associated with parkinsonian and negative symptoms may be of clinical importance as the prodromal phase of psychosis is believed to be characterized by dopaminergic dysregulation that alters the appraisal of stimuli through a process of aberrant salience (Howes and Kapur, 2009). Motor and negative symptoms may be early markers of this dopaminergic imbalance, since they are experienced by individuals with an increased risk of developing psychosis, including genetic and clinical high risk individuals (Yung et al., 2012; Koning et al., 2011; Scala et al., 2012). OIDs may be another early dopaminergic marker that exhibits in medication-naive patients with first-episode psychosis (Nguyen et al., 2010), unaffected relatives (Turetsky et al., 2008; Roalf et al., 2006), schizotypy patients (Park and Schoppe, 1997), and individuals in the putative prodromal phase (Brewer et al., 2003).

In Parkinson’s disease, olfactory functioning is already considered to be a strong biomarker for pre-symptomatic disease detection. Prospective studies in first-degree relatives of Parkinson’s disease patients have established hyposmia as a pre-motor sign of Parkinson’s disease that can precede the onset of motor symptoms by as long as five years (Ponsen et al., 2010; Berendse et al., 2011; Haehner et al., 2011). Deeb and colleagues even found that a basic smell test is as sensitive as a dopamine transporter scan for the diagnosis of Parkinson’s disease (Deeb et al., 2010). In comparison to the body of research in Parkinson’s disease it is remarkable how little attention has been drawn to the predictive value of OIDs in psychosis. This is especially true since the need to improve psychosis prediction is high. Current ultra high risk (UHR) criteria only predict subsequent psychosis in 15-30% of cases, which restricts early intervention initiatives to delay, attenuate or even prevent development of psychosis (de Koning et al., 2009; Yung et al., 2007). To our knowledge, to date only two longitudinal studies have investigated the possible predictive value of OIDs for transition to psychosis (Brewer et al., 2003; Woodberry et al., 2010). Both studies found that olfactory identification performance was lower in UHR subjects that would subsequently develop schizophrenia. The use of OIDs as a possible predictor of psychosis in high-risk individuals therefore seems a promising topic of research that deserves further evaluation. In addition, OIDs as a marker of dopaminergic sensitivity may predict antipsychotic response in terms of both efficacy and side-effects. The prognostic validity of such procedures needs to be assessed.

Our findings should be viewed in the light of some limitations. The current study used only one behavioural measure of olfactory processing. Odour identification tasks, like the one used
here, are considered the most highly standardized and reliable measures of psychophysical olfactory processing in humans (Hummel et al., 2001). Nevertheless, studies have shown that dopaminergic agents such as methylphenidate may differentially affect different aspects of olfactory performance, including odour acuity, discrimination and identification (Schecklmann et al., 2011; Romanos et al., 2008). To test the role of dopamine in various olfactory processes a broader test battery would be required. Second, the variance in olfactory identification that could be explained by the UPDRS was small. Hence, it would be interesting to investigate whether a more elaborate assessment of motor symptoms, including e.g. an objective measure of motor symptoms (Mera et al., 2012), may explain larger proportions of variance in OIDs. Third, although we corrected the analyses for antipsychotic dosage, we did not take into account the affinity to the D2 receptor which is known to influence the development of extrapyramidal symptoms (Seeman, 2010) and possibly also OIDs. This would need to be addressed in a future study.

In conclusion, the current study in a large sample of patients with non-affective psychosis showed that the level of parkinsonian and negative symptoms significantly predicted OIDs. Results suggest that OIDs in patients may be influenced, in part, by functional dopaminergic hypoactivity. Future studies should evaluate the clinical value of this finding in order to see whether OIDs may be used as an early detection marker of psychotic disorders.

REFERENCE LIST

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