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Associations between olfactory identification and (social) cognitive functioning: A cross-sectional study in schizophrenia patients and healthy controls

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ABSTRACT

Schizophrenia patients have difficulties identifying odors, possibly a marker of cognitive and social impairment. This study investigated olfactory identification (OI) differences between patients and controls, related to cognitive and social functioning in childhood and adolescence, to present state cognition and to present state social cognition. 132 schizophrenia patients and 128 healthy controls were assessed on OI performance with the Sniffin' Sticks task. Multiple regression analyses were conducted investigating OI in association with cognitive and social functioning measures in childhood/adolescence and in association with IQ, memory, processing speed, attention, executive functioning, face recognition, emotion recognition and theory of mind. Patients had reduced OI performance compared to controls. Also, patients scored worse on childhood/adolescence cognitive and social functioning, on present state cognitive functioning and present state social cognition compared to controls. OI in patients and controls was significantly related to cognitive and social functioning in childhood/adolescence, to present state cognition and to present state social cognition, with worse functioning being associated with worse OI. In this study, findings of worse OI in patients relative to controls were replicated. We also showed associations between OI and cognitive and social functioning which are not specific to schizophrenia.

1. Introduction

Schizophrenia patients have difficulties identifying odors (Moberg et al., 2014). The degree of this reduced odor identification (OI) compared to healthy controls has been examined extensively. A meta-analysis by Cohen et al. (2012) showed that OI in schizophrenia is nearly a standard deviation below the mean of controls.

Schizophrenia is also characterized by cognitive and social cognitive deficits, particularly in IQ, memory, processing speed, attention, executive functioning, emotion recognition and theory of mind (Mesholam-Gately et al., 2009). These deficits appear to be present before illness onset, as previous birth cohort studies showed that on average, subjects who later develop schizophrenia report poorer cognitive and social functioning in childhood and adolescence (Welham et al., 2009). Interestingly, impairments in social behavior and social cognition (i.e. emotion recognition) in schizophrenia have been related to OI deficit (Malaspina and Coleman, 2003; Kohler et al., 2007 resp.). Furthermore, previous studies have shown that OI and cognition are positively associated in schizophrenia (Brewer et al., 1996; Compton et al., 2006; Good et al., 2002; Goudsmit et al., 2004; Malaspina and Coleman, 2003; Moberg et al., 2006; Purdon, 1998; Saoud et al., 1998; Seckinger et al., 2004; Seidman et al., 1997, 1991; Stedman and Clair, 1998) and in controls (Brewer et al., 1996; Compton et al., 2006; Seidman et al., 1991), with moderate strength in both groups. However, in the majority of these studies only one or two cognitive domains were examined in relation to OI and often a range of possible confounders such as age, gender, smoking and the use of antipsychotics associated with OI (Moberg et al., 2014) was not taken into account. Moreover, most studies lacked a control group.

Olfactory development is dependent on the development of frontal and temporal lobe areas (Nguyen et al., 2010; Turetsky et al., 2009) and its cognitive (i.e. IQ, memory, processing speed, attention, executive

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functioning) and social cognitive related functioning (Aleman, 2014). Since cognitive and social functioning in childhood and adolescence is already dependent on the brain maturation of these areas early in life we expect a relationship between OI and cognitive and social functioning in childhood and adolescence. To date, no studies have been performed linking OI to cognitive and social functioning in childhood and adolescence and to present state functioning on multiple social cognitive domains. In this study we therefore comprehensively examine whether OI is related to cognitive and social functioning in childhood and adolescent, as well as to a range of present state social cognitive domains in a large sample of schizophrenia patients and healthy controls. Furthermore, we aim to replicate whether olfactory functioning is associated with present state cognition.

2. Methods

2.1. Study design and population

Data from this cross-sectional study pertain to the multicenter 'Genetic Risk and Outcome in Psychosis'- project (GROUP). This trial was part of an add-on study during the second measurement of this Dutch longitudinal GROUP–project. Participants were assessed extensively and were invited to participate in diagnostic interviews, questionnaires and neuropsychological tasks. The study protocol was approved by the accredited Medical Ethics Review Committee. All participants signed informed consent. More detail on the GROUP study is described by Korver et al. (2012). A subsample of 132 patients with a diagnosis of schizophrenia (DSM-IV: 295.1/295.3/295.6/295.9; mean ± *SD* age: 30.68 ± 7.03) and 128 healthy controls (mean ± *SD* age: 32.41 ± 9.50), assessed on present state OI, present state cognitive functioning and present state social cognitive functioning, as well as a retrospective questionnaire on childhood social and cognitive functioning were included in the current study. Nine participants missed cognitive data and three missed social cognitive data. Controls had no diagnosis according to DSM-IV and no first degree family member with a lifetime psychotic disorder.

2.2. OI, cognitive and social measures

OI was assessed with the Sniffin' Sticks, based on pen–like odor dispensing sticks (Hummel et al., 2001). Participants identified 16 odors by multiple choice from four descriptions. Odor sticks were presented birhinally in a fixed order by a trained researcher. The time interval between odor presentations was 30 s. OI was defined as number of correct responses. Although tests of odor threshold and discrimination are also available, only OI was assessed due to time constraints, and since this olfactory domain is most commonly affected in schizophrenia patients (Cohen et al., 2012). The Sniffin' Sticks have been employed previously to assess OI in patients with psychosis (Meijer et al., 2016; Kamath et al., 2014; Rupp et al., 2005; Ugur et al., 2005).

Cognitive and social functioning in childhood/adolescence was measured retrospectively with the Premorbid Adjustment Scale (PAS; Cannon-Spoor et al., 1982; Quee et al., 2014). Scores of cognitive functioning and social functioning were calculated separately by summing scores of corresponding cognitive (school performance and school adaptation) and social (social behavior, peer relations and social-sexual aspect) subscales across age epochs and subsequently divided by the number of scores.

Informants were either a parent, another family member of the patient, or the patients themselves. Healthy controls provided the information themselves. With an ANOVA we compared whether PAS informants differed in their assigned scores.

A cognition composite score was calculated as a mean of seven transformed *z*-scores for each tested cognitive domain, accordant with Quee et al. (2011; i.e. these domains were an assessment of present state cognitive functioning), which were (1) IQ measured with the Wechsler adult intelligence scale-third edition, using the subtasks: Arithmetic, Information, Digit–Symbol Coding and Block Design, (2) immediate recall, (3) delayed recall and (4) recognition measured with the 15-word learning task, (5) attention and (6) processing speed measured with the continuous performance task-HQ, and (7) executive functioning measured with the response set-shifting task.

A social cognition composite score was calculated, which is an average of four following domains (i.e. assessment of these domains was of present state social cognition), converted to *z*-scores: (1) face recognition measured with the Benton facial recognition task, (2) emotion recognition measured with the degraded affect recognition task and (3) theory of mind of emotions and (4) theory of mind of beliefs measured with the emotional mentalizing task. For references of the tasks, see Korver et al., (2012); emotional mentalizing task reference is Shaw et al. (2004).

We found predictive validity of childhood/adolescence functioning for present state functioning in patients and controls: Pearson's correlation between mean scores of childhood/adolescence measures and mean scores of both present state measures indicated significant correlations in patients ($r = -0.213$; $p < 0.001$), and in controls ($r = -0.325$; $p = 0.015$).

2.3. Statistical analyses

Separate multiple linear regression models were built for cognitive functioning and social functioning in childhood/adolescence, for present state cognition composite score and present state social cognition composite score. First, we investigated whether group (patient versus controls) had a main effect on OI. Patients were set as the reference group in the regressions. Second, we investigated whether cognitive and social functioning in childhood/adolescence, present state cognition composite score and present state social cognition composite score (predictors) were associated with OI (dependent variable). Interaction terms were added to test whether associations between OI and each predictor differed between patients and controls. If the interaction term was not significant it was removed from the model, containing only main effects and covariates. Regressions were repeated, adjusting for gender ratio, age, APD use and smoking. For multiple comparisons correction, False Discovery Rate (FDR) was applied at alpha = 0.05. Post-hoc analyses were performed to look at the associations between individual domains comprising our four composite score and OI. These latter results are interpreted at $p = 0.05$.

3. Results

3.1. Sample characteristics

Table 1 summarizes socio-demographic differences between patients and controls. Clinical characteristics of patients are also summarized in Table 1. OI, cognitive and social functioning in childhood/adolescence, present state cognition and present state social cognition were significantly lower in patients compared to controls (see Table 2). Lower OI performance in patients compared to controls remained significant after correcting for gender, age, APD use and smoking. The R^2 did not change when adding each of our covariates. Informant group (parent, other family member, participant) used for the PAS did not have a significant effect on PAS cognitive score ($F(2,101) = 1.23$; $p = 0.297$) nor on PAS social score ($F(2,101) = 0.05$; $p = 0.954$).

3.2. OI and childhood/adolescence cognitive and social functioning associations

Results from the regression models showed that there was a significant main effect of status on OI ($\beta = 0.143$, $p = 0.021$). Cognitive functioning in childhood/adolescence ($\beta = -0.193$, $p = 0.003$) and

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