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Neural substrates of olfactory processing in schizophrenia patients and their healthy relatives

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Abstract

Odorants represent powerful stimuli capable of eliciting various emotional responses. In schizophrenia patients and their non-affected relatives, olfactory and emotional functions are impaired, revealing a familial influence on these deficits. We aimed at determining the neural basis of emotional olfactory dysfunctions using odors of different emotional valence for mood induction and functional magnetic resonance imaging (fMRI) by comparing 13 schizophrenia patients, their non-affected brothers and 26 matched healthy controls. Blood-oxygen-level-dependent (BOLD) effects and subjective mood changes were assessed during negative (rotten yeast), positive (vanilla) and neutral (ambient air) olfactory stimulation. Group comparisons of brain activation were performed in regions of interest. Subjective ratings were comparable between groups and indicated successful mood induction. However, during stimulation with the negative odor, hypofunctional activity emerged in regions of the right frontal and temporal cortex in the patients. A familial influence in the neural substrates of negative olfactory dysfunction was indicated by a similar reduced frontal brain activity in relatives. Dysfunctions therefore appeared to be located in regions involved in higher cognitive processes associated with olfaction. No familial influences were indicated for cerebral dysfunctions during positive olfactory stimulation. Results point to a differentiation between trait and state components in cerebral dysfunctions during emotional olfactory processing in schizophrenia.

Keywords: Olfaction; Emotion; Mood induction; Genetic influences; fMRI

1. Introduction

Olfactory stimuli represent powerful triggers for emotional reactions. Dysfunctions in emotional processing and experience have been demonstrated in schizophrenia patients (Schneider et al., 1998; Schneider et al., 2006a; Habel et al., 2006a,b) as well as their non-affected relatives (Nuechterlein et al., 2002), who are at heightened risk of developing schizophrenia. Although it has been found that patients with affective flattening experience emotions normally and only the expression is impaired, our results also point to differences in patients' experiences. Adult schizophrenia patients were

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investigated during a standardized mood-induction procedure where both happiness and sadness were induced (Schneider et al., 1995; Habel et al., 2000). While a significant mood-induction effect was found in patients, it was weaker than in controls, i.e. due to less positive affect during happy mood. At the same time, patients revealed inappropriate affect (i.e. higher happy ratings during sad mood and/or higher sad ratings during happy mood), both in accordance with typical symptoms of affective flattening and inadequate affect.

The same applies to olfactory dysfunctions in patients as well as relatives where mainly odor identification, discrimination and detection threshold sensitivity were investigated (Moberg et al., 1997; Kopala et al., 2001; Ugur et al., 2005). Hence, results in relatives may reflect a genetic vulnerability to olfactory deficits. This is supported by morphological and functional changes in the olfactory system of relatives (Turetsky et al., 2003) that parallel those demonstrated previously in patients (Turetsky et al., 2000). Clark and colleagues (1991) were among the first to verify hypoactivations, with PET, in frontal and thalamic regions of schizophrenia patients with olfactory agnosia. PET also revealed greater right-sided hypometabolism within the frontal and superior temporal lobe as well as the supramarginal and angular gyri during olfactory identification (Malaspina et al., 1998). In a $H_2^{15}O$–PET-study, Crespo-Facorro and colleagues (2001) examined the neural substrates of emotional responses in schizophrenia patients during stimulation with pleasant (vanilla) and unpleasant (4-methylvaleric acid) odors. Patients evaluated unpleasant odors in a similar manner to that of the controls, but demonstrated lower valence ratings for the pleasant odors. Furthermore, the results demonstrated functional impairments in limbic areas.

In investigating the neural substrates of olfaction in healthy first-degree relatives of schizophrenia patients (FDRSP) using functional magnetic resonance imaging, two main issues were addressed: (i) determination of a familial similarity due to a familial marker or a genetic trait of possible cerebral dysfunctions in schizophrenia and (ii) comparison of the emotional valence effects of the odors on cerebral activation in siblings with and without schizophrenia. We hypothesized familial similarities in regions that are involved in olfactory-triggered emotional responses and revealed structural and functional deficits in schizophrenia in previous studies; basically, the amygdala, the anterior cingulate and the prefrontal cortex. Based on our previous results applying a visual mood-induction procedure (Schneider et al., 1995, Habel et al., 2000, 2004), a reduced mood-induction effect is also suggested with olfactory-induced emotions in patients. Hence, due to our experience of weaker BOLD responses to olfactory stimulation (Schneider et al., 1999, 2000; Stöcker et al., 2006), we relied on a region of interest approach to maximize sensitivity for group differences in a subset of functionally relevant brain areas. We explored group differences across 11 predefined volumes of interest (VOIs) on the basis of their involvement in olfactory and emotional processing as well as in the pathophysiology of schizophrenia: thalamus, anterior cingulate gyrus, orbitofrontal cortex, dorsolateral prefrontal cortex (middle frontal gyrus), temporal cortex, insula, amygdala, hippocampus, and nucleus accumbens. The amygdala receives direct input from the olfactory system, which plays a major role in emotional responses (Zald and Pardo, 1997; Zald et al., 1998; Anderson et al., 2003; Royet et al., 2003; Schneider et al., 1998, 1999, 2000) and is also known to be dysfunctional in schizophrenia patients (Schneider et al., 1998; Habel et al., 2004). The latter applies to all other regions. The insula has been reported to be especially relevant for disgust (Phillips et al., 1998; Wicker et al., 2003), the predominant emotion elicited by our negative odor. The nucleus accumbens is involved in positive (Berridge, 2003) but also negative affect (Paradiso et al., 1999). The orbitofrontal cortex, hippocampus, insula, cingulate cortex and thalamus furthermore pertain to secondary olfactory regions receiving information from the primary olfactory cortex (Gottfried and Zald, 2005; Weismann et al., 2001). The anterior cingulate (BA 24/25) the prefrontal cortex are part of the cerebral network underlying emotion processing (Gündel et al., 2003; Zubieta et al., 2003). Activation of the temporal cortex has been observed during olfaction and emotion (Levy et al., 1997; Gündel et al., 2003; Mitchell et al., 2003).

2. Methods

2.1. Subjects

Male schizophrenia patients ($n=13$), their non-affected brothers ($n=13$), and healthy controls ($n=26$) were investigated. Patients were included in the study if they had an unaffected male sibling who was willing to participate. One sibling (brother) was included per patient. All subjects also participated in another fMRI paradigm, reported previously (Habel et al., 2004). Patients were required to meet DSM-IV criteria for schizophrenia whilst relatives must have had no history of any psychiatric illness (SCID I/II; German Version: Wittchen et al., 1997; performed by an experienced psychiatrist and psychologist). A further exclusion criterion for patients was psychiatric comorbidity (DSM-IV,