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Reduced activation in ventral striatum and ventral tegmental area during probabilistic decision-making in schizophrenia

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ABSTRACT

Patients with schizophrenia suffer from deficits in monitoring and controlling their own thoughts. Within these so-called metacognitive impairments, alterations in probabilistic reasoning might be one cognitive phenomenon disposing to delusions. However, so far little is known about alterations in associated brain functionality.
A previously established task for functional magnetic resonance imaging (fMRI), which requires a probabilistic decision after a variable amount of stimuli, was applied to 23 schizophrenia patients and 28 healthy controls matched for age, gender and educational levels. We compared activation patterns during decision-making under conditions of certainty versus uncertainty and evaluated the process of final decision-making in ventral striatum (VS) and ventral tegmental area (VTA).
We replicated a pre-described extended cortical activation pattern during probabilistic reasoning. During final decision-making, activations in several fronto- and parietocortical areas, as well as in VS and VTA became apparent. In both of these regions schizophrenia patients showed a significantly reduced activation.
These results further define the network underlying probabilistic decision-making. The observed hypo-activation in regions commonly associated with dopaminergic neurotransmission fits into current concepts of disrupted prediction error signaling in schizophrenia and suggests functional links to reward anticipation. Forthcoming studies with patients at risk for psychosis and drug-naive first episode patients are necessary to elucidate the development of these findings over time and the interplay with associated clinical symptoms.

1. Introduction

Schizophrenia patients are impaired in detecting, monitoring and controlling their own cognition ("thinking about one's thinking") and synthesizing their mental states. These so-called metacognitive deficits include a reduced ability to appraise and weigh information effectively, to select appropriate responses including decisions based on perceptions and to cope with cognitive limitations (Lysaker et al., 2011, 2013b). Deficits in metacognitive domains are a highly stable property of psychotic patients (Vohs et al., 2014), predicting learning abilities (Tas et al., 2012) and treatment response (So et al., 2014), impairing quality of life (Tas et al., 2013) and outcome (Lysaker et al., 2013a), and consequently have been implicated into theories about the formation of delusions (Hemsley and Garety, 1986; Bentall et al., 2009; Speechley et al., 2010; Murray, 2011; So et al., 2012). Therefore specific training interventions targeting metacognitive deficits in psychosis have been invented (Moritz and Woodward, 2007; Van Donkersgoed et al., 2014). However, neural representations of these metacognitive deficits in schizophrenia are widely unclear. The present study was targeted on investigating two key functions of metacognition: probabilistic reasoning and decision-making.

First insight into general neural processes during probabilistic reasoning and decision-making was based on lesion (Xi et al., 2011; Lunt et al., 2012) as well as functional magnetic resonance imaging (fMRI) studies. These studies localized the neural organization of uncertainty (risk or ambiguity) in the course of decision-making represented in a fronto-striatal-thalamic network (Grinband et al., 2006; Bach and Dolan, 2012). Probabilistic reasoning leading to decisions might well be perceived as a specific situation of building up beliefs or perceptions (Deco et al., 2013). Experiences derived from sensory input have to be integrated into prior knowledge. Within this process, prediction errors

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are counterbalanced in a hierarchical Bayesian inference framework between lower- and higher-level systems. On a functional level, the encoding of the precision or uncertainty of prediction errors might be parallel to the encoding of reward uncertainty (Juckel et al., 2006b; Murray et al., 2008; Schultz, 2013). Interestingly, in schizophrenia patients a disruption in prediction error signaling in parallel to a hypo-activation of the ventral striatum (VS) can be found (Lee and Mumford, 2003; Fletcher and Frith, 2009; Friston, 2010; Dura-Bernal et al., 2012). Moreover, it is known from sensitive probabilistic learning or reward prediction tasks (Weickert et al., 2009; Koch et al., 2011; Morris et al., 2012) that schizophrenia patients show differential activation patterns in the fronto-striatal-thalamic network. Hence, these alterations can be assumed to be a neural correlate of deficits in probabilistic reasoning and decision-making in schizophrenia.

Several studies applied the classical beads task regarding probabilistic reasoning and decision-making in healthy volunteers. Blackwood et al. (2004) reported the involvement of cerebellum as well as parietal and occipital cortex. Furl and Averbeck (2011) modified the beads task towards reward-related decision-making and observed less draws until decision than predicted by a Bayesian model. Moreover, in an event-related analysis, an increased activation was found in a network comprising parietal, insular, anterior cingulate and striatal regions at the time of decision in comparison to the time of preceding draws. Finally, our group developed a modified version of the beads task and observed activations in cerebellum and prefronto-parietal executive functioning network as well as in medial parieto-occipital regions during the whole process of probabilistic reasoning in healthy volunteers. During the decision process itself, activity in ventral tegmental area (VTA) and VS, comprising the nucleus accumbens (Nacc), was detected (Esslinger et al., 2013).

However, to our knowledge until now there is only one published study exploring decision-making under uncertainty in schizophrenia (Krug et al., 2014). The authors found reduced activation in the prefrontal cortex, but not in subcortical dopaminergic regions in schizophrenia.

In the present study we applied our modified beads task to schizophrenia patients and matched healthy controls. We intended to replicate the activation patterns of our previous study and to evaluate differential activation patterns in schizophrenia patients. It was assumed that patients inappropriately weight evidence during probabilistic reasoning (Fine et al., 2007; Speechley et al., 2010), going along with reduced activation in VS and VTA during final decision-making.

2. Methods

2.1. Participants

This study was approved by the local ethics committee of the Medical Faculty Mannheim of the University of Heidelberg (AZ 2009-296N-MA). Inpatients were recruited in a stable phase of treatment and fulfilled predefined inclusion criteria: diagnosis of schizophrenia according to the Diagnostic and Statistical Manual, IVth revised edition (DSM-IV R), antipsychotic monotherapy, age between 18 and 60 years, ability to provide informed consent and sufficient German language skills. We excluded patients with severely exacerbated schizophrenia (Positive and Negative Syndrome Scale (PANSS) score ≥90), current substance dependence excluding nicotine or other disorders of the central nervous system requiring treatment. Current antipsychotic treatment with second generation antipsychotics was quantified using chlorpromazine (CPZ) equivalents (Andreasen et al., 2010), with a mean CPZ equivalent of 406.01 ± 186, indicating intermediate dose ranges. Due to anxiety or agitation seven patients were additionally treated with lorazepam. Control subjects were matched for sex, age and levels of education (Table 1), had no positive family history of schizophrenia, bipolar disorder or suicide in first-degree relatives and no previous or current psychiatric disorders according to the M.I.N.I. (Mini-International Neuropsychiatric Interview) or psychopharmacological therapy.

2.2. Psychometric rating scales and neuropsychological characterization

Psychotic symptoms were characterized by trained raters (FR, SE, SE) using PANSS and PSYRATS (Psychotic Symptoms Rating Scale). We further evaluated negative symptoms (Scale for the Assessment of Negative Symptoms: SANS), comorbid depressive symptoms (Calgary Depression Scale for Schizophrenia: CDSS), general severity of illness (Clinical Global Impression: CGI) and psychosocial functioning (Global Assessment of Functioning: GAF; Personal and Social Performance Scale: PSP).

Neuropsychological assessment included the Trail Making Tests A and B (TMT-A, -B), the Wisconsin Card Sorting Test (WCST) and the Multiple Choice Word Test version B (MWT-B, Table 1).

2.3. Modified beads task

Our modification of the classical beads task had been described earlier (Esslinger et al., 2013). In short, subjects viewed fish of two colors jumping out of a lake and had to decide from which of two lakes they were coming at a color ratio of 80/20% or 20/80%. After each fish, subjects were asked if they wanted to see another fish and could answer the question by pressing according buttons. The colored fish were presented in a previously defined fashion (e.g. 1–1–1–2–1–1–1–1–2–1), recapitulated eight times with alternative starting points. For methodological reasons, the number of fish per block was restricted to ten. After presentation of the selected number of fish or a maximum of ten fish, subjects had to decide for one lake and to rate on a four-point scale how confident they were regarding their decision (1 = a little uncertain, 2 = fairly certain, 3 = very certain, 4 = totally certain). In the control condition, subjects had to indicate the colors of fish. To ensure a standardized duration of the experiment, unequal lengths of the experimental blocks were counterbalanced by the number of control trials. Eight experimental blocks and eight control blocks were presented adding up to eight times at 2.04 min (16.32 min for the whole experiment).

2.4. Acquisition and evaluation of fMRI data

Blood oxygen level-dependent (BOLD) fMRI was performed on a 3 T Siemens Trio (Siemens Medical Systems, Erlangen, Germany) by using echo-planar imaging (28 axial slices; 4-mm thickness; 1-mm gap; TR/TE 2000/28 ms; FOV 19.2 cm; matrix 64 × 64). FMRI data was analyzed using SPM8 (www.fil.ion.ucl.ac.uk/spm/software/spm8/) as described earlier (Esslinger et al., 2013). Prior to analysis, data was preprocessed including realignment, slice timing, and normalization to a standard EPI template volume with resampling to a 3 × 3 × 3 mm voxel size and smoothing with a 9 mm full-width half-maximum Gaussian filter. Task-specific brain activation was analyzed in a hybrid model according to Visscher et al. (2003). We compared neural processes during lake reasoning (decision out of which lake fish were jumping) versus color naming (decision about the color of fish). In addition, we compared the neural response to the last fish, followed by a final decision, in comparison to all previous fish that were not followed by a decision for a lake. To control for possible movement-related artifacts, six further regressors were entered into the model, containing information from the realignment. Contrasts of interest were entered into second-level random-effects group analyses, applying one-sample and two-sample T-tests. Since groups slightly differed in gender distribution, gender was used as a covariate.

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