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Reward-dependent modulation of working memory is associated with negative symptoms in schizophrenia

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ABSTRACT

The negative symptoms of schizophrenia have been associated with altered neural activity during both reward processing and cognitive processing. Even though increasing evidence suggests a strong interaction between these two domains, it has not been studied in relation to negative symptoms. To elucidate neural mechanisms of the reward–cognition interaction, we applied a letter variant of the n-back working memory task and varied the financial incentives for performance. In the interaction contrast, we found a significantly activated cluster in the rostral anterior cingulate cortex (ACC), the middle frontal gyrus, and the bilateral superior frontal gyrus. The interaction did not differ significantly between the patient group and a healthy control group, suggesting that patients with schizophrenia are on average able to integrate reward information and utilize this information to maximize cognitive performance. However within the patient group, we found a significant inverse correlation of ACC activity with the factor diminished expression. This finding is consistent with the model that a lack of available cognitive resources leads to diminished expression. We therefore argue that patients with diminished expression have difficulties in recruiting additional cognitive resources (as implemented in the ACC) in response to an anticipated reward. Due to this lack of cognitive resources, less processing capacity is available for effective expression, resulting in diminished expressive behavior.

1. Introduction

Negative symptoms – comprising the domains of blunted affect, alogia, asociality, anhedonia, and avolition – are an integral component of schizophrenia. They are a strong predictor of poor prognosis and contribute to functional impairment (Azorin et al., 2014; Kirkpatrick et al., 2006; Milev et al., 2005; Rabinowitz et al., 2012). A recent consensus suggests that negative symptoms can be grouped into two factors. One factor is referred to as diminished expression, comprising blunted affect and alogia. The other factor is referred to as diminished motivation and pleasure, or apathy, and comprises asociality, anhedonia and avolition (Kring and Barch, 2014; Strauss et al., 2012). This distinction might allow a more differentiated approach in the search of underlying pathophysiological mechanisms (Blanchard and Cohen, 2006; Foussias and Remington, 2010; Liemburg et al., 2013; Messinger et al., 2011).

Negative symptoms have been consistently associated with dysfunctional reward processing, in particular with diminished reward anticipation. On a neural level, this has been linked to a reduction in ventral striatal activity (Juckel et al., 2006; Nielsen et al., 2012; Schlagenhauf et al., 2008; Simon et al., 2010; Waltz et al., 2008). Negative symptoms have also been linked to neurocognitive deficits, although this association is rather modest (Lin et al., 2013; Milev et al., 2005; Ventura et al., 2009, 2013). The cognitive deficits, and to a lesser extent negative symptoms, have been associated with abnormal activity in the prefrontal cortex, particularly the dorsolateral prefrontal cortex (dlPFC; Barch and Ceaser, 2012; Manoach, 2003).

Recent work suggests that there is a strong interaction of reward anticipation with cognitive performance. Knowing that a certain cognitive effort might result in the receipt of a reward leads to the prioritization of the respective process and influences the assignment of limited cognitive resources (Beck et al., 2010; Braver et al., 2014; Kennerley and Wallis, 2009; Krawczyk et al., 2007; Locke and Braver, 2008; Rowe et al., 2008). On the neural level, the anterior cingulate cortex (ACC) has been suggested to play an essential role in this interaction and to act as a hub linking reward and cognition (Krebs et al., 2012; Pessoa,

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2008, 2009; Vassena et al., 2014). It is presumed that the ACC receives reward information from the ventral striatum (VS), thereby enhancing cognitive performance (Holroyd and Yeung, 2012; Pessoa, 2009; van Steenbergen et al., 2014). It remains unknown how negative symptoms in schizophrenia relate to the reward–cognition interaction at the neural level.

In the current study, we measured cognitive performance with a letter variant of the n-back working memory (WM) task and varied the financial incentives for the performance. We hypothesized that patients with schizophrenia would show impairments in the modulation of cognitive performance by reward and that these impairments are correlated with the severity of negative symptoms. On a neural level, we expected that the prospect of a future reward leads to the activation of the ACC as well as to a stronger activation in WM related regions in the lateral PFC. We expected that these effects are diminished in the patient group and show an inverse correlation with the severity of negative symptoms.

2. Methods

2.1. Participants

We studied 29 individuals meeting the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; American Psychiatric Association, 2000) criteria for schizophrenia ($n = 23$) or schizoaffective disorder ($n = 6$) and 27 healthy control subjects with no personal history of a DSM-IV axis 1 disorder. All participants provided written informed consent to participate in the study, which was approved by the local Ethics committee. Patients were recruited either as inpatients ($n = 16$) or outpatients ($n = 13$) from the Psychiatric Hospital, University of Zurich, or from affiliated institutions. All inpatients were at the end of their hospitalization and they participated in a multimodal treatment program that encouraged them to engage in daily activities outside the hospital. All patients were clinically stable and received constant doses of medication for at least two weeks prior to testing, with the exception of one patient receiving a small increase of clozapine dose seven days before testing. Exclusion criteria included a daily lorazepam dosage greater than 1 mg, florid positive symptoms, i.e. any positive subscale item score of the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987) >4, extrapyramidal side effects, measured with the Modified Simpson-Angus Scale (MSAS; Simpson et al., 1970), >3, or any other DSM-IV axis 1 diagnosis. For confirmation, all participants were assessed using the Mini-International Neuropsychiatric Interview (M.I.N.I.; Sheehan et al., 1997).

2.2. Clinical and neuropsychological assessment

All patients were further assessed using the Brief Negative Symptom Scale (BNSS; Strauss et al., 2012), the Scale for the Assessment of Negative Symptoms (SANS; Andreasen NC, 1982), the PANSS, the Global Assessment of Functioning scale (GAF; Frances et al., 1994), the Personal and Social Performance Scale (PSP; Schaub and Juckel, 2011) and the Calgary Depression Scale for Schizophrenia (CDS, Addington et al., 1993). We used the BNSS as our main measurement for negative symptoms since it was designed to facilitate a clear distinction of the factors apathy and diminished expression. For the total BNSS score, the assessment of the inter-rater reliability showed an intra-class correlation coefficient (ICC) of 0.97. The subscales reached ICCs from 0.87 to 0.97.

To characterize the sample and to disentangle the effects of neuropsychological functioning, the following cognitive domains were tested: verbal learning (Auditory Verbal Learning Memory Test, VLMT; Helmstaedter and Durwen, 1990), verbal and visual short-term working memory (Digit Span, DS; Stieglitz, 2000) and Corsi block-tapping test (CBT; Kessels et al., 2000), processing speed (Digit-Symbol Coding, DSC; Von Aster et al., 2006), planning (Tower of London, ToL; Shallice, 1982), and semantic and phonetic fluency (animal naming, AN; s-words, SW; Delis et al., 2001).

2.3. Functional magnetic resonance imaging

2.3.1. Imaging acquisition

Two runs containing 185 whole brain T2* weighted echo-planar images (EPI) were acquired in ascending order using a Philips Achieva 3.0 T magnetic resonance scanner with a 32 channel SENSE head coil (Philips, Best, The Netherlands). Further specifications were: $3 \times 3 \times 3 \times mm^3$ in-plane resolution, 0.5 mm gap width, 240×240 mm field of view, 2000 ms TR, 25 ms TE, flip angle 82°. Slices were aligned with the anterior–posterior commissure. The first five scans were discarded to eliminate the influence of T1 saturation effects. A T1-weighted high-resolution anatomical scan was obtained for registration: 160 sagittal plane slices, $1 \times 1 \times 1\ mm^3$.

2.3.2. Task and stimuli

A modified version of a previously employed letter n-back task was used (Owen et al., 2005; Pochon et al., 2002). The task was presented as a two by two factorial design with the factors cognitive load (0-back vs. 2-back) and reward (reward vs. no reward), resulting in a total of four different conditions: 0-back/reward (0R), 0-back/no reward (0N), 2-back/reward (2R), 2-back/no reward (2N). Each condition was presented four times, resulting in a total of 16 blocks. The 16 blocks were split into 2 runs. The order of presentation was equal for all subjects and as follows: 0R, 2R, 0N, 2N, 2N, 0N, 2R, 0R; 0R, 0N, 2R, 2N, 2N, 2R, 0N, 0R (see Fig. 1).

2.3.3. Behavioral analyses

The sensitivity index d′ (Haatveit et al., 2010; Green and Swets, 1988) and reaction times were used to analyze the behavioral performance. D′ is calculated as the standardized probability of a hit minus the standardized probability of a false alarm: $d' = z(\text{probability(hits)}) - z(\text{probability(false alarms)})$. To test for differences in behavioral performance, d′ and reaction times were entered into separate mixed-design ANOVAs with group (patient group, healthy control group) as between-subjects factor and cognition (0-back, 2-back) and reward (no reward, reward) as within-subject factors. To relate behavioral performance to psychopathological ratings of negative symptoms, we calculated Pearson's r. All analyses were performed using IBM SPSS Statistics Version 21.

2.3.4. fMRI analyses

Functional MRI data were analyzed using SPM8 (Statistical Parametric Mapping, Wellcome Department of Cognitive Neurology, London, UK). Differences in EPI slice acquisition timing were corrected using the central slice as reference. To reduce artifacts from head movements, functional images were realigned using a least squares approach and a six-parameter rigid body spatial transformation, using the first image as a reference. A voxel displacement map, calculated from double phase and magnitude field map data, was applied for a combined static and dynamic distortion correction. After co-registration, the "New Segment" toolbox was used for spatial normalization. Finally, images were smoothed using a Gaussian kernel of 6 mm width.

For our block design, we used a general linear model (GLM) with a two-stage approach. On the first stage of analysis, two levels of cognitive load (0-back/2-back) and two levels of reward (reward/no reward) were modeled. To study the cognition/reward interaction effect, i.e., the effect of reward-dependent modulation of working memory, the following contrast images were constructed: ((2-back/reward)–(0-back/reward))–((2-back/no reward)–(0-back/no reward)). These images were taken to the second stage of analysis for random-effects inference.

Due to our a priori hypothesis, we restricted our search volume to the PFC and ACC (Barch and Dowd, 2010; Cai and Padoa-Schioppa,

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