



Diminishing striatal activation across adolescent development during reward anticipation in offspring of schizophrenia patients

Matthijs Vink ^{*,1}, Max de Leeuw ¹, Ruby Pouwels, Hanna E. van den Munkhof, René S. Kahn, Manon Hillegers

Brain Center Rudolf Magnus, Department of Psychiatry, University Medical Center Utrecht, Utrecht, The Netherlands

ARTICLE INFO

Article history:

Received 10 September 2015

Received in revised form 13 November 2015

Accepted 17 November 2015

Available online 26 November 2015

Keywords:

Schizophrenia offspring

Adolescence

Striatum

Reward

Orbitofrontal cortex

ABSTRACT

Schizophrenia is a severe psychiatric disorder associated with impaired fronto-striatal functioning. Similar deficits are observed in unaffected siblings of patients, indicating that these deficits are linked to a familial risk for the disorder. Fronto-striatal deficits may arise during adolescence and precede clinical manifestation of the disorder. However, the development of the fronto-striatal network in adolescents at increased familial risk for schizophrenia is still poorly understood. In this cross-sectional study, we investigate the impact of familial risk on fronto-striatal functioning across age related to reward anticipation and receipt in 25 adolescent offspring of schizophrenia patients (SZ offspring) and 36 age-matched healthy controls (range 10–19 years). Subjects performed a reward task while being scanned with functional MRI. Overall response times and the amount of money won did not differ between the groups. Striatal activation during reward anticipation decreased across age in the SZ offspring, while it did not in the healthy controls. Activation in the orbitofrontal cortex during reward receipt did not differ between the groups. These results, taken together with data from adult schizophrenia patients and their siblings, indicate that the diminishing striatal activation across adolescence may signify a familial vulnerability for schizophrenia.

© 2015 Elsevier B.V. All rights reserved.

1. Introduction

Schizophrenia is a highly heritable psychiatric disorder that is characterized by positive symptoms such as delusions and hallucinations, negative symptoms including affective flattening, as well as cognitive impairments (van Os and Kapur, 2009). Underlying these symptoms may be dysfunctions in the frontal lobe and the striatum (Emsley et al., 2015; Hahn et al., 2012; McGuire et al., 2008; van Veelen et al., 2010, 2011; Waltz and Gold, 2007; Weinberger and Gallhofer, 1997; Zandbelt et al., 2011). Indeed, the striatum is the primary target of effective antipsychotics. Functional MRI studies in adult schizophrenia patients have consistently demonstrated abnormal fronto-striatal activity in the context of various cognitive tasks (Ehrlich et al., 2012; Koch et al., 2008; Murty et al., 2011; Quidé et al., 2013; Tu et al., 2006; van Veelen et al., 2010, 2011; Vink et al., 2006; Wolf et al., 2011; Zandbelt et al., 2011), in particular those that require the processing of rewards (Esslinger et al., 2012; Juckel et al., 2006; Morris et al., 2011; Murray et al., 2008; Nielsen et al., 2012; Schlagenhauf et al., 2009). These studies report blunted ventral striatum activation during reward anticipation (Esslinger et al., 2012; Juckel et al., 2006; Morris et al., 2011; Murray

et al., 2008; Nielsen et al., 2012; Schlagenhauf et al., 2009) and decreased orbitofrontal activation (Schlagenhauf et al., 2009) during reward receipt. Fronto-striatal deficits are also present in first-degree relatives (de Leeuw et al., 2013, 2014, 2015; Raemaekers et al., 2006; Vink et al., 2006; Zandbelt et al., 2011). Specifically, as in patients, we recently observed hypoactivation in the ventral striatum during reward anticipation in unaffected siblings of schizophrenia patients compared to matched healthy controls (de Leeuw et al., 2014), but found orbitofrontal cortex activation to be increased during receipt of reward. These findings are consistent with those of Grimm et al. (2014), who also identified reduced ventral striatum activation in relatives of patients. Taken together, these findings underscore the fact that impaired fronto-striatal function is associated with the familial vulnerability of the disorder.

This familial vulnerability, probably in interaction with environmental factors, may be at the basis of an abnormal fronto-striatal brain development (Paus et al., 2008) preceding the overt manifestation of schizophrenia. Evidence in support of such a developmental hypothesis of schizophrenia comes primarily from neuropsychological studies showing deficits in cognition and behavior (Keshavan et al., 2008; Rapoport et al., 2012) in at-risk adolescents prior to the clinical diagnosis. However, to date almost no functional neuroimaging studies have been performed to investigate the development of fronto-striatal functioning in young subjects at risk for schizophrenia. For the current study, we included adolescent offspring of schizophrenia patients, as they are clearly at increased familial risk: they have a tenfold increased incidence

* Corresponding author at: Brain Center Rudolf Magnus, University Medical Center Utrecht, Dept of Psychiatry, Room A.01.126, P.O. Box 85500, NL-3508 GA Utrecht, The Netherlands.

E-mail address: m.vink@umcutrecht.nl (M. Vink).

¹ Both authors contributed equally.

of schizophrenia-related or not otherwise specified psychosis in adulthood (Erlenmeyer-Kimling and Cornblatt, 1987). Importantly, and in contrast to clinical at-risk adolescents (i.e. at-risk mental state), these adolescents are selected based on familial risk alone and are usually not symptomatic or treatment seeking; therefore, they typically have not been exposed to psychotropic medication, including antipsychotic medication.

In this cross-sectional study, we investigate the impact of familial risk on fronto-striatal functioning across adolescence. We obtained functional MRI data from 25 adolescent offspring of schizophrenia patients and 36 age-matched healthy controls across the age range of 10–19 years. Subjects performed a modified version of the Monetary Incentive Delay task (Knutson et al., 2001a, 2001b) which was optimized to analyze changes in brain activation related to the anticipation and receipt of reward separately (Figuee et al., 2011; van Hell et al., 2010; Vink et al., 2015). Two bilateral anatomical ROIs were a priori selected, based on their known involvement in the anticipation and outcome of reward (Haber and Knutson, 2010; Knutson et al., 2001a, 2001b): the ventral striatum and orbitofrontal cortex. Based on findings of reduced ventral striatum activation levels in both adult schizophrenia patients and their siblings, combined with what is already known from normal adolescent development (Hoogendam et al., 2013), we hypothesized that ventral striatum activation will either (a) be reduced or (b) diminish across adolescence in offspring of schizophrenia patients compared to that in healthy control adolescents. Formulating a hypothesis for the cross-sectional development of orbitofrontal cortex activation is less clear cut, as activation levels during adulthood differ between patients (reduced levels; Schlagenhauf et al., 2009) and their siblings (increased levels; de Leeuw et al., 2014) and this region has never been investigated in the context of reward processing in adolescent offspring of patients. Furthermore, the frontal cortex is one of the last regions to reach its mature state, so that the impact of the increased familial risk may be expressed only at the very end of adolescence (Casey et al., 2010).

2. Methods

2.1. Participants

Twenty-five adolescent offspring of patients with schizophrenia (14.2 ± 2.7 years, 9 males) and 36 unrelated healthy control subjects (13.1 ± 1.9 years, 21 males) participated in this study. All subjects were right-handed. None of the participants received psychotropic medication, had any contraindications for MRI, suffered from alcohol or drug dependence, had a history of a neurological diagnosis or psychotic disorder. Psychopathology in SZ-offspring and controls was operationalized as current and past (lifetime) DSM-IV axis I disorders, assessed by the Schedule for Affective Disorders and Schizophrenia for School Age Children Present and Lifetime Version (K-SADS-PL). Children and their parents were interviewed separately. None of the healthy controls had an affected first degree relative. DSM-IV axis I disorders and age of onset of parents in the SZ offspring group were ascertained during in-person interviews by the Structured Clinical Interview for DSM-IV Axis I Disorders (First, 1997) and further confirmed by the treating psychiatrist. Control parents were screened for psychiatric disorders by the MINI-SCAN (Nienhuis et al., 2010), prior to participation.

Head motion parameters were investigated to ensure there were no differences in motion between the groups and that the maximum motion did not exceed predefined thresholds (scan-to-scan: >3 mm) (Van Dijk et al., 2012).

Participants received monetary compensation for participation. Written informed consent was obtained from both parents or caregivers and offspring older than 12 years of age. The ethics committee of the University Medical Center of Utrecht approved this study.

2.2. Monetary incentive delay task

Participants performed a modified reward task (Fig. 1) based on the Monetary Incentive Delay task. This task has been extensively described elsewhere (de Leeuw et al., 2014; Figuee et al., 2011, 2013; Hoogendam et al., 2013; van Hell et al., 2010). Trials were potentially rewarding (30 trials) or non-rewarding (30 trials), as indicated by a cue (smiling or neutral face, respectively) at the start of the trial. Following this cue and a fixation star, the target (exclamation mark) was presented. Participants were instructed to respond as fast as possible to the target by pressing a button, irrespective of cue type. Subjects could win €0.50 in a potentially rewarding trial when they responded within the time limit (duration of the target being presented on the screen). Subsequent feedback notified participants of their performance, indicating if they had earned money on that trial, as well as their cumulative total at that moment. Participants were informed that they would receive the total amount of reward (about €7.50) of the actual experiment in addition to the standard compensation for participation.

Target duration was individually adjusted to ensure that each participant could succeed in 50% of the trials. This adjustment was based on twenty practice trials, presented prior to the start of the experiment. From these practice data, the shortest reaction time to the target was used as individual response limit. In 50% of the trials, the target was presented for the duration of the individual response limit plus 200 ms, enabling participants to be successful. In the other trials, the response limit was decreased with 150 ms, making it virtually impossible to respond in time.

The task was designed in such a way that maximum statistical power concerning the fMRI analyses could be reached in a relatively short time period: only one level of reward was used (i.e. one amount of money) and there were no loss trials. Collinearity between the factors coding for anticipation (i.e. time between presentation of the cue and presentation of the target) and feedback was minimized by varying the duration of the anticipation time randomly (mean duration 3286 ms, range 779–6729 ms) and the inter-trial interval (mean duration 3535 ms, range 1029–6979 ms). In this way, the blood-oxygen level-dependent (BOLD) signal in response to reward anticipation could be modeled independently from that to reward outcome (Figuee et al., 2011; Hoogendam et al., 2013; van Hell et al., 2010). The actual task consisted of 60 trials with a mean duration of 9571 ms (range 4946–16,107 ms), resulting in a total task duration of 9 m 35 s.

2.3. Functional magnetic resonance imaging

2.3.1. Measurements

All imaging was performed on a Philips 3.0-T Achieva whole-body MRI scanner (Philips Medical Systems, Best, The Netherlands). Functional images were obtained using a two dimensional echo planar imaging–sensitivity encoding (EPI–SENSE) sequence with the following parameters: voxel size 4 mm isotropic; repetition time (TR) = 1600 msec; echo time (TE) = 23 msec; flip angle = 72.5° ; 30-slice volume; SENSE-factor R = 2.4 (anterior–posterior). Three hundred twenty functional images were acquired during the task. In addition, a whole-brain three-dimensional fast field echo T1-weighted structural image was acquired for within-subject registration purpose. Scan parameters: voxel size 1 mm isotropic; TR = 25 msec; TE = 2.4 msec; flip angle = 30° ; 150 slices.

2.3.2. Image preprocessing

Image preprocessing and analyses were carried out with SPM5 (<http://www.fil.ion.ucl.ac.uk/spm>). After realignment, the structural scan was coregistered to the mean functional scan. Next, using unified segmentation, the structural scan was segmented, and normalization parameters were estimated. Subsequently, all scans were registered to a Montreal Neurological Institute T1-standard brain using these

Download English Version:

<https://daneshyari.com/en/article/10307897>

Download Persian Version:

<https://daneshyari.com/article/10307897>

[Daneshyari.com](https://daneshyari.com)