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Social functioning as vulnerability marker in adolescents at high risk for Bipolar Disorder.

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Abstract

Background: Bipolar disorder (BD) is associated with deficits in social behavior and social cognition. The disorder typically begins to manifest in early adolescence, but the early symptoms are clinically difficult to distinguish from behavior during normal adolescence. In this study, adolescents at high risk to develop BD are investigated using behavioural, neuropsychological, and functional brain measures of social functioning to identify early vulnerability factors for BD.

Methods: 47 offsprings of BD patients and 32 healthy controls (HC) aged between 10-16 years are included in this study. Social behaviour is measured using standardized ratings of the Social Responsiveness Scale and the 'Junior Nederlandse Persoonlijkheids Vragenlijst', social cognitive performance is measured by the ANT, and functional MRI data are acquired during an emotional rating task.

Results: Adolescents at high risk for BD displayed impaired social behaviour compared to HC. Their scores were still below cut-off for actual problems in social functioning. No difference between adolescents at high risk and HC in social cognitive functioning was found. Finally, adolescents at high risk showed hyperactivation in the amygdala and hypoactivation in the orbitofrontal cortex (OFC) during affective processing.

Conclusion: These results show that adolescents at high risk for developing BD already show deficits related to social functioning in a period essential for social development. The combination of behavioural, neuropsychological, and functional brain data may provide sensitive markers to identify vulnerability factors for the development of BD. These combined measures may guide novel treatments in adolescents geared towards preventing or minimizing the impact of BD.

Bridge

The current study is part of the BRIDGE study (Brain Imaging, Development & Genetics) at University Medical Centre Utrecht (UMCU). The purpose of the study is to identify how increased genetic risk for developing a psychotic disorder affects brain development by studying neurobiological and neuropsychological, clinical and environmental markers in off spring of patients with schizophrenia (SZ) and bipolar disorder (BD). The delineation of trait markers of vulnerability, or potential endophenotypes for psychiatric illnesses could facilitate (early) diagnosis and treatment.

Introduction

Bipolar disorder (BD) is a highly hereditable, affective disorder characterized by a dysfunction of mood, varying between states of euthymia, (hypo) mania and depression (Sadock & Sadock, 2007) (box 1). BD greatly impacts patients as well as the people surrounding them and is associated with deficits in social behavior, social cognition, and brain networks involved in affective processing (Goodwin & Jamison, 2007).

Different episodes in BD

(American Psychiatric Association, 1994)

Depression
A state of severe, persistent depression combined with anhedonia, lack of appetite, chronic fatigue and sleep problems.

Mania
A state of abnormally elevated or irritable mood, arousal, and/or energy levels.

Hypomania
A state comparable to mania, with less severe symptoms

Euthymia
A neutral state of normal, non-depressed, reasonably positive mood.

Box1. Different episodes in Bipolar disorder (American Psychiatric Association, 1994).

BD, like many other psychiatric illnesses, has its onset in early adolescence. That is not surprising, because in this period individuals undergo major developmental changes, making them vulnerable for genetic and environmental risk factors associated with psychiatric illness. To understand BD, we need to know how these risk factors impact the developing brain. Research therefore needs to focus on early adolescence. Offspring of BD may be the best group to study, because they are clearly at increased risk; about 10-15% will develop BD (Hillegers *et al.*, 2005). Studying children of parents with BD may provide insights in the elusive disease process, which can guide selective monitoring and early (pharmacological) interventions to minimize the potential impact of the disorder in adulthood.

Combining behavioural, neuropsychological, and brain data on social functioning will help identify vulnerability markers for BD. Indeed in 1991, Pennington proposed a model for the development of psychopathology by integrating behaviour, cognition and brain functions (Pennington, 1991).

First, the neuro-cognitive model of Pennington will be reviewed. Second, an overview of research in adult BD patients will be provided. Understanding the end stage of the illness development will help identifying relevant markers for studies in adolescents.

Model

Pennington (1991) proposed a model to describe the development of psychopathology (see figure 1), which is still valid. This neurocognitive model integrates etiology, brain mechanisms, cognition, and behaviour to make predictions about the path between genotype and behaviour (Rappin, 1987, Pennington, 2005).

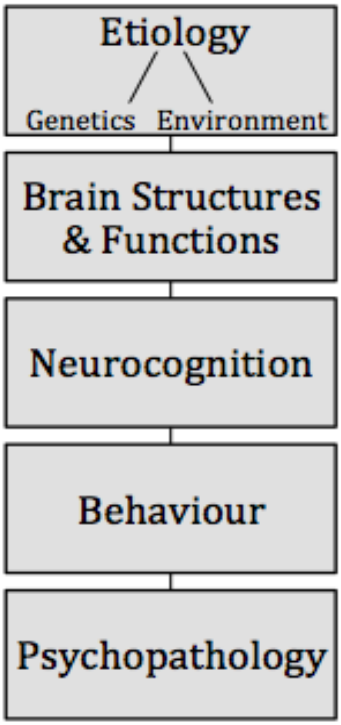

Figure 1. Neuro-cognitive model of psychopathology according to Pennington (2005).

The etiology of many psychiatric disorders involve both environmental and genetic factors which may impact brain development. According to the model, functional brain abnormalities can contribute to neurocognitive deficits. Subsequently these neurocognitive deficits affect behaviour, which can involve psychopathology. Pennington (2005) suggests that neuro-cognition has the potential to bridge the gap separating brain and behaviour. Considering each level of the model in a high risk population can clarify development of psychopathology by a top down approach.

BD is one of the most familial and heritable psychiatric illnesses. Children of BD patients have a tenfold increased risk to develop BD, and about 50% will be diagnosed with mood disorders (Hillegers *et al.,* 2005). Although genetic risk for BD is well established, early signs for later illness development in those at high risk remain poorly understood. In the current study children of patients with BD will be considered as the high risk population (HR). High risk research in adolescents has the unique potential to identify markers in individuals who are prone to or are in the process of developing BD (Correl *et al.,* 2007). The advantage of this specific offspring group is that there is no present medicine use or psychopathology. Therefore studying such a group can help to describe the way psychopathology develops in adolescents.

Social behaviour

Social behaviour refers to interaction between people. Problems in social behaviour are reported in BD patients; they show impairment in maternal and peer relationships as compared to a control group (Geller, Bolhofner, Craney, Williams & Del Bello, 2002). Research suggests that patients have trouble maintaining social relationships because of difficulties in social adjustment (Scott, 2006). According to Scott and colleagues (Scott, Stanton, Garland & Ferrier, 2000) BD patients show greater difficulties finding solutions to social problems and show higher levels of dysfunctional attitudes and sociotropy compared to controls. In youth with BD problems (psycho)social functioning are clearly reported (Goldstein *et al.,* 2009).

If deficits in social behaviour come to surface during adolescence it will be devastating in social development.

Bella and colleagues (Bella *et al.,* 2011) found that children of BD patients shows mildly impaired social function compared to control. Also, Cannon and colleagues (Cannon *et al.,* 1997) found an association between poor social functioning in adolescence and developing BD. Evenmore, research in premorbid functioning of adults with BD found that poor social functioning in adulthood is associated with developing BD (Cannon *et al*., 1997). Few studies examined social functioning in HR adolescents and findings are inconsistent. A causal factor in research indicates that impairments in social cognition may be a cause of poor social functioning.

Social Cognition

Social cognition refers to the perception, processing and interpretation of information related to social interaction (Brothers, 1990). An important social cognitive ability is emotion processing, which includes identifying and appraise emotions displayed by other people (Samamé, Matino & Strejilevich, 2012). Given the affective nature of BD, emotion processing has focus in many studies on BD. The ability to process affective cues impact how people cope with the social environment.

BD patients show deficits in identifying and discriminating facial emotion compared to controls (Kohler, Hoffman, Eastman, Healey & Moberg, 2011; Wessa & Linke, 2009). Studies have shown deficits in social cognition in youths with paediatric bipolar disorder and in euthymic patients (Samamé *et al*., 2012; McClure *et al.*,

2005). Also, first-degree relatives of BD patients show deficits in face emotion identification (Olsavsky *et al.,* 2012). Evenmore, Brotman and colleagues (Brotman *et al.,* 2012) found that children with a parent or sibling with BD, made more errors than control subjects when identifying emotion on child and adult faces. The importance of emotions in interpersonal communication has been confirmed in neuropsychological studies (Ross, 1981). Understanding affective information is crucial in recognizing and interpreting emotional and interpersonal cues of others in order to respond appropriate in social situations, which motivates to engage in social interactions with others (Constantino *et al.,* 2003).

Brain

Deficits in social cognition may be paralleled by functional brain abnormalities. Specifically, these abnormalities may be associated with dysfunctions in the affective network that is involved in the evaluation and modulation of emotions. This network is composed of prefrontal regions such as the orbitofrontal cortex (OFC) and temporal-limbic areas such as the amygdala (Van der Schot, Kahn, Ramsey, Nolen & Vink, 2010). Damage in the OFC results in disinhibited or social inappropriate behavior and emotional changes (Berlin, Rolls & Kischa, 2004). The amygdala plays a role in signaling the emotional salience of information to the rest of the brain in preparation for an appropriate response (LeDoux, 2000). Normally, the OFC control the activation in the amygdala. This frontal control develops from early adolescence until adulthood. In BD patients this development may not adequately develop because of etiological vulnerability.

A number of functional imaging studies in BD patients report subtle abnormalities in areas relevant for affective processing compared to healthy subjects (HC) (Yurgelun-Todd & Ross, 2006; Stuhrman, Suslow, & Dannlowski 2011; Beyer & Krishnan, 2002; Hajek, Carrey & Alda 2005). BD patients show hyperactivation across mood states in amygdala both at rest and during tasks compared to HC (Van Der Schot *et al.*, 2010; Blond *et al*., 2012; Townsend & Altshuler, 2012). Reduced activation in the OFC during emotional processing is reported consistently in adult BD patients (Blond *et al*., 2012) and paediatric BD (Kim *et al*., 2012). Furthermore, several studies report hypoactivation in the orbitofrontal cortex and hyperactivation in the left amygdala in those at familial risk (Whalley *et al.,* 2011; McDonald *et al.,* 2006). Compared to

healthy controls, Olsavsky and colleagues (Olavsky *et al.*, 2012) report amygdala hyperactivation during face emotion processing in adolescents at familial risk. Surprisingly, only few imaging studies have investigated these functional abnormalities of an affective network in adolescents at high risk for developing BD.

Current study

The current study will investigate adolescents at high risk to develop BD using behavioural, neuropsychological, and functional brain measures of social functioning to identify early vulnerability factors for BD. Based on existing literature it is hypothesized that compared to healthy controls, adolescents at high genetic risk to develop BD will; 1) have problems with social behaviour; 2) have social cognitive deficits compared to control subjects and 3) show dysfunction in the neural circuitry of affective processing specifically, amygdala hyper activation and orbito-frontal hypo activation. It is expected that measures on behaviour, cognition, and brain mechanisms and will be correlated; 4) adolescents at high risk show more problems in social functioning, deficits in affective face processing and dysfunctions in the affective brain network, compared to healthy controls.

To test the hypothesis, 47 offspring of BD patients and 32 healthy controls are included. To measure social behaviour two questionnaires are administered. Social cognitive performance is measured by an affective face-processing task. Also, to test brain functioning Functional magnetic imaging (fMRI) data is acquired during an emotional rating task.

Methods

Subjects

In the current study 47 adolescents at high risk for BD (HR) and 32 non-clinical controls (HC) with the age between 10-16 years participated. In 22 HRs and 30 HCs brain activity is measured with functional magnetic resonance imaging (fMRI). HR offspring participants are defined as having at least one parent with BD by means of the DSM-IV (American Psychiatric Association, 1994). The HC subjects meet the criteria that they do not have a history of psychiatric illness, by themselves or in their first-degree family members. All participants have no medical history and provide written informed consent (by child and parent). Additional criteria for MRI are the absence of psychotropic medication and absentia of ferrous objects in or around the body. Subjects were excluded when; not Dutch speaking, history of neurological illness, major medical history, history of epilepsy in first degree relatives, claustrophobia or having IQ lower than 70. All subjects were approached to follow the standard procedure, including the inventories and cognitive tasks described in the following sections. Adolescents who could not participate in the MRI parts of the study, were nevertheless included, also adolescents with not all data available were included. All subjects were included in accordance with the Bridge project of the DETACT-Policlinic from University Medical Centre Utrecht (UMCU). For recruitment of BD offspring outpatient departments, general practitioners and Dutch patients associations were approached. Control children were enrolled trough schools.

Measurements

Social behavior

To assess social behaviour both the child and a parent filled in questionnaires.

The Social responsiveness scale (SRS; Constantino and Gruber, 2005) assesses various dimensions of interpersonal behaviour and communication (Aldridge, Gibbs, Schmidhofer & Williams, 2012). Parents filled in this questionnaire. The SRS is a 65-item questionnaire that examines a child's ability to engage in emotionally appropriate reciprocal social interactions (Constantino *et al.,* 2003). Claims such as 'he or she is too tense in social situations' must be estimated on a 1 to 4 rating scale. Total scores were converted to scaled t-scores. Scores less than 59 were considered to be in the normal range, t-scores of 60-75 are suggestive of clinically significant social

impairment in the mild-moderate range, and t-scores of 76 or above indicate severe social impatient' (Aldridge *et al.*, 2012).

The social inadequacy scale (SIA), a specific subscale of the 'Junior Nederlandse Persoonlijkheids Vragenlijst', assessed social functioning reported by the child (NPV-J; Luteijn, van Dijk & Barelds, 2005). The items referred to avoiding social contacts or feeling unhappy in social contacts (Luteijn *et al.,* 2005). This subscale consisted of 13 claims, such as 'I only feel comfortable with people I know well' on a 0-2 scale. Raw scores from the SIA were compared to norm scores from 3194 healthy children. The standardized t-scores are rated on a 1-7 scale. Higher scores indicate the child is avoiding, or feeling unhappy in social contacts. The participant fills in this questionnaire.

Social cognition

In order to measure emotion processing of the subjects the Identification of Facial Emotions (IFE), a subtask of the Amsterdamse Neuropsychologische Taken (ANT; De Sonneville, 2000) is administered. Participants were instructed to indicate whether the target matches the specified emotion (angry, happy or sad, anxious). Parameters were mean reaction time (RT) and rating accuracy (specifically mean errors and mean missings).

Brain

Functional Magnetic resonance Imaging (fMRI) is performed with a Philips 3.0-T Achieva whole body MRI Scanner (Philips Medical Systems, Best, The Netherlands). During scanning, subjects perform an emotional rating task (ERT). The task consisted of the presentation of a set of 96 pictures from the international affective picture system (IAPS; Lang, Bradley & Cuthbert, 1997). According to validated ratings of the IAPS these pictures were divided into three conditions; neutral, positive, and negative. Each condition consisted of 32 pictures, and the content of the pictures in the three conditions were comparable (human figures, scenery, objects, and animals). Participants were instructed to view each picture and then rate the picture neutral, positive or negative by pressing a button (Van Buuren, Vink, Rapcencu & Kahn, 2011). Using a region of interest (roi) approach, the average activation level in the amygdala and OFC were obtained for both positive and negative pictures. Also,

behavioural data was analyzed; parameters are the rating accuracy of the subject (specifically the child's correct ratings compared to the established IAPS ratings) and mean RT of the correctly rated trials.

Statistical analyses

Data was analysed using Statistical Package for Social Science version 21 (SPSS, Inc., Armonk NY).

Social Behaviour

To measure for group differences on the SRS total scores were converted to a normalized total score. SRS normalized total scores in both the HR and the CS group were compared using a two samples t-test. Also, mean standardized SIA scores were compared using a two samples t-test between separate groups.

Cognition

To measure for group differences on performance, two repeated-measures analyses (GLM) were used to test between group differences in RT, and accuracy on the IFE task. Two repeated-measures analyses (GLM) with emotion (four levels; happy/anger/fear/sad) as within-subjects and group (HR,CS) as between-subject variable were performed for mean rating accuracy (errors and missings). A Similar analysis is performed for mean RT on the correctly rated trials of the ERT data. To compare rating performance on the ERT a GLM is performed. On this analysis emotion (two levels; positive/negative) is the within-subjects and group (HR, CS) is the between-subject variable for mean rating accuracy. A Similar analysis is performed for mean RT on the correctly rated trials of the ERT.

Brain

To measure group differences in activation, independent samples T-tests are performed for the amygdala and OFC (both bilateral), the chosen regions of interest (roi).

Correlation

To study the relation between the levels a bivariate two-tailed correlation is performed. The activation in the roi, ANT parameters, and scores on SRS and NPV-J were be compared.

Results

In the currents study we analysed the data of 47 adolescents at high risk for BD (HR) with mean age 13.2 (*SD*= 2.4) and 32 non-clinical controls (HC) with mean age 13.3 (*SD* = 2.1).

Behaviour

To test for the first hypothesis that children of parents with bipolar disorder (HR) have problems with social behaviour compared to matched controls (HC) a two samples t-test between separate groups is conducted for both inventories.

Social Responsiveness Scale (SRS)

Analysis of mean scaled total scores of the SRS revealed a significant difference between 39 HC and 31 HC (main effect of group: $T(1,68) = 3.14$, $p = 0.003$) with higher scores in HR than HC (fig. 2). Since data was not normally distributed non-parametric testing was required. An independent samples Mann-Whitney-U test confirmed rejecting the ($U = 486.00$, $Z(1,68) = -2.89$, $p = 0.001$).

Note, that according to Aldridge and colleagues (Aldridge *et al*., 2012) means scores of the HR group ($M = 53.14$, $SD = 9.46$) are in the normal range. Total t-scores of 76 or above indicate severe social impatient. In the total sample one subject (HR) met criteria for this cut-off. Thus, results implicated no social behavioral deficits in HR. Despite a lack of clinically significant impairment, HR adolescents had higher mean score compared to HC ($M = 46.04$, $SD = 9.35$), indicating more problems in social interactions.

Social Inadequacy Scale (SIA)

Analysis of mean standardized, total scores of SI, revealed no difference between 30 HR and 46 HC (main effect of group: $T(1,74) = 0.33$, $p = 0.739$) with higher scores in HR than HC. Results of self-reports showed no difference between HR and a HC in social inadequacy. Thus, HR adolescents did not experience more problems in their social life.

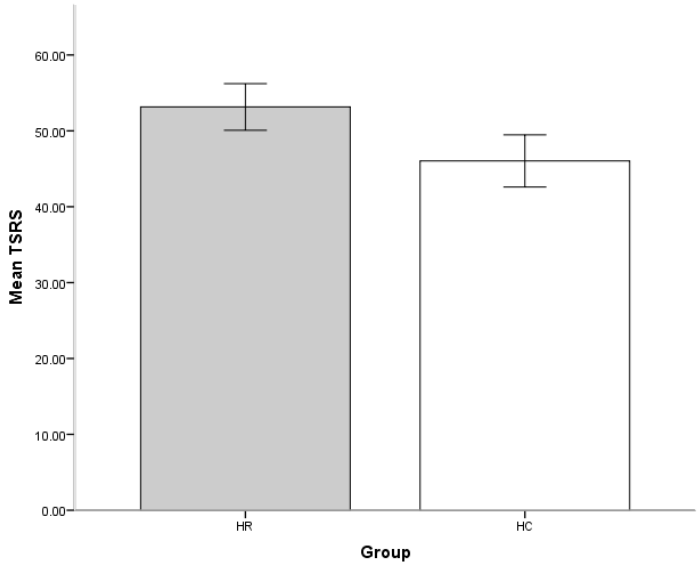

Figure 2. Bar chart of the mean Social Responsiveness Scale (SRS) scores for High risk group (HR) and health controls (HC). Error bars represent 95% confidence interval (CI).

Social cognition

To test the second hypothesis that HR adolescents will have social cognitive deficits compared to HC three repeated-measures analyses (GLM) were conducted.

Identification of Facial Emotions (IFE)

Repeated measure analysis of the reaction times (RT) on the IFE revealed no significant difference between groups of 37 HR and 24 HC (main effect of group: $F(2,61) = 2.61$, $p = 0.081$) or across emotion (interaction of group by emotion: $F(2,61) = 0.00$, $p = 0.996$) in accuracy. Suggesting equal performance for both groups. Also, the groups did not differ on accuracy. Analysis of mean errors revealed no difference between the groups (main effect of group $F(2,61) = 0.24$, $p = 0.788$) or emotions (interaction of group by emotion $F(2,61) = 0.09$, $p = 0.912$). The groups did not differ on mean missings (main effect of group $F(2,61) = 0.65$, $p = 0.425$) and emotions (interaction of group by emotion $F(2,61) = 0.38$, $p = 0.771$). Results showed no difference on performance in rating affective faces between HR and a HC.

Brain

To test for the third hypothesis that HR adolescents show dysfunction in the neural circuitry of affective processing specifically, amygdala hyper activation and orbito-frontal hypo activation compared to HC, independent samples T-tests are performed.

Analysis of the fMRI data revealed a significant difference between the HR (21) and HC (29) in the left amygdala (main effect of group: $F(1,49) = -2.295$, $p = 0.026$) in activation, with higher amygdala activation in HR compared to HC. A difference in mean activation between the groups found in the OFC (main effect of group: $F(1,49) = 2.394$, $p = 0.021$), with lower OFC activation in HR adolescents compared to HC. (fig. 3)

Emotional Rating Task (ERT)

Analysis of the performance data of the ERT revealed no significant difference between the HR (21) and HC (29) (main effect of group: $F(1,49) = 0.61$, $p = 0.44$) in accuracy for both the negative and positive pictures. Also, analysis of the reaction time revealed no significant difference between the groups (main effect of group: $F(1,49) = 3.46$, $p = 0.069$). A significant effect of emotion is found (interaction of group by emotion: $F(1,50) = 4.99$, $p = 0.030$).

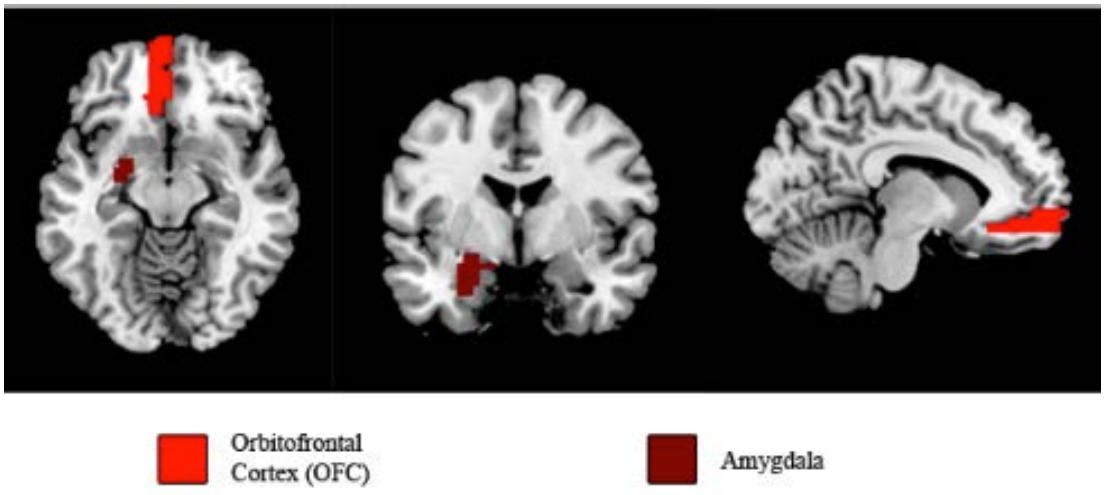

Figure 3. fMRI data revealed hyperactivation in the amygdala and hypoactivation in OFC during affective processing in adolescents at high risk compared to HC.

Correlation

For the fourth hypothesis that HR adolescents show more problems in social functioning, deficits in affective face processing and dysfunctions in the affective brain network, compared to HC, a bivariate two-tailed correlation is performed.

Here, only the participants with all data were available are included (N= 35, including 15 HR subjects and 20 HC). Analysis of a correlation between the activation in the roi, ANT parameters, and scores on SRS and NPV-J revealed no significance. No significant correlation was observed between SIA, SRS and scores on the IFE and ERT. Also, analysis revealed no significant difference between IFE, ERT and average activation in the roi.

Discussion

In this study behavioural, neuropsychological, and functional brain measures of social functioning in a high risk group of 47 adolescent offspring of patients with bipolar disorder (BD) and 32 matched healthy controls (HC) were investigated.

Measures of the adolescents' social behaviour revealed that parents reported more problems in those at high risk compared to HC. Self-reports showed no difference in social behaviour between adolescents at high risk and HC. No difference between adolescents at high risk and HC in social cognitive functioning is found. However, brain data revealed that compared to healthy controls, adolescents at high risk showed hyperactivation in the amygdala and hypoactivation in the orbitofrontal cortex (OFC). Group differences in social behaviour and affective processing suggest that social functioning can provide a sensitive marker in developing BD.

Behaviour

In this study a significant difference in parent ratings of their child's social behaviour between groups is found. These parent ratings suggest that adolescents at high risk showed more problems in social behaviour. However, these scores failed to reach the cut-off for significant problems in social functioning according to Aldridge and colleagues (Aldridge *et al.,* 2012). This suggests that adolescents at high risk were capable to engage appropriate in social interactions. Indeed scores on the social inadequacy scale confirmed that on average, adolescents experienced no problems in their social contacts. This finding fit with data from clinical practice that it is difficult to distinguish between normal adolescent behaviour and early signs of BD. Indeed, a twelve-year follow-up study of Hillegers and colleagues (Hillegers *et al.,* 2005) clinically evaluated offspring of BD patients and found no early signs of developing BD. They indicated unipolar depression as the first sign of development of BD. In our sample adolescents at high risk had higher scores on measurements of social functioning compared to HC, however scores did not represent any impairments in behavior. Our finding is inconsistent with a recent high risk study. Bella and colleagues (Bella *et al.,* 2009) report mildly impaired social functioning in adolescent offspring at high risk. In the current study only one subject had social impairment relevant on a clinical level. A longitudinal follow up study is needed to know if children of parents with BD will develop social behavior problems in late adolescence. Because adolescents are in a period essential in social development, we

expect that the difference between the groups will increase. Indeed, Reichart and collegues (Reichart *et al.,* 2005) found that after the age of 18 years those bipolar offspring with mild mood disorder developed impaired social functioning. In the currents study adolescents at high risk already drop out on social behaviour compared to HC, which makes them relatively vulnerable. Expected is that 15% of the adolescents at high risk will go on developing deficits in social behaviour and eventually BD (Hillegers *et al.,* 2005). Hence interventions and monitoring in development is needed to reduce the risk for long-term functional impairment in offspring.

It is also known that impaired social functioning is often related to environmental factors such as low family cohesion and high family conflict. This situation is typical for families with a parent diagnosed with BD (Du Rocher Schudlich, Youngstrom, Calabrese & Findling, 2009; Bella *et al*., 2009). Further research need to confirm if impaired social functioning is inherent on being at high genetic risk. Possibly, functional impairment is not inherently associated with being the offspring of a parent with BP, but emerges in the face of parental impairment.

Social cognition

In the current study, no significant difference in affective face processing between BD offspring and HC is found. Our findings suggested that both groups perform equally well. This is inconsistent with findings of impaired social cognition in (euthymic) patients (Kohler *et al.,* 2011; Wessa & Linke, 2009) and pediatric BD (Samamé *et al.,* 2012; McClure *et al*., 2005). Moreover, a study of Brotman and collegues (Brotman *et al.,* 2008) report face-labeling deficits in a high risk population, off spring and siblings from BD patients made more errors than control subjects when identifying emotion on child and adult faces. The equal performance on social cognition between both groups in the present study possibly is caused by a lack of sensitivity of the face-labeling task we used to measure social cognition. Next, as noted before, it is not expected that all high risk subjects will go on developing BD. The latter can explain that no developmental deviations in social cognition were found between the high risk group and the HC group. Also, in the current study subjects are in early adolescence. As such a long-term study is needed to find out if social cognition will impair during late adolescence.

Brain

Although no evident group difference in social cognition was found in this study, BD offspring showed different brain activity in the affective network during the rating of affective pictures. Hyperactivation in the amygdala and hypoactivation in the orbitofrontal cortex (OFC) are found in adolescents at high risk compared to HC. This is consistent with research in adult patients (Stuhrman *et al.*, 2011; Yurgelun-Todd & Ross, 2006) and paediatric BD (Kim *et al.*, 2012), showing abnormalities in both the amygdala (Townsend & Altshuler, 2012; Blond *et al.,* 2012) and OFC (Van Der Schot *et al.,* 2010). Whalley and colleagues (Whalley *et al.,* 2011) found increased activation in family members of bipolar disorder in the left amygdala versus comparison subjects. The current study replicates the finding of Olsavsky and colleagues (Olavsky *et al.,* 2012) that adolescents at familial risk for BD show amygdala hyperactivation in response to rating their fear of fearful faces. We extended this finding with evidence for OFC hypoactivation in adolescents at high risk. Our finding of OFC hypoactivation is not surprising, since both the amygdala and the OFC are part of the affective network involved in BD. Specifically, frontal regions control the activation in the subcortical regions. This control is thought to develop from early adolescence to adulthood. Studies in adult BD patients have consistently shown functional deficits in these regions during affective processing (Schot *et al.,* 2010). Deficits in brain activity in adolescents at high risk during affective processing suggest that this network develops inadequately. We expect that those adolescents who will develop BD fail to develop accurate frontal control from the OFC over the amygdala. The fact that in early adolescence frontal control is still lacking in all adolescents, makes it difficult to differentiate abnormal development from typical development trajectories. However, our results show that HR adolescents already show impairments during development of frontal control, which can be devastating in development of the affective network involved in emotion processing.

Correlation

In this study no correlation between measurements of social behaviour, social cognition and brain functioning is found. Thus, using Penningtons approach (2005), no top down relation between reported social functioning, affective face processing, and dysfunctions in the affective brain network is found. However, measurements of social functioning on levels of Penningons (1991) model revealed that adolescents at

high risk clearly are vulnerable, while in the high risk group subtle deviations in development are found in early adolescence on social behaviour and affective processing. Although clinically insignificant, parent rating suggests that adolescents show more problems in social behavior. Even more, functional deficits in affective brain network compared to healthy controls are found in adolescents at high risk. Note that deficits in social behaviour alone do not predict BD. However, when problems in social behaviour are combined with deficits in social cognition, a person is more vulnerable. Transition to BD is probably best predicted by a combination of functional, cognitive, and behavioral deficits in an additive manner. Indeed, not all adolescents included in the high risk group will develop psychopathology. Possibly, combining the levels of Penningtons model in an additive manner can identify those adolescents who are at the highest risk. It is to be expected that those adolescents who show combined deficits in social behaviour, social cognition and brain functioning in the affective networks will actually go on to develop BD. These adolescents may benefit the most from early intervention treatments.

It should be noted that the present study has limitations. First, sample sizes were relatively small, especially to analyze the correlations. Second, the identification of facial emotions (IFE) task used to measure processing of affective faces could be lacking sensitivity to detect subtle differences in social cognition in adolescents. Future follow up studies need to confirm the predictive value of affective processing (brain and cognition) and related social dysfunction. Also, longitudinal follow-up data need to confirm if differences between adolescents at high risk and HC will increase over time.

In this study we investigated affective processing (brain and cognition) and related social dysfunction as possible vulnerability marker for developing BD. We found that parents reported more problems in social functioning in the high risk group. Also, adolescents at high risk showed functional deficits in the affective brain network compared to HC. These findings suggest that adolescents at high risk are vulnerable in their social development. It is important to stress that these dysfunctions are already apparent during adolescence, when the social neural circuits supporting emotion regulation are not yet matured. Early detection and intervention during development can prevent irreversible impairments. Research of innovative

interventions could be directed toward early detection of social dysfunctions before onset.

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