Title

Vulnerabilities in sequencing and task switching in healthy youth offspring of parents with mood disorders.

Journal

Journal of Clinical and Experimental Neuropsychology, 40(6)

Authors

Singh, Manpreet

Leslie, Sara

Bhattacharjee, Kalpa

et al.

Publication Date

2018-08-01

DOI

10.1080/13803395.2017.1401597

Peer reviewed

HHS Public Access

Author manuscript

J Clin Exp Neuropsychol. Author manuscript; available in PMC 2019 August 01.

Published in final edited form as:

J Clin Exp Neuropsychol. 2018 August ; 40(6): 606–618. doi:10.1080/13803395.2017.1401597.

Vulnerabilities in Sequencing and Task Switching in Healthy Youth Offspring of Parents with Mood Disorders

Manpreet K. Singh, M.D. M.S., **Sara M. Leslie, B.A.**, **Kalpa Bhattacharjee, M.A.**, **Melina Gross**, **Elizabeth F. Weisman, B.A.**, **Laila M. Soudi, M.S.**, **Owen R. Phillips, Ph.D.**, and **Alexander Onopa, M.S.**

Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA

Abstract

Introduction: Visuospatial processing and task switching are impaired in individuals with mood disorders. It is unknown whether early deficits are present before the onset of a mood disorder or related to risk for a specific type of mood disorder. To answer these questions, we aimed to compare cognitive and neural assessments of visual attention and task-switching during sequencing among never-disordered youth with parental family histories of bipolar (BD) and major depressive disorders (MDD) and healthy controls with no personal or family history of psychopathology.

Methods.—8–17 year old youth of parents with BD (N=31, “BD risk”), youth of parents with MDD (N=49, “MDD risk”), and demographically similar HC (N=31, “HC”) were examined using the Delis-Kaplan Executive Functioning System Trail Making Test. Seed-based resting-state functional connectivity (RSFC) was collected from a subset of 88 participants (25 BD risk, 37 MDD risk, 26 HC) to investigate group differences in RSFC related to visuospatial processing.

Results.—BD risk and MDD risk offspring showed impairments in sequencing and task-switching, demonstrated by reduced scores on visual scanning ($F(2, 108) = 4.12$, $p=0.02$), number sequencing ($F(2, 88) = 4.75$, $p=0.01$), letter sequencing ($F(2, 108) = 4.24$, $p=0.02$), and set shifting performance on number-letter sequencing ($F(2, 108) = 4.66$, $p=0.01$) compared to scores in healthy controls. RSFC between the posterior cingulate (PCC) and clusters in the subcallosal cortex, amygdala, and hippocampus, significantly differed among HC, BD risk, and MDD risk groups. PCC-subcallosal/limbic RSFC was positively coupled in the MDD risk and BD risk groups. and negatively coupled in the HC group.

Conclusions.—Youth at familial risk for mood disorders demonstrate visuospatial deficits early in the processing stream. Improved methods for identifying at-risk children with the earliest possible neurocognitive impairments may inform neurocognitive remediation strategies that could prevent the onset of mood disorders.

Correspondence to: Manpreet Kaur Singh, M.D. M.S., Stanford University School of Medicine, Division of Child and Adolescent Psychiatry, 401 Quarry Road, Stanford, CA 94305-5719 (mksingh@stanford.edu; Phone: (650) 725-5922; Fax: (650) 724-7389).

CONFLICTS OF INTEREST

Dr. Singh receives research support from Stanford’s Child Health Research Institute, National Institute of Mental Health, Office of Research on Women’s Health, National Institute of Aging, Neuronetics, Johnson and Johnson, and the Brain and Behavior Foundation. She has been on the advisory board for Sunovion. No other authors report any conflicts of interest.

Keywords

Bipolar Disorder; Major Depressive Disorder; task-switching; family risk; offspring; visuospatial processing; resting state

INTRODUCTION

Among the most widely reported correlates of resilience found within youth include intelligence, self-regulation, problem-solving skills, and achievement motivation (Rutter, 2013). All of these qualities encompass executive functions necessary for concentrating, thinking, decision-making, and inhibiting impulses. A core executive function is task-switching, or the ability to switch between different rules, concepts, or strategies in response to changes in task demands or in the environment (Diamond, 2013). Task-switching has two dissociable components: rule-based processing and visuospatial processing, which includes visual attention and sequencing (Ravizza & Carter, 2008). Deficits in visuospatial processing and task-switching can manifest as downstream impairments in problem-solving, multitasking, goal completion, or planning. Early identification of these cognitive deficits among children may promote more resilient outcomes through building competencies in executive functions that are malleable early in brain development (Greenberg, 2006).

Mood disorders in children, including Bipolar Disorder (BD) and Major Depressive Disorder (MDD), are frequently associated with deficits in visuospatial processing (Dickstein et al., 2004; Favre et al., 2009; Franklin et al., 2010; Pardo, Pardo, Humes, & I Posner, 2006; Pavuluri, West, Hill, Jindal, & Sweeney, 2009) and in task-switching (Dickstein et al., 2007, 2016; Evans, Kouros, Samanez-Larkin, & Garber, 2016; Han et al., 2016). In fact, deficits in these executive function domains predict subsequent onset of affective illness in healthy but high-risk individuals (Vinberg, Miskowiak, & Kessing, 2013). Downstream deficits in task-switching have been described in individuals with BD regardless of age, gender, or overall cognitive ability, and appear to persist across the transition from childhood to young adulthood (Wegbreit et al., 2016). In contrast, there is a lack of consensus about whether task-switching deficits are present or absent among youth with MDD (Vilgis, Silk, & Vance, 2015). Disagreements come from several methodological challenges in the extant literature, including how these executive functions are defined, variable sample selection and inclusion criteria, diagnostic status (current versus past MDD), comorbidities, and medication status. Importantly, deficits in executive function appear to linger even after mood symptom improvement among youth after antidepressant treatment. This finding highlights the importance of understanding the temporal relation between mood symptoms and cognitive deficits over the course of development and treatment (Shehab, Brent, & Maalouf, 2016).

High-risk studies provide an opportunity to understand the temporal relation between mood symptoms and deficits in visuospatial processing and task-switching that may relate to the development of major mood disorders. Offspring of parents with BD and MDD are at high risk for developing mood disorders themselves, and have been characterized by impairments in task-switching, attention, motor inhibition, and processing speed (Klimes-Dougan,

Ronsaville, Wiggs, & Martinez, 2006a; Micco et al., 2009; Patino et al., 2013; Singh, DelBello, Fleck, Shear, & Strakowski, 2009). However, most high-risk studies were conducted in already symptomatic youth offspring with a variety of mood and other psychiatric disorders, including attention deficit with hyperactivity (ADHD) and anxiety (Klimes-Dougan et al., 2006a; Singh et al., 2009), and have controlled for such symptoms in their analyses (Klimes-Dougan, Ronsaville, Wiggs, & Martinez, 2006b). Moreover, other studies have shown no evidence that task-switching is a trait vulnerability in high-risk offspring (Micco et al., 2009; Wagner, Abramson, & Alloy, 2015). This makes it challenging to definitively know whether related neurocognitive deficits are early trait features that *precede* the onset of BD or MDD. It is also unclear whether impairments in task-switching are selective vulnerability markers for BD, for MDD, or for both of these mood disorders. Importantly, although BD and MDD may be clinically indistinguishable during the depressive phase of illness, they have distinct interventions and long-term trajectories (Singh, Ketter, & Chang, 2014). Few measures have been found to reliably differentiate BD from MDD among youth, which has often led to misdiagnosis and ineffective treatments that, in some cases, accelerate the onset and progression of these mood disorders. Identifying distinct antecedent pathways to developing BD versus MDD could mitigate consequences from misdiagnosis and incorrect or delayed treatment.

Finally, the neural basis of visuospatial processing deficits associated with risk for mood disorders has not been extensively described. Resting-state functional connectivity uses functional magnetic resonance imaging to provide information about functionally interconnected brain regions which display synchronized activity during undirected or internally-directed states, and which tend to deactivate during performance of externally-directed or goal-oriented tasks such as visuospatial processing and task-switching.

The occipital cortex and related visual processing networks have been implicated in the expression and processing of emotions (Vanlessen, De Raedt, Koster, & Pourtois, 2016). Importantly, recent data suggest that a risk for depression may be related to deficits in top-down motivated attention, that may be localized to the occipitotemporal, posterior cingulate (PCC), and inferior temporal cortices (Kayser et al., 2017). Aberrant PCC activation during visuospatial processing has also been reported in pediatric BD (Chang et al., 2004). Indeed, the PCC is a key node of the default mode network and extensively connected with other cortical and subcortical structures. Given its prominent role in both visuospatial processing (Chen, Weidner, Vossel, Weiss, & Fink, 2012; Kravitz, Saleem, Baker, & Mishkin, 2011) and the default-mode network in the context of depression (Renner et al., 2017), connectivity of the PCC may be a useful neurobiological target for therapeutic intervention.

Few prior studies have examined or compared visuospatial processing and task-switching in youth at familial risk for BD and MDD *before* the onset of these disorders. Moreover, to our knowledge, no prior study has determined whether impairment in task-switching is selectively associated with a risk for BD versus a risk for MDD among healthy but at-risk youth. To examine these questions, we used the Delis Kaplan Executive Functioning System (Delis, Kaplan, & Kramer, 2001) Trail Making Test and resting state functional connectivity to assess cognitive and neural evidence of sequencing and task-switching in never-disordered offspring of parents with either BD or MDD and comparison youth without any

personal or family history of psychopathology (HC). The three never-disordered groups of youth were neurotypical, did not present with any co-occurring psychiatric conditions, and were treatment naïve. We aimed to distinguish these differentially at risk groups by assessing them on their visuospatial sequencing and task-switching performance, early symptom profiles, overall global functioning, and brain-based functional connectivity measures. Based on limited prior research, we hypothesized that youth at risk for BD and MDD would show impaired performance in visuospatial processing and during task-switching compared to HC youth, as demonstrated by slower completion time while switching conditions on the Trail Making Test. We also hypothesized that BD risk and MDD risk youth would show impaired PCC-related functional connectivity compared to HC, and that these differences would relate to impaired Trail Making Test performance.

METHODS

Participants

111 children between the ages of 8 and 17 years took part in this study. Healthy youth of parents with bipolar I disorder (“BD risk,” n=31) and major depressive disorder (“MDD risk,” n=49) were recruited from an academic pediatric mood disorders program and from the community for this IRB approved study. Youth offspring were excluded for concomitant medical (e.g. seizures, prolonged loss of consciousness, other neurological conditions) and psychiatric conditions, history of learning disabilities, or contraindications for MRI (e.g. metallic implants due to concurrent MRI studies). Healthy control subjects were excluded for these reasons or if they had any current or past Axis I psychiatric diagnoses or any family history of psychopathology. Healthy control children with comparable age, Tanner stage, race, sex, socioeconomic status and handedness were recruited for study participation from community advertisements and local schools (“HC” N=31). Written informed consent and assent were obtained from parents and youth, respectively, prior to study participation.

Assessment of Psychiatric Health

Youth participants in all three groups were ruled out for any current or lifetime psychiatric disorders, using the semi-structured Washington University in St. Louis Kiddie Schedule for Affective Disorders and Schizophrenia (WASH-U KSADS) (Geller et al., 2001) and the Kiddie–Schedule for Affective Disorders and Schizophrenia Present and Lifetime version (KSADS-PL) (Kaufman et al., 1997) diagnostic interviews for assessment of mood and other psychiatric disorders. The WASH-U KSADS was administered to currently euthymic parents about their children and separately to children about themselves.

Parental diagnosis of Bipolar I Disorder, Bipolar II Disorder, or Major Depressive Disorder was determined by the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) (First, 1997) during which a documented clinical history was reported by parents in the BD or MDD groups. The SCID was used to rule out psychopathology in both parents in the healthy control group. The Family History Research Diagnostic Criteria assessed first- or second-degree relatives for psychopathology in all three groups (Andreasen, Endicott, Spitzer, & Winokur, 1977).

To assess the presence of any early symptom levels of mania or depressive mood symptoms in the absence of any psychiatric diagnoses, youth from all groups were interviewed using the Young Mania Rating Scale (YMRS) (Young, Biggs, Ziegler, & Meyer, 1978) and the Children's Depressive Rating Scale-Revised (CDRS-R) (Poznanski et al., 1984). Global functioning (current and most severe past) was determined by the Children's Global Assessment Scale (CGAS) (Shaffer et al., 1983). Finally, age, sex, race, socioeconomic status (Hollingshead Four Factor Index) (Cirino et al., 2002), pubertal stage (Pubertal Development Scale) (Carskadon & Acebo, 1993), and handedness (Edinburgh Handedness Inventory) (Oldfield, 1971) were also assessed.

Cognitive Assessment

IQ was assessed using the Wechsler Abbreviated Scale of Intelligence (WASI) (Psychological Corporation., 1999). By measuring cognitive abilities through block design, vocabulary testing, matrix reasoning, and similarities, the WASI captured multiple aspects of intellectual capacity in study participants.

We used the Delis-Kaplan Executive Functioning System (DKEFS) Trail Making Test (Trails A and Trails B). The D-KEFS Trail Making Test, which consists of a visual cancellation task and a series of connect-the-circle tasks to assess task-switching during this visual-motor sequencing task. The five conditions of the DKEFS Trail Making Test include visual scanning (condition 1), number sequencing (condition 2), letter sequencing (condition 3), number-letter switching (condition 4), and motor speed (condition 5). The condition 4 scaled scores, which measured the scaled (controlling for age) (Delis et al., 2001) time taken to complete the letter/number-switching task, were of interest to investigate task-switching performance. This switching task combines the cognitive tasks of number sequencing, letter sequencing, and the processing speed required to flexibly switch from sequencing letters to sequencing numbers. We were also interested in the contrast scores for condition 4, which measured the capacity to switch between numbers and letters while controlling for processing speed and visual tracking ability. This contrast 4 score was calculated by subtracting the mean of scaled scores for condition 2 plus scaled scores for condition 3 from scaled scores from condition 4 to isolate the effect of switching from the mean of letter and number sequencing (C4 contrast score = C4 scaled -[scaled C2+C3]) (Delis et al., 2001).

Neuroimaging Data Acquisition

Participants were first familiarized with the scanning environment in an MRI simulator before whole-brain images were acquired on a 3T GE Signa Excite (General Electric Co., Milwaukee, WI) scanner equipped with an 8-channel head coil. Functional images were collected at rest using a spiral pulse sequence with the following parameters: repetition time (TR) = 2000 ms, echo time (TE) = 30 ms, flip angle (FA) = 80°, field of view (FOV) = 22 cm, number of slices = 30 slices in the axial plane, and slice thickness = 4 mm with a gap of 1 mm. High-order shimming was used before acquisition of resting-state data to improve field homogeneity. To allow for stabilization of longitudinal magnetization, the first four volumes of each participant's resting-state scan were discarded at the scanner. High-resolution structural images, used to assist in the registration of functional data to standard space, were collected using fast spoiled gradient recalled (3D FSPGR) pulse sequence with

the following parameters: TR = 8.2 ms (TR = 8.5), TE = 3.24 ms (TE = 3.4), TI = 400 ms, flip angle = 15°, field of view(x) = 22cm, matrix of 256 × 256, 124 slices in the coronal plane, and a slice thickness of 1.5 mm. For 25 participants, structural images were collected with an updated protocol using a fast spoiled gradient recalled (3D FSPGR) pulse sequence with the following parameters: TR = 8.5 ms, TE = 3.32 ms, TI = 400 ms, flip angle = 15°, field of view(x) = 25.6 cm, matrix of 256 × 256, 186 slices in the axial plane, and a slice thickness of 1 mm. The distribution of structural scan acquisitions did not differ between groups, as indicated by a Kruskal-Wallis test ($\chi 2(2) = 3.054$, $p = 0.217$).

Functional MRI Preprocessing

Of the 111 youth across all three groups characterized on TRAILS performance, 88 youth had usable resting state functional data available for analysis. Pre-processing of resting-state data was carried out using FEAT Version 6.00 within FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). Each participant's 210-volume functional dataset was realigned to compensate for small head movements using MCFLIRT (Jenkinson, Bannister, Brady, & Smith, 2002), skull-stripped using BET (Smith, 2002); spatially smoothed using a Gaussian kernel of 5mm FWHM, intensity normalized by a single multiplicative factor, and band-pass filtered to correct for baseline drift and high frequency noise (high-pass temporal filter: Gaussian-weighted least-squares straight line fitting, with sigma=50.0s; low-pass temporal filter: Gaussian with sigma=2.8s). Functional images were registered to participants' corresponding high-resolution T1-weighted structural images and then normalized to Montreal Neurological Institute (MNI) space using a 12-parameter transformation. Masks of white matter and cerebrospinal fluid (CSF) generated from each subject's anatomical images were applied to the functional data to extract white matter and CSF time-series. These timeseries were used together with 6 motion parameters as nuisance regressors in a voxel-wise regression of the fMRI data. Data scrubbing was additionally performed following the method of Power and colleagues(Power, Barnes, Snyder, Schlaggar, & Petersen, 2013), excluding any volume in which either the value for DVARS (the root mean squared change in BOLD signal from the prior volume) or the value for framewise displacement exceeded the upper boxplot threshold (the 75th percentile plus 1.5 times the interquartile range), along with the previous volume and the 2 following volumes. Participants were only included in further analyses if less than 33% of the volumes were removed. The number of censored volumes was not significantly different among groups as indicated by Kruskel-Wallis H ($\chi 2(2) = 2.753$, $p = 0.252$) and median tests ($\chi 2(2) = 0.502$, $p = 0.778$).

Functional Connectivity Analysis

A seed-based, whole-brain approach was used to examine RSFC with the bilateral posterior cingulate cortex (PCC). The PCC was selected as a seed due to its involvement in visuospatial and attentional processes. Probabilistic maps from the Harvard-Oxford Subcortical Structural Atlas (http://www.cma.mgh.harvard.edu) were used to define anatomically based ROIs of the PCC, incorporating voxels that had 25% or greater probability of being labeled as posterior cingulate cortex (left: 11,488 mm3, right: 11,112 mm3). PCC ROIs were registered to the preprocessed fMRI data, and the mean time series of voxels in these regions were extracted and used as a primary regressor in a GLM analysis

of all other voxel time series, resulting in whole-brain PCC resting state functional connectivity (RSFC) maps.

Group differences in resting-state functional connectivity were determined using a voxel-wise F-test that covaried for age and sex. Resulting statistical maps were thresholded using a height threshold of $z > 2.0$ and an extent threshold of $p < 0.05$, corrected using Gaussian random field theory. To clarify the group differences in the significant cluster resulting from the voxel-wise omnibus test, parameter estimates (proportional to fMRI signal change) of BOLD signal response were extracted for every participant using featquery (fsl.fmrib.ox.ac.uk/fsl/fsl4.0/feat5/featquery.html). Parameter estimates from the emergent cluster were fed into a univariate GLM in SPSS (v.22; www.ibm.com/analytics/us/en/technology/spss/) that modeled the parameter estimate as the dependent variable and age, sex and group as independent variables. Planned pairwise comparisons identified which groups drove significance in the omnibus test.

Data Analysis

All analyses were conducted in R and SPSS v.22. We examined the QQ plots of all variables to assess normality of data distributions. Analysis of variance (ANOVA) and chi-squared tests were used to screen for possible confounding differences in group demographics. IQ and age-scaled TRAILS scores of healthy and at-risk groups were compared using ANOVA. Since there are no studies examining TRAILS performance in *healthy* youth at risk for BD in comparison with MDD-risk and control groups, and because we have a priori hypotheses, the main findings of this study with relatively a small sample size are presented without controlling for multiple comparisons. We used correlation testing to explore the relations between TRAILS performance and early clinical signs of mood symptom severity and impairments in global functioning.

To examine whether RSFC patterns were related to clinical and cognitive variables, we conducted exploratory correlation analyses using the parameter estimates extracted from regions that showed a significant main effect of group in our voxel-wise F test. Partial correlation analyses were used to investigate the relationship between RSFC parameter estimates and Trail Making Test scaled scores (age-normed), controlling for sex. Correlations between RSFC parameter estimates and scores on the CDRS-R and YMRS were assessed using Spearman correlation coefficients, to accommodate the data skew towards health among these clinical scales.

RESULTS

Participant Characteristics

Of the 111 participants in this study between the ages of 8 and 17, 57 females and 53 males were divided across three groups of 31 BD risk offspring, 49 MDD risk offspring, and 31 HC offspring. There were no significant group differences in age ($F(2, 107) = 2.32$, $p = 0.11$), gender (X^2 (1, N=111) = 1.80, $p = 0.41$), race (X^2 (2, N=108) = 2.7, $p = 0.26$), or socioeconomic status ($F(2, 89) = 0.70$, $p = 0.50$). Similarly, there were no significant

differences in IQ ($F(2, 105) = 2.14$, $p = 0.12$) or handedness (X^2 (2, N=109) = 3.97, $p = 0.14$) among groups.

Although risk offspring were undiagnosed for any psychiatric disorders, they had subclinical but significantly higher levels of depression symptom severity scores ($F(2, 95) = 4.19$, $p = 0.02$) and mania symptom severity scores ($F(2, 100) = 2.96$, $p = 0.05$) than HC offspring. Risk offspring also demonstrated significantly lower levels of current ($F(2, 97) = 17.3$, $p < 0.001$), and most severe past ($F(2, 96) = 5.18$, $p = 0.007$) global functioning. See table 1 for participant demographic and clinical characteristics.

Neurocognitive Performance on the Trail Making Test

BD risk and MDD risk youth showed reductions compared to HC offspring in performance during visual scanning (condition 1), number sequencing (condition 2), letter sequencing (condition 3), and number-letter switching (condition 4), suggesting impairments in visuospatial processing among risk offspring (Figure 1). Specifically, performance on number-letter task switching (condition 4), operationalized by the C4 scaled score, was significantly different across the three groups ($F(2, 108) = 4.66$, $p = 0.01$). Post-hoc t-tests revealed that performance for BD risk ($M = 9.42$, $SD = 3.05$) and MDD risk ($M = 9.32$, $SD = 3.24$) offspring did not differ significantly from each other, but were both significantly lower than performance in HC offspring ($M = 11.23$, $SD = 1.98$). In addition, BD risk and MDD risk youth also showed reductions compared to HC offspring in performance during conditions 1, 2, and 3, suggesting impairments in visuospatial processing. No significant group differences were seen in motor speed (condition 5) (p=0.47) or in the C4 contrast score (p=0.75) (Table 2).

Early Clinical and Functional Correlates of TRAILS Performance

While all scaled TRAILS condition scores were not significantly correlated with either depression or mania symptom scores (ps > 0.05), the C4 contrast score was found to be inversely correlated with mania symptom severity score using a nonparametric test to account for data skew toward health across all three groups, even after the removal of sub-threshold symptomatic outliers (Spearman's rho = −0.23, p = 0.02). There were no significant correlations between any of the other condition scores and depression symptom severity, mania symptom severity, or global functioning in any of the offspring groups (all ps>0.05).

Group Differences in RSFC

The initial F-test, corrected for multiple comparisons with a cluster threshold of z > 2.0 and p < 0.05, revealed significant group differences in connectivity between the posterior cingulate and a collective cluster comprised of the subcallosal cortex and extending into limbic regions including bilateral amygdala and hippocampus (774 voxels, peak MNI coordinates = 0/12/−10). Extracted connectivity estimates were analyzed using a general linear model in SPSS, including age and sex as covariates. Post-hoc decomposition of multifactor effects indicated that PCC-subcallosal/limbic connectivity differed between all three groups; discordant connectivity was observed in the HC group, while the BD-risk and

MDD-risk groups showed concordant connectivity which was relatively greater in the BD-risk group (Figure 2).

Exploratory RSFC Associations with TRAILS Performance and Early Symptom Variables

Across all participants, PCC-subcallosal/limbic RSFC estimates correlated significantly with scaled C3 scores (r=−0.252, p=0.018) and scaled C4 scores (r=−.235, p=0.029). However, no significant correlations between RSFC and scaled C3 or C4 scores were found within individual groups.

Across all participants, PCC-subcallosal/limbic RSFC estimates correlated significantly with CDRS-R scores (r=0.236, p=0.027); however, no correlations between CDRS-R and RSFC were seen within groups. No significant correlations were seen between RSFC and YMRS scores.

DISCUSSION

This study compared visuospatial processing, task-switching, and functional connectivity among healthy youth offspring of parents with BD and MDD to HC youth without any family history of psychopathology. Our results provided evidence that never-disordered youth with a familial risk for BD or MDD had significantly lower performance on visual scanning, number-sequencing, letter-sequencing, and number-letter switching than HC youth. Similarly, significant differences in PCC-subcallosal/limbic intrinsic connectivity patterns emerged between at-risk youth and healthy controls. However, there were no significant differences across groups in motor speed or in flexible number-letter switching after controlling for processing speed and visual tracking ability. Compared to HC offspring, BD risk and MDD risk offspring showed statistically significant but clinically insignificant increases in depression and mania symptom severity and decreases in global functioning. Poorer performance on number-letter switching may be associated with higher levels of mania symptom severity across all groups. Further, PCC-subcallosal/limbic connectivity was associated with poorer performance on letter sequencing and number-letter switching as well as higher levels of depression severity across all groups. However, due to the relative health of the sample, these relations merits replication with larger sample sizes with greater variation in mood symptom severity.

Our study adds new results to the extant literature, now in healthy offspring, that impaired visuospatial processing in individual conditions of the Trail Making Test may represent deficits that are present in individuals at familial risk for BD (Balanzá-Martínez et al., 2008; Bora, Yucel, & Pantelis, 2009; Glahn et al., 2010) and MDD (Clark, Sarna, & Goodwin, 2005; Papmeyer et al., 2015) preceding the onset of a mood disorder and are present early in the processing stream. Mood state-dependent (Katz et al., 1994) and mood state-independent (Pan, Hsieh, & Liu, 2011; Rive, Koeter, Veltman, Schene, & Ruhé, 2016) alterations or compensated visuospatial processing has been observed in individuals with MDD and BD but the results are inconclusive in high risk cohorts (Frantom, Allen, & Cross, 2008; McCormack et al., 2016; Rajajärvi et al., 2010), and may have been confounded by a failure to control for motor speed. Further, contrary to our prediction but consistent with prior studies in already symptomatic high risk offspring (Klimes-Dougan et al., 2006a; Micco et

al., 2009), healthy youth offspring at risk for BD and MDD did not differentiate from HC in cognitive flexibility during task-switching when taking into account the significant effects of visual tracking ability and motor speed. Together, these results suggests that the individual conditions in the Trail Making Test may be sensitive markers of vulnerability, but when taken together as a contrast score for flexible responding, they are rather insensitive to differentiate healthy youth with and without a risk for major mood disorders. Indeed, the ability to switch tasks is a multifactorial construct that evolves with development (Dick, 2014), which motivated our use of age-scaled condition scores in our analyses. However, it is possible that a prospective evaluation of reduced baseline visuospatial functioning in youth at risk for mood disorders over time might better elucidate the dynamics of this potential early impairment through development.

The PCC is an extensively connected node of the default mode network and highly involved in visuospatial processing (Kravitz et al., 2011). Leech and Sharp (2014) postulate that subregions of the PCC assist in regulating attention and are particularly involved in balancing external and internal cognition in response to changing information. Typically, default mode network (DMN) activity is decreased in response to external tasks. In a triple network model (Menon, 2011), stimuli corresponding with activation of the salience network engage cognitive control processes in the executive network that result in inhibition of the default mode network as attention is turned toward external task demands. Suppression of PCC activity has been association with the activation of cognitive control (Hayden, Smith, & Platt, 2010), while increased PCC activation during tasks has been associated with lapses in attention (Mason et al., 2007). Many studies have shown that the default mode is less inhibited by task demands in those with depression or other mood disorders, and that this lack of decreased DMN activity correlates with decreases in task performance.

The observed differences in intrinsic functional connectivity between the PCC and the subcallosal and limbic regions in MDD-risk, BD-risk, and HC participants suggest that PCC-subcallosal/limbic activation concordantly coupled in the risk groups and discordantly coupled in healthy controls. Difficulties suppressing DMN activity or hyperactivation of the subcallosal area may explain the differing pattern of activity seen in the risk groups. Reduced deactivation of the subcallosal area, and specifically the subgenual ACC (sgACC), has been observed in depressed patients both while engaged in cognitive tasks and at rest (Davey, Harrison, Yücel, & Allen, 2012). This pattern may reflect the failure of the executive, salience, and default networks to engage in regulatory processes required to direct cognitive resources toward external tasks. Connectivity between the sgACC and default mode network is thought by some researchers to reflect rumination processes (Berman et al., 2011; Hamilton, Farmer, Fogelman, & Gotlib, 2015); thus, increased concordance between PCC and subcallosal activity may represent a dysregulatory connection between internally-directed cognition and mood-related activation, and thus reduced adaptation to meeting the needs of external task demands. Our data support this relation, given the positive correlation between PCC-limbic connectivity and depression severity scores across all groups.

Although the coactivation of the PCC and subcallosal/limbic regions was observed during rest and not while youth were performing the TRAILS task, functional imaging studies have

found coactivation patterns during rest and task performance to correspond (Di, Gohel, Kim, & Biswal, 2013). Moreover, functional connectivity between the PCC and the subcallosal cingulate has been shown to be elevated in depressed subjects during both resting-state and while engaged in an emotion-processing task, with an increased connectivity relating to an earlier age of depression onset (Ho et al., 2015). Importantly, functional connectivity scores were not significantly predictive of TRAILS performance after accounting for risk status; however, the group-level connectivity differences suggest that at-risk subjects may have aberrant patterns of intrinsic connectivity in regions subserving visuospatial processing and attentional processes associated with the expression and regulation of mood.

The Trail Making Test may be an easy to administer initial screening procedure for neurocognitive impairment among at-risk youth ages 8 and older (Reitan & Wolfson, 2004). Although limited by small sample size, our results in a subsample of healthy but high-risk youth with emerging symptoms suggest that task-shifting may be sensitive to mania symptom severity. Thus, this test may have some utility in monitoring progression of mania symptoms (Schmid & Hammar, 2013). This potential clinical application warrants further prospective investigation with larger sample sizes, as associations between neurocognitive performance during task-shifting and mania (Chaves et al., 2011) or depression severity (Kyte, Goodyer, & Sahakian, 2005) are not always present among individuals who have already developed a mood disorder. This may be due to recovery of task-shifting or related skills between mood episodes. Nevertheless, as cognitive symptoms lag behind mood symptoms in improvement (Shehab et al., 2016), early identification and monitoring of these deficits during development or treatment may improve outcome and reduce health costs (Walker et al., 2015).

BD risk youth also showed nonsignificant trends for more severe relative symptom severities and lower overall global functioning compared to MDD risk and HC youth. However, symptom and functional severities that separate the risk groups from the healthy controls are statistically but not clinically significant, and may represent the earliest levels of symptoms that remain below threshold levels to meet criteria for diagnosis (either by time criteria or by severity). These early symptom severities at their worst are mild and represent “no more than slight impairment in functioning” or “good functioning.” Thus, granular differentiation between BD risk and MDD risk on TRAILS performance may not be achieved at the stage of an endophenotype because depressive phenotypes are common precursors or initial presentations for BD (Hafeman et al., 2016). Moreover, poorer task-shifting performance may represent a nonspecific marker of poor cognitive health rather than risk for mania. Additional work in staging mood disorders is needed to deepen our understanding of when or if visual attention or task-switching in BD risk and MDD risk diverge because it has the potential to inform treatment decisions (Noto et al., 2013). Nevertheless, our study provides the new insight that dysfunction in visual attention and task-switching may be an important preventative target for pediatric onset mania that could lead to more resilient mood outcomes that have been demonstrated in broader populations (Genet & Siemer, 2011; Hildebrandt, McCall, Engen, & Singer, 2016).

The findings of this study should be interpreted in the context of a few limitations. Our sample sizes were limited to understand the array of potential factors and interactions that

could be contributing to our results. Inclusive of these factors are IQ (Fine, Delis, & Holdnack, 2011), which although was not significantly different across groups, showed some trends for lower scores in the risk populations compared to healthy controls. A major strength of our pursuit of an early cognitive risk factor for mood disorders was to characterize BD risk and MDD risk offspring on visuospatial processing while they were relatively psychiatrically well. However, this challenged our ability to investigate beyond exploration the relations between TRAILS performance or other cognitive contributors to the earliest potential signs of clinical symptomatology that was limited in variability and skew toward health at the time of our assessment. In addition, we assessed task-switching cross-sectionally and were therefore not able to evaluate developmental continuity versus changes in cognitive performance on the Trail Making Test and its impact on the emergence of mood symptoms. Future studies using a prospective design and sampling multiple cognitive domains across various stages in the development of major mood disorders would advance our understanding of how impairments in task-switching and other cognitive domains could relate to the development of a major mood disorder (Chaves et al., 2011). Finally, BD risk and MDD risk youth also showed reductions compared to HC offspring in performance during number and letter sequencing, suggesting impairments across multiple cognitive domains. Using more focused assessments that isolate task-switching from other fundamental cognitive processes that potentially influence performance could delineate more precise links between clinical symptoms and underlying neurocognitive dysfunction in this domain.

CONCLUSIONS

Our findings indicate that even preceding the onset of any mood or other psychiatric symptoms, youth at familial risk for mood disorders may be at risk for impaired visuospatial processing and commensurate aberrant posterior cingulate-subcallosal/limbic connectivity compared to typically developing healthy controls with no family history of psychopathology. Further longitudinal studies are necessary to determine if these very early signs of neurocognitive dysfunction can predict the development and progression to chronic forms of mood disorders. Improved methods for identifying children with certain neurocognitive vulnerabilities, such as using the Trail Making Test as a simple screening tool in yet healthy youth at familial risk for mood disorders, may inform preventive and early cognitive remediation strategies prior mood symptom or disorder onset.

ACKNOWLEDGEMENTS

This work was supported by Stanford’s Child Health Research Institute and the National Institute of Mental Health (K23MH085919). We would like to express appreciation to our research participants and families and members of our Pediatric Emotion And Resilience Lab for their contributions to this work.

REFERENCES

Andreasen NC, Endicott J, Spitzer RL, & Winokur G (1977). The family history method using diagnostic criteria. Reliability and validity. Archives of General Psychiatry, 34, 1229–1235. [PubMed: 911222]

Balanzá-Martínez V, Rubio C, Selva-Vera G, Martinez-Aran A, Sánchez-Moreno J, Salazar-Fraile J, … abarés-Seisdedos R (2008). Neurocognitive endophenotypes (endophenocognitypes) from studies of

relatives of bipolar disorder subjects: a systematic review. Neuroscience and Biobehavioral Reviews, 32, 1426–1438. [PubMed: 18582942]

Berman MG, Peltier S, Nee DE, Kross E, Deldin PJ, & Jonides J (2011). Depression, rumination and the default network. Social Cognitive and Affective Neuroscience, 6, 548–555. [PubMed: 20855296]

Bora E, Yucel M, & Pantelis C (2009). Cognitive endophenotypes of bipolar disorder: a meta-analysis of neuropsychological deficits in euthymic patients and their first-degree relatives. Journal of Affective Disorders, 113, 1–20. [PubMed: 18684514]

Carskadon MA, & Acebo C (1993). A self-administered rating scale for pubertal development. The Journal of Adolescent Health: Official Publication of the Society for Adolescent Medicine, 14, 190–195. [PubMed: 8323929]

Chang K, Adleman NE, Dienes K, Simeonova DI, Menon V, & Reiss A (2004). Anomalous prefrontal-subcortical activation in familial pediatric bipolar disorder: a functional magnetic resonance imaging investigation. Archives of General Psychiatry, 61, 781–792. [PubMed: 15289277]

Chaves OC, Lombardo LE, Bearden CE, Woolsey MD, Martinez DM, Barrett JA, … Glahn DC (2011). Association of clinical symptoms and neurocognitive performance in bipolar disorder: a longitudinal study. Bipolar Disorders, 13, 118–123. [PubMed: 21320259]

Chen Q, Weidner R, Vossel S, Weiss PH, & Fink GR (2012). Neural mechanisms of attentional reorienting in three-dimensional space. The Journal of Neuroscience: The Official Journal of the Society for Neuroscience, 32, 13352–13362. [PubMed: 23015426]

Cirino PT, Chin CE, Sevcik RA, Wolf M, Lovett M, & Morris RD (2002). Measuring socioeconomic status: reliability and preliminary validity for different approaches. Assessment, 9, 145–155. [PubMed: 12066829]

Clark L, Sarna A, & Goodwin GM (2005). Impairment of executive function but not memory in first-degree relatives of patients with bipolar I disorder and in euthymic patients with unipolar depression. The American Journal of Psychiatry, 162, 1980–1982. [PubMed: 16199852]

Davey CG, Harrison BJ, Yücel M, & Allen NB (2012). Regionally specific alterations in functional connectivity of the anterior cingulate cortex in major depressive disorder. Psychological Medicine, 42, 2071–2081. [PubMed: 22954259]

Delis DE, Kaplan E, & Kramer JH (2001). Delis–Kaplan executive function system. San Antonio, TX: Psychological Corporation.

Di X, Gohel S, Kim EH, & Biswal BB (2013). Task vs. rest-different network configurations between the coactivation and the resting-state brain networks. Frontiers in Human Neuroscience, 7, 493. [PubMed: 24062654]

Diamond A (2013). Executive functions. Annual Review of Psychology, 64, 135–168.

Dick AS (2014). The development of cognitive flexibility beyond the preschool period: an investigation using a modified Flexible Item Selection Task. Journal of Experimental Child Psychology, 125, 13–34. [PubMed: 24814204]

Dickstein DP, Axelson D, Weissman AB, Yen S, Hunt JI, Goldstein BI, … Keller MB (2016). Cognitive flexibility and performance in children and adolescents with threshold and sub-threshold bipolar disorder. European Child & Adolescent Psychiatry, 25, 625–638. [PubMed: 26438382]

Dickstein DP, Nelson EE, McClure EB, Grimley ME, Knopf L, Brotman MA, … Leibenluft E (2007). Cognitive flexibility in phenotypes of pediatric bipolar disorder. Journal of the American Academy of Child and Adolescent Psychiatry, 46, 341–355. [PubMed: 17314720]

Dickstein DP, Treland JE, Snow J, McClure EB, Mehta MS, Towbin KE, … Leibenluft E (2004). Neuropsychological performance in pediatric bipolar disorder. Biological Psychiatry, 55, 32–39. [PubMed: 14706422]

Evans LD, Kouros CD, Samanez-Larkin S, & Garber J (2016). Concurrent and Short-Term Prospective Relations among Neurocognitive Functioning, Coping, and Depressive Symptoms in Youth. Journal of Clinical Child and Adolescent Psychology: The Official Journal for the Society of Clinical Child and Adolescent Psychology, American Psychological Association, Division 53, 45, 6–20.

Favre T, Hughes C, Emslie G, Stavinoha P, Kennard B, & Carmody T (2009). Executive functioning in children and adolescents with Major Depressive Disorder. Child Neuropsychology: A Journal on

Normal and Abnormal Development in Childhood and Adolescence, 15, 85–98. [PubMed: 19089695]

Fine EM, Delis DC, & Holdnack J (2011). Normative adjustments to the D-KEFS trail making test: corrections for education and vocabulary level. The Clinical Neuropsychologist, 25, 1331–1344. [PubMed: 21951052]

First MB (1997). Structured clinical interview for DSM-IV axis I disorders SCID-I: clinician version, administration booklet. Washington, DC: American Psychiatric Press.

Franklin T, Lee A, Hall N, Hetrick S, Ong J, Haslam N, … Vance A (2010). The association of visuospatial working memory with dysthymic disorder in pre-pubertal children. Psychological Medicine, 40, 253–261. [PubMed: 19607749]

Frantom LV, Allen DN, & Cross CL (2008). Neurocognitive endophenotypes for bipolar disorder. Bipolar Disorders, 10, 387–399. [PubMed: 18402627]

Geller B, Zimerman B, Williams M, Bolhofner K, Craney JL, DelBello MP, & Soutullo C (2001). Reliability of the Washington University in St. Louis Kiddie Schedule for Affective Disorders and Schizophrenia (WASH-U-KSADS) mania and rapid cycling sections. Journal of the American Academy of Child and Adolescent Psychiatry, 40, 450–455. [PubMed: 11314571]

Genet JJ, & Siemer M (2011). Flexible control in processing affective and non-affective material predicts individual differences in trait resilience. Cognition & Emotion, 25, 380–388. [PubMed: 21432680]

Glahn DC, Almasy L, Barguil M, Hare E, Peralta JM, Kent JW, … Escamilla MA (2010). Neurocognitive endophenotypes for bipolar disorder identified in multiplex multigenerational families. Archives of General Psychiatry, 67, 168–177. [PubMed: 20124116]

Greenberg MT (2006). Promoting resilience in children and youth: preventive interventions and their interface with neuroscience. Annals of the New York Academy of Sciences, 1094, 139–150. [PubMed: 17347347]

Hafeman DM, Merranko J, Axelson D, Goldstein BI, Goldstein T, Monk K, … Birmaher B (2016). Toward the Definition of a Bipolar Prodrome: Dimensional Predictors of Bipolar Spectrum Disorders in At-Risk Youths. The American Journal of Psychiatry, 173, 695–704. [PubMed: 26892940]

Hamilton JP, Farmer M, Fogelman P, & Gotlib IH (2015). Depressive Rumination, the Default-Mode Network, and the Dark Matter of Clinical Neuroscience. Biological Psychiatry.

Han G, Helm J, Iucha C, Zahn-Waxler C, Hastings PD, & Klimes-Dougan B (2016). Are Executive Functioning Deficits Concurrently and Predictively Associated with Depressive and Anxiety Symptoms in Adolescents? Journal of Clinical Child and Adolescent Psychology: The Official Journal for the Society of Clinical Child and Adolescent Psychology, American Psychological Association, Division 53, 45, 44–58.

Hayden BY, Smith DV, & Platt ML (2010). Cognitive Control Signals in Posterior Cingulate Cortex. Frontiers in Human Neuroscience, 4. doi:10.3389/fnhum.2010.00223

Hildebrandt LK, McCall C, Engen HG, & Singer T (2016). Cognitive flexibility, heart rate variability, and resilience predict fine-grained regulation of arousal during prolonged threat. Psychophysiology, 53, 880–890. [PubMed: 26899260]

Ho TC, Connolly CG, Henje Blom E, LeWinn KZ, Strigo IA, Paulus MP, … Yang TT. (2015). Emotion-dependent functional connectivity of the default mode network in adolescent depression. Biological Psychiatry, 78, 635–646. [PubMed: 25483399]

Jenkinson M, Bannister P, Brady M, & Smith S (2002). Improved optimization for the robust and accurate linear registration and motion correction of brain images. NeuroImage, 17, 825–841. [PubMed: 12377157]

Katz MM, Maas JW, Frazer A, Koslow SH, Bowden CL, Berman N, … Stokes PE (1994). Drug-induced actions on brain neurotransmitter systems and changes in the behaviors and emotions of depressed patients. Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology, 11, 89–100. [PubMed: 7530963]

Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, … Ryan N (1997). Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-

SADS-PL): initial reliability and validity data. Journal of the American Academy of Child and Adolescent Psychiatry, 36, 980–988. [PubMed: 9204677]

Kayser J, Tenke CE, Abraham KS, Alschuler DM, Alvarenga JE, Skipper J, … Weissman MM. (2017). Motivated attention and family risk for depression: Neuronal generator patterns at scalp elicited by lateralized aversive pictures reveal blunted emotional responsivity. NeuroImage. Clinical, 14, 692–707. [PubMed: 28393011]

Klimes-Dougan B, Ronsaville D, Wiggs EA, & Martinez PE (2006a). Neuropsychological functioning in adolescent children of mothers with a history of bipolar or major depressive disorders. Biological Psychiatry, 60, 957–965. [PubMed: 16934765]

Klimes-Dougan B, Ronsaville D, Wiggs EA, & Martinez PE (2006b). Neuropsychological functioning in adolescent children of mothers with a history of bipolar or major depressive disorders. Biological Psychiatry, 60, 957–965. [PubMed: 16934765]

Kravitz D, Saleem K, Baker C, & Mishkin M (2011). A new neural framework for visuospatial processing. Journal of Vision, 11, 319–319.

Kyte ZA, Goodyer IM, & Sahakian BJ (2005). Selected executive skills in adolescents with recent first episode major depression. Journal of Child Psychology and Psychiatry, and Allied Disciplines, 46, 995–1005. [PubMed: 16109002]

Mason MF, Norton MI, Horn JD Van, Wegner DM., Grafton ST, Macrae CN., … Macrae CN. (2007). Wandering minds: Stimulus-independent thought. Science, 315, 393–395. [PubMed: 17234951]

McCormack C, Green MJ, Rowland JE, Roberts G, Frankland A, Hadzi-Pavlovic D, … Mitchell PB. (2016). Neuropsychological and social cognitive function in young people at genetic risk of bipolar disorder. Psychological Medicine, 46, 745–758. [PubMed: 26621494]

Menon V (2011). Large-scale brain networks and psychopathology: a unifying triple network model. Trends in Cognitive Sciences, 15, 483–506. [PubMed: 21908230]

Micco JA, Henin A, Biederman J, Rosenbaum JF, Petty C, Rindlaub LA, … Hirshfeld-Becker DR (2009). Executive functioning in offspring at risk for depression and anxiety. Depression and Anxiety, 26, 780–790. [PubMed: 19434624]

Noto MN, de Souza Noto C, de Jesus DR, Zugman A, Mansur RB, Berberian AA, … Brietzke E. (2013). Recognition of bipolar disorder type I before the first manic episode: challenges and developments. Expert Review of Neurotherapeutics, 13, 795–806; quiz 807. [PubMed: 23898851]

Oldfield RC (1971). The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia, 9, 97–113. [PubMed: 5146491]

Pan Y-J, Hsieh MH, & Liu S-K (2011). Visuospatial working memory deficits in remitted patients with bipolar disorder: susceptibility to the effects of GABAergic agonists. Bipolar Disorders, 13, 365–376. [PubMed: 21843276]

Papmeyer M, Sussmann JE, Hall J, McKirdy J, Peel A, Macdonald A, … McIntosh AM. (2015). Neurocognition in individuals at high familial risk of mood disorders with or without subsequent onset of depression. Psychological Medicine, 45, 3317–3327. [PubMed: 26189425]

Pardo JV, Pardo PJ, Humes SW, & I Posner M (2006). Neurocognitive dysfunction in antidepressant-free, non-elderly patients with unipolar depression: alerting and covert orienting of visuospatial attention. Journal of Affective Disorders, 92, 71–78. [PubMed: 16458363]

Patino LR, Adler CM, Mills NP, Strakowski SM, Fleck DE, Welge JA, & Delbello MP (2013). Conflict monitoring and adaptation in individuals at familial risk for developing bipolar disorder. Bipolar Disorders. doi:10.1111/bdi.12059

Pavuluri MN, West A, Hill SK, Jindal K, & Sweeney JA (2009). Neurocognitive function in pediatric bipolar disorder: 3-year follow-up shows cognitive development lagging behind healthy youths. Journal of the American Academy of Child and Adolescent Psychiatry, 48, 299–307. [PubMed: 19182689]

Power JD, Barnes KA, Snyder AZ, Schlaggar BL, & Petersen SE (2013). Steps toward optimizing motion artifact removal in functional connectivity MRI; a reply to Carp. NeuroImage.

Poznanski EO, Grossman JA, Buchsbaum Y, Banegas M, Freeman L, & Gibbons R (1984). Preliminary studies of the reliability and validity of the children's depression rating scale. Journal of the American Academy of Child Psychiatry, 23, 191–197. [PubMed: 6715741]

Corporation Psychological. (1999). Wechsler Abbreviated Scale of Intelligence (WASI). San Antonio, TX: Harcourt Brace & Company.

Rajajärvi E, Antila M, Kieseppä T, Lönnqvist J, Tuulio-Henriksson A, & Partonen T (2010). The effect of seasons and seasonal variation on neuropsychological test performance in patients with bipolar I disorder and their first-degree relatives. Journal of Affective Disorders, 127, 58–65. [PubMed: 20466433]

Ravizza SM, & Carter CS (2008). Shifting set about task switching: Behavioral and neural evidence for distinct forms of cognitive flexibility. Neuropsychologia, 46, 2924–2935. [PubMed: 18601941]

Reitan RM, & Wolfson D (2004). The Trail Making Test as an initial screening procedure for neuropsychological impairment in older children. Archives of Clinical Neuropsychology: The Official Journal of the National Academy of Neuropsychologists, 19, 281–288. [PubMed: 15010091]

Renner F, Siep N, Arntz A, van de Ven V, Peeters FPML, Quaedflieg CWEM, & Huibers MJH (2017). Negative mood-induction modulates default mode network resting-state functional connectivity in chronic depression. Journal of Affective Disorders, 208, 590–596. [PubMed: 27810271]

Rive MM, Koeter MWJ, Veltman DJ, Schene AH, & Ruhé HG (2016). Visuospatial planning in unmedicated major depressive disorder and bipolar disorder: distinct and common neural correlates. Psychological Medicine, 46, 2313–2328. [PubMed: 27198937]

Rutter M (2013). Annual Research Review: Resilience--clinical implications. Journal of Child Psychology and Psychiatry, and Allied Disciplines, 54, 474–487.

Schmid M, & Hammar A (2013). A follow-up study of first episode major depressive disorder. Impairment in inhibition and semantic fluency-potential predictors for relapse? Frontiers in Psychology, 4, 633. [PubMed: 24062714]

Shaffer D, Gould MS, Brasic J, Ambrosini P, Fisher P, Bird H, & Aluwahlia S (1983). A children's global assessment scale (CGAS). Archives of General Psychiatry, 40, 1228–1231. [PubMed: 6639293]

Shehab AAS, Brent D, & Maalouf FT (2016). Neurocognitive Changes in Selective Serotonin Reuptake Inhibitors-Treated Adolescents with Depression. Journal of Child and Adolescent Psychopharmacology. doi:10.1089/cap.2015.0190

Singh MK, DelBello MP, Fleck DE, Shear PK, & Strakowski SM (2009). Inhibition and attention in adolescents with nonmanic mood disorders and a high risk for developing mania. Journal of Clinical and Experimental Neuropsychology, 31, 1–7. [PubMed: 18608697]

Singh MK, Ketter T, & Chang KD (2014). Distinguishing bipolar disorder from other psychiatric disorders in children. Current Psychiatry Reports, 16, 516. [PubMed: 25315116]

Smith SM (2002). Fast robust automated brain extraction. Human Brain Mapping, 17, 143–155. [PubMed: 12391568]

Vanlessen N, De Raedt R, Koster EHW, & Pourtois G (2016). Happy heart, smiling eyes: A systematic review of positive mood effects on broadening of visuospatial attention. Neuroscience and Biobehavioral Reviews, 68, 816–837. [PubMed: 27395341]

Vilgis V, Silk TJ, & Vance A (2015). Executive function and attention in children and adolescents with depressive disorders: a systematic review. European Child & Adolescent Psychiatry, 24, 365–384. [PubMed: 25633323]

Vinberg M, Miskowiak KW, & Kessing LV (2013). Impairment of executive function and attention predicts onset of affective disorder in healthy high-risk twins. The Journal of Clinical Psychiatry, 74, e747–753. [PubMed: 24021515]

Wagner C, Abramson LY, & Alloy LB (2015). Brief report: Executive functions in adolescent offspring of mothers with a history of depression. Journal of Adolescence, 44, 32–36. [PubMed: 26208078]

Walker V, Patel H, Kurlander JL, Essoi B, Yang J, Mahableshwarkar AR, … Akhras KS (2015). Association Between Cognitive Function and Health Care Costs 3 Months and 6 Months After Initiating Antidepressant Medication for Depressive Disorders. Journal of Managed Care & Specialty Pharmacy, 21, 742–752, 752a–752e. [PubMed: 26308222]

Wegbreit E, Cushman GK, Weissman AB, Bojanek E, Kim KL, Leibenluft E, & Dickstein DP (2016). Reversal-learning deficits in childhood-onset bipolar disorder across the transition from childhood to young adulthood. Journal of Affective Disorders, 203, 46–54. [PubMed: 27280962]

Young RC, Biggs JT, Ziegler VE, & Meyer DA (1978). A rating scale for mania: reliability, validity and sensitivity. The British Journal of Psychiatry: The Journal of Mental Science, 133, 429–435. [PubMed: 728692]

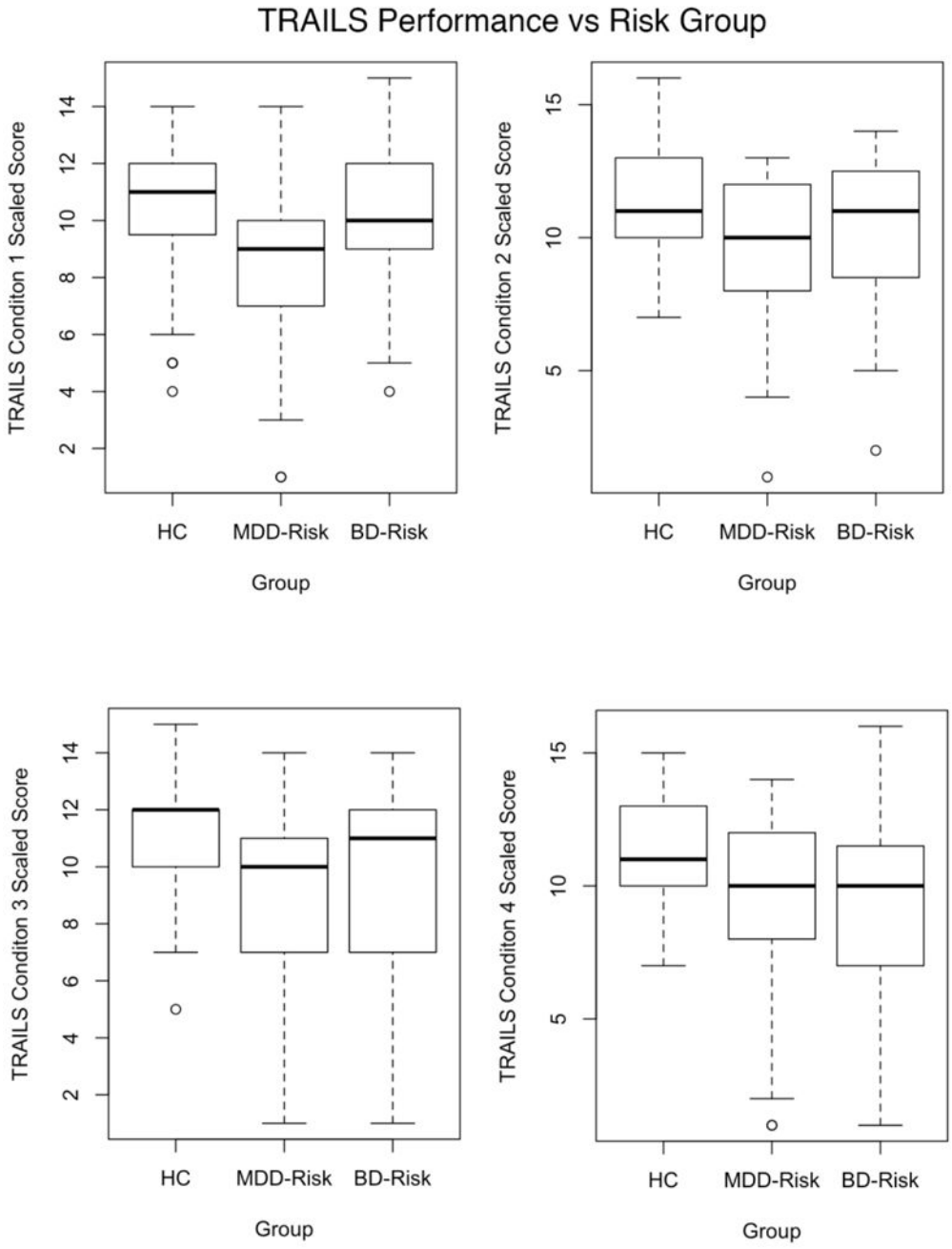

Figure 1.

Scaled TRAILS score versus risk group for conditions 1–4. HC subjects scored significantly better on average than both risk groups for each task.

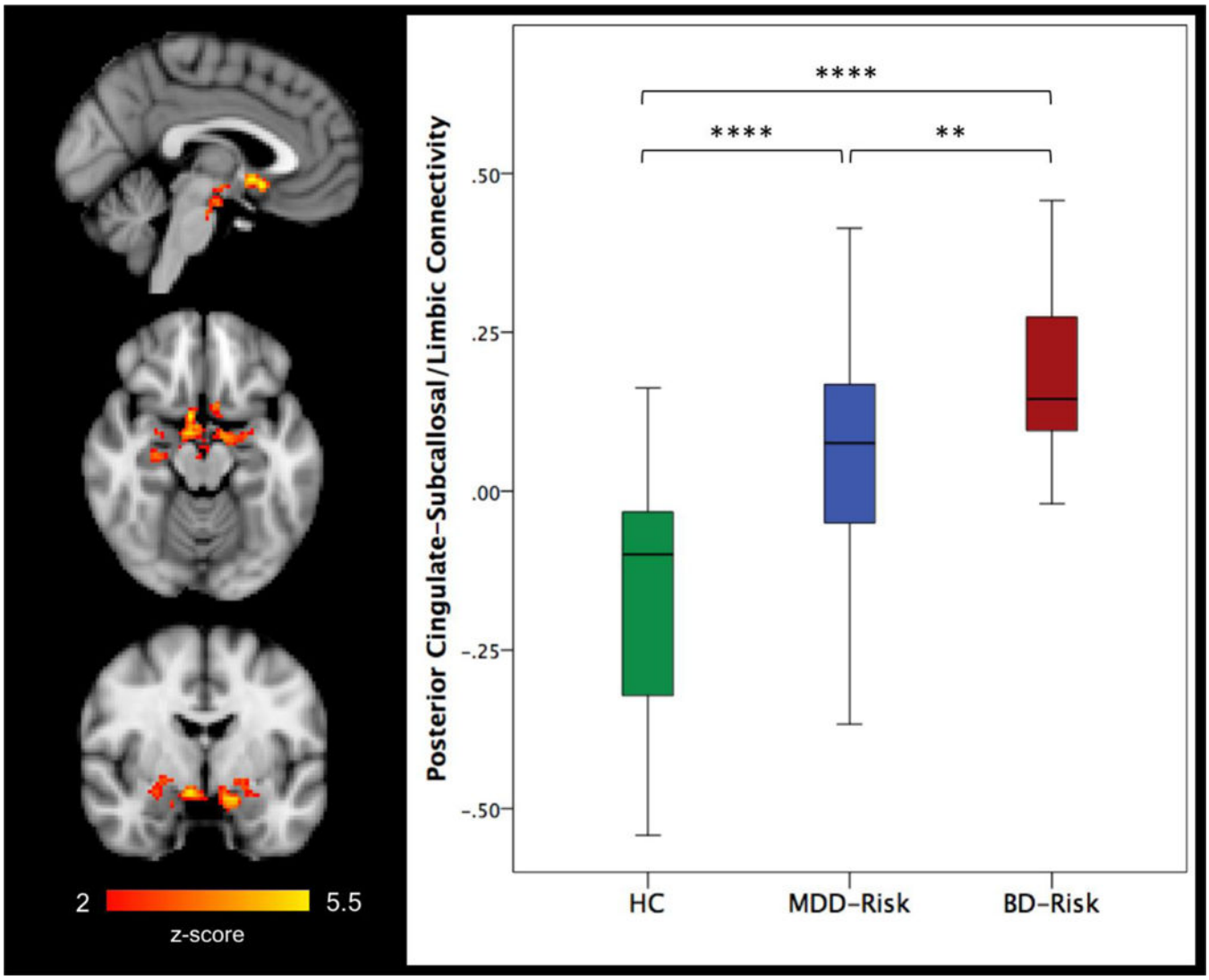

Figure 2.

Average resting-state functional connectivity between the posterior cingulate seed and regions of the subcallosal cortex, amygdala, and hippocampus. Significant differences in connectivity are seen between each group ($p<0.001$ for all pairwise comparisons except between MDD-risk and BD-risk, $p=0.005$).

Table 1.

Participant Characteristics

Subject Group	BD risk Mean (SD/%)	MDD risk Mean (SD/%)	HC Mean (SD/%)	F or χ^2	P
N	31	49	31		
Age	11.61 (2.70)	12.98 (2.62)	12.55 (3.04)	2.32	.11
Female	19 (61%)	22 (45%)	16 (51%)	1.80	.41
Caucasian Race	27 (87%)	40 (82%)	29 (93%)	2.7	.26
SES	3.96 (0.93)	4.23 (.96)	4.17 (.78)	0.70	.50
Pubertal Stage	2.48 (.52)	2.75 (.62)	2.70 (.74)	0.96	.39
Handedness	19/21 (90%)	39/42(93%)	20/26 (77%)	3.96	.14
IQ	112.9 (12.22)	111.7 (13.79)	117.77 (12.42)	2.14	.12
YMRS	2.54 (4.03)	1.53 (3.04)	0.57 (1.03)	2.96	.05
CDRS-R	22.68 (9.15)	19.76 (3.23)	18.59 (2.41)	4.19	.02
CGAS – current	86.34 (5.68)	87.36 (5.20)	93.03 (2.77)	17.33	00
CGAS – most severe past	80.0 (7.58)	82.5 (6.95)	86.53 (8.70)	5.18	.01

Legend: MDD= Major Depressive Disorder; BD= Bipolar Disorder; HC=Healthy Controls; SD = Standard Deviation; SES = Socioeconomic status; YMRS = Young Mania Rating Scale; CDRS-R = Children's Depression Rating Scale-Revised; CGAS = Children's Global Assessment Scale; IQ = Intellectual Quotient

Table 2.

Group Results for All Conditions on the Delis-Kaplan Trail Making Test

Trail Making Condition Score	BD risk Mean (SD/%)	MDD risk Mean (SD/%)	HC Mean (SD/%)	F	P
C1 scaled	10.19 (2.55)	8.63 (3.01)	10.13 (2.63)	4.12	0.019
C2 scaled	10.16 (2.86)	9.61 (2.70)	11.32 (1.96)	4.23	0.017
C3 scaled	9.64 (3.27)	9.06 (3.31)	10.96 (2.21)	3.78	0.026
C4 scaled	9.42 (3.05)	9.33 (3.24)	11.22 (1.98)	4.66	0.012
C5 scaled	11.03 (2.97)	10.33 (2.91)	10.97 (2.64)	0.76	0.469
C4 contrast	−0.94 (3.57)	−0.42 (2.95)	−0.57 (2.27)	0.29	0.749

Legend: scaled: scores controlling for age; contrast: C4 contrast score = C4 scaled -[scaled C2+C3]