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Decreased functional connectivity in the fronto-parietal network in children with mood disorders compared to children with dyslexia during rest: An fMRI study

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ABSTRACT

Background: The DSM-5 separates the diagnostic criteria for mood and behavioral disorders. Both types of disorders share neurocognitive deficits of executive function and reading difficulties in childhood. Children with dyslexia also have executive function deficits, revealing a role of executive function circuitry in reading. The aim of the current study is to determine whether there is a significant relationship of functional connectivity within the fronto-parietal and cingulo-opercular cognitive control networks to reading measures for children with mood disorders, behavioral disorders, dyslexia, and healthy controls (HC).

Method: Behavioral reading measures of phonological awareness, decoding, and orthography were collected. Resting state fMRI data were collected, preprocessed, and then analyzed for functional connectivity. Differences in the reading measures were tested for significance among the groups. Global efficiency (GE) measures were also tested for correlation with reading measures in 40 children with various disorders and 17 HCs.

Results: Significant differences were found between the four groups on all reading measures. Relative to HCs and children with mood disorders or behavior disorders, children with dyslexia as a primary diagnosis scored significantly lower on all three reading measures. Children with mood disorders scored significantly lower than controls on a test of phonological awareness. Phonological awareness deficits correlated with reduced resting state functional connectivity MRI (rsfcMRI) in the cingulo-opercular network for children with dyslexia. A significant difference was also found in fronto-parietal global efficiency in children with mood disorders relative to the other three groups. We also found a significant difference in cingulo-opercular global efficiency in children with mood disorders relative to the Dyslexia and Control groups. However, none of these differences correlate significantly with reading measures.

Conclusions/significance: Reading difficulties involve abnormalities in different cognitive control networks in children with dyslexia compared to children with mood disorders. Findings of the current study suggest increased functional connectivity of one cognitive control network may compensate for reduced functional connectivity in the other network in children with mood disorders. These findings provide guidance to clinical

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professionals for design of interventions tailored for children suffering from reading difficulties originating from different pathologies.

1. Introduction

Diagnostically, mood and behavioral disorders are distinct categories as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). Mood disorders include bipolar spectrum, depression, and anxiety disorders, while behavioral disorders include attention deficit hyperactive disorder (ADHD) and oppositional defiant disorder (ODD) and conduct disorder. In individuals with mood disorders, MRI has shown abnormal brain activity and structure in the limbic system and prefrontal cortex, areas related to the disorder's core characteristics of deficits in emotional regulation and executive functions (EFs) (Cerullo et al., 2012; Pavuluri et al., 2008; Soares and Mann, 1997; Strakowski et al., 2005). Those with a behavioral disorder show similarities in altered resting state functional connectivity in frontal regions, which underlie their executive dysfunction (Zang et al., 2007; Li et al., 2014). EFs are a wide array of complex monitoring and organizational processes utilized for goal-directed behavior related to frontal lobe activity and frontal networks (Alvarez and Emory, 2006). Both disorders exhibit different symptoms and neural mechanisms, but they share neurocognitive deficits such as difficulties in EF (Walshaw et al., 2010) and academic difficulties in reading (Pavuluri et al., 2006). Poorer scores of working memory and attention were correlated with reading and writing difficulties in children with mood and behavioral disorders, suggesting an overall role of EF in academic performance (Pavuluri et al., 2006; Fristad et al., 1992; Goldston et al., 2007; Arnold et al., 2005; Maughan et al., 2003).

Recent studies verified that children with mood or behavioral disorders do suffer from reading challenges, but with different levels of difficulty (Horowitz-Kraus et al., 2017). Children with mood disorders showed lower scores in phonemic awareness and reading comprehension abilities compared to children with behavioral disorders and typical readers. These differences were correlated with higher density of specific white matter tracts and reading measures: phonemic awareness correlated with greater left Inferior Longitudinal Fasciculus (ILF) Fractional Anisotropy (FA) values for children with mood disorders and greater left Arcuate Fasciculus (AF) FA values for children with behavioral disorders (Horowitz-Kraus et al., 2017). Connections of the ventral and dorsal communications streams along the ILF and AF in the left hemisphere support word level phonologic and orthographic processes (Horowitz-Kraus et al., 2017) and relate to reading ability (Wandell and Yeatman, 2013). Although we previously suggested that the lateralization of the left ILF found in children with mood disorders may explain deficits in reading comprehension and phonemic awareness, altered activation in characteristic brain regions of mood disorders may also contribute to these specific reading deficits (Horowitz-Kraus et al., 2017). The current report on functional connectivity in key networks supporting executive function relating to reading is a sequel to our previous report describing differences in structural connectivity in major white matter tracts connecting neural pathways relating to reading (Horowitz-Kraus et al., 2017).

Behavioral disorders have long been recognized in children, and have been highlighted as one of the most ubiquitous of childhood mental disorders (Goldman et al., 1998). Mood disorders in youth are often accompanied by comorbid behavioral disorders, confounding our understanding and treatment of both types of disorders [for review see Kowatch et al., 2005; Wozniak et al., 2004]. The few neuropsychological studies of pediatric bipolar disorder have found deficits in verbal learning and interference control; however, impairments in processing speed (Henin et al., 2007) and working memory (Doyle et al., 2005) also appear in this mood disorder even after adjusting for comorbid behavioral disorders. Youth with behavioral disorders such as Attention Deficit Hyperactive Disorder (ADHD) have reduced performance in a variety of EFs (working memory, inhibition, and sustaining attention) (Willcutt et al., 2005).

The functional and anatomical characteristics of each type of disorder have also provided further clarification of their etiology and pathophysiology. Fronto-limbic pathways and amygdala volumes appear to be altered for children with mood disorders (Caetano et al., 2005). Negative emotional stimuli resulted in increased activation of amygdala and anterior cingulate cortex coupled with reduced ventrolateral and dorsolateral prefrontal cortex in children with mood disorders (Pavuluri et al., 2008). The aberrant activity of these areas supports a weakened system to regulate emotions and execute control over higher cognitive processes (Pavuluri et al., 2008; Fleck et al., 2012). Individuals with behavioral disorders show altered activity in the prefrontal cortex, caudate, anterior cingulate cortex, putamen, and parietal regions of fronto-striatal and fronto-parietal circuits supporting top-down control of cognitive processes (see review: Bush et al., 2005; Castellanos and Tannock, 2002; Dickstein et al., 2006; Rubia et al., 1999). Though the appearance of common frontal lobe dysfunction between mood and behavioral disorders may explain their general shared cognitive control and learning challenges, identifying these differences objectively can allow for the proper interventions for these youth.

Another clinical group that suffers from reading difficulties and executive dysfunction includes individuals with dyslexia (Horowitz-Kraus, 2014). Though dyslexia is clinically defined as a specific type of reading difficulty involving deficits in word decoding skills that persist despite repeated intervention and language exposure, EF impairment is also related to the condition. An Event-Related Potentials (ERP) study using a computerized Wisconsin Card Sorting Test (WCST) suggested that the difficulty subjects with dyslexia have may be due either to slow processing speed or a deficit in working memory and attentional control, which are more basic aspects of EF (Horowitz-Kraus, 2014). Working memory deficits in those with behavioral disorders such as ADHD imply a cognitive basis for deficits in reading related to processing speed and fluency (Jacobson et al., 2011). Recently we found that individuals with dyslexia demonstrated lower functional connectivity in neural networks supporting EFs at rest (Horowitz-Kraus et al., 2017).

Resting state functional connectivity magnetic resonance imaging (rsfcMRI) is a neuroimaging technique that uses measures the co-activation of brain regions to represent inherent connectivity within functional brain networks. Resting state functional connectivity analysis has revealed two networks of brain regions involved in EFs: fronto-parietal and cingulo-opercular (Fair et al., 2009). This dual network model incorporates the fronto-parietal network for initiating and orienting attention and the cingulo-opercular network for maintaining control (Dosenbach et al., 2008; Wallis et al., 2015). RsfcMRI is particularly useful when studying the developing brain, when cognitive networks mature by shifting communication from nearby to more distant regions (Fair et al., 2009). This maturation process of cognitive networks has been suggested as a neural correlate of the underlying problems for children behavioral disorders (Fair et al., 2010); and particularly for children with mood disorders (Sylvester et al., 2012). Abnormal connectivity in the fronto-parietal network in teenagers and young adults with dyslexia (Wolf et al., 2010) has previously been reported. The authors suggested that enhanced connectivity of fronto-parietal regions typically used in phonological processing (inferior frontal cortex and angular gyrus) to hippocampal and thalamic regions, compensated for the reduced connectivity of dorsolateral prefrontal cortex and posterior parietal regions during a working memory task. This suggests that the development of the fronto-parietal network adapts to executive deficits by relying more heavily on classical reading and memory pathways. Increased global efficiency of the cingulo-opercular network as measured by global efficiency (GE, a measure of the closeness of the time course of activations of the network with neighboring regions) has also been reported in association with reading improvement in children with dyslexia, which compares to high GE of both the cingulo-opercular and fronto-parietal networks in typical readers (Horowitz-Kraus et al., 2017). Despite the tight connections between cognitive control networks, EFs and reading ability, we know little about how functional connectivity within these networks varies for children with different clinical disorders.

The primary goal of the current study was to compare the relationship between reading measures and the functional connectivity of the fronto-parietal and cingulo-opercular networks in children with mood disorders, behavioral disorders, dyslexia, and healthy controls. To investigate this relationship, we compared phonological, orthographical and reading comprehension scores among the 4 groups and correlated the within-network functional connectivity of the cingulo-opercular and fronto-parietal networks during rest with reading measures in the 4 groups. We hypothesized that since reading difficulty is the primary deficit in dyslexia, children with dyslexia would exhibit the most profound deficits in all reading measures and that these deficits would be related to reduced functional connectivity in the cingulo-opercular network (Horowitz-Kraus et al., 2017). In contrast, we hypothesized that children with mood disorders would display increased cingulo-opercular connectivity and reduced fronto-parietal connectivity. We tested these hypotheses using resting state functional connectivity data to examine the relationship between GE within the dual executive function networks of interest and reading skills across diagnoses (mood disorders, behavioral disorders, dyslexia and typical controls).

2. Methods and materials

2.1. Participants

Fourteen (n = 14) youth with mood disorders (mean age: 15.47 ± 1.80; 11 female), 11 youth with behavioral disorders (mean age: 14.68 ± 1.79; 3 female), 15 children with dyslexia (mean age: 10.27 ± 1.48; 7 female), and 17 healthy control participants (mean age: 9.77 ± 1.44; 9 female) were part of this study.

Part of the participant data (youth with mood and behavioral disorders) included in this study is from a multisite longitudinal study, known as the Longitudinal Assessment of Manic Symptoms (LAMS), examining the dimensional and categorical characteristics of youth exhibiting emotional and behavioral dysregulation. LAMS neuroimaging participants were diagnosed using several standard tools for the evaluation of hypomania/mania, depressive symptoms, anxiety symptoms and symptoms in the behavioral disorders with more details for the imaging cohort included in this report provided in Versace (Versace et al., 2015). These included assessment of mood symptoms and behaviors at 6 month intervals over the course of 10 years. The assessment battery included the Parent Guardian Behavioral Inventory (PGBI-10M) (Youngstrom et al., 2008), the Screen for Child Anxiety Related Emotional Disorders (SCARED) (Birmaher et al., 1997), and annual assessments of manic and depressive symptom severity using respectively the Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS) Mania Rating Scale (KMRS) (Axelson et al., 2003) and Depression Rating Scale (KDRS) (Kaufman et al., 1997). SCARED, KDRS, and KMRS were repeated on scan day. Participants were categorized into broad diagnostic categories of those with mood dysregulation disorders and those with behavioral dysregulation disorders. Based on interviews and questionnaires (Versace et al., 2015) we took a dimensional approach and categorized youth into broad diagnostic categories of 1) youth with behavioral dysregulation disorders (attention deficit hyperactive disorder and/or behavioral dysregulation disorders, no mood disorder) and 2) youth with mood dysregulation disorders (including bipolar disorder, depressive disorder, anxiety disorders, and combinations of them, no ADHD or other behavioral disorders). Youth who had both behavioral dysregulation and mood dysregulation were included in the latter group (see also Versace et al., 2015). Youth in this study provided assent and their parents signed consent to participate, using procedures and forms approved by Institutional Review Boards at Cincinnati Children's Hospital Medical Center, Case Western Reserve University, and University of Pittsburgh Medical Center.

Youth with dyslexia were identified by standard scores that fell 1.5 standard deviations or more below the normative mean on at least 2 of the reading measures described below. The healthy control and dyslexic groups did not have any prior history of diagnosis or treatment for psychiatry or disorders and parents confirmed no history mental health disorders by completing a neurological questionnaire. Participants in these groups were excluded from the study if they had a history of head trauma or use of medications for mental illness or other neurologic disease. Participants in the study were compensated with payment for their time and travel costs.

2.2. Behavioral measures

Since reading acquisition relies on 3 main components (phonological awareness, decoding and orthography), we chose to focus only on these 3 domains in our study. Therefore, we chose the 3 tests designed to assess these 3 reading components. Measures of phonological awareness from the Comprehensive Test of Phonological Processing (Elision subtest from the CTOPP) (Wagner et al., 1999), as well as decoding and orthographic ability from the Woodcock-Johnson – III Tests of Achievement (Woodcock et al., 2001) (Word Attack subtest, Letter-Word Identification subtest) were collected. The Elision subtest required participants to orally manipulate a word by omitting a sound at the beginning, middle, or end to create a new nonsense word. The Word Attack subtest measures how accurate the participant can read aloud a list of non-words and the Letter-Word Identification subtest required participants to read a list of letters then a list of words at a pace comfortable to them. Form A of the CTOPP and WJ-III subtests were completed by all participants.

Raw scores from the reading tests are normalized by age during the conversion to standard scores. Standard scores from each test were entered into statistical analysis in SPSS. Statistical analysis of behavioral data was conducted post-hoc, by performing a separate, four-way (4 groups) analyses of variance (ANOVA) for each reading measure we administered using SPSS Version 21 (IBM, 2012). Significance of the differences in reading scores reported between the groups is Bonferroni corrected for the three scores that we compared. Additionally, bivariate *t*-tests were performed post-hoc between each group for each reading measure. This results in 6 comparisons for each of the 3 reading measures, so we applied a Bonferroni correction to the significance level estimated for the 18 comparisons performed.

2.3. Neuroimaging measures

Resting-state fMRI data was collected with the following protocol. Participants were instructed to attend to a grey cross on the projector screen for 5.5 min without closing their eyes or falling asleep. A Phillips Achieva 3 T MRI scanner was used to acquire images (Philips Medical Systems, Best, The Netherlands) with a T2-weighted gradient-echo, echo-planar imaging (EPI) sequence using the following parameters: TR/TE = 2000/38 ms, matrix size = 64 × 64, slice thickness = 5 mm, producing a voxel size of $4 \times 4 \times 5\,\text{mm}^3$. 165 whole-brain volumes were collected during the resting-state condition. To reduce T1 effects, the first 10 time points were discarded. Inversion Recovery (IR)-

prepared turbo gradient-echo acquisition protocol was used to obtain a high-resolution T1-weighted 3D structural scan with a 1 × 1 × 1 mm^3 spatial resolution. To maximize comfort and minimize head movement during the scan, participants were given time before to become familiar with the MRI and an elastic strap was placed around the head, within the RF-coil apparatus.

2.4. MRI data analysis

Reconstructed fMRI data were initially pre-processed using SPM8 software (www.fil.ion.ucl.ac.uk/spm/), including slice-timing correction, realignment for motion correction, coregistration of the anatomical image to the mean aligned functional image, segmentation by grey matter, white matter, and cerebrospinal fluid tissue classes, normalization of all images to the Montreal Neurological Institute (MNI) space, and spatial smoothing with an 8-mm full width at half-maximum (FWHM) Gaussian kernel. We performed 3-dimensional affine transformation to align volumes. This resulted in six motion parameters; three translational and three rotational. In addition, time points with excessive motion were rejected from the post processing pipeline. We used a mutual information cost function for rejecting motion-corrupted frames of fMRI data as previously described (Szaflarski et al., 2006). All data met the criterion of median voxel displacement < 2 mm in the center of the brain.

MNI coordinates for the regions of interest (ROI) for the cingulo-opercular and fronto-parietal networks were adapted from (Fair et al., 2009; Neta et al., 2014), and were used to generate ROI masks in the WFU pick atlas toolbox (http://fmri.wfubmc.edu/research/PickAtlas) for group analysis in SPM8. Each ROI was a spherical seed with a 10 mm radius in 2 mm standard space. These ROIs were applied to the normalized imaging data from each subject in order to extract the time-course of the seed and calculate the network metrics.

2.5. Functional connectivity analysis

Following spatial pre-processing, resting-state data were processed in CONN (v.13.p, https://www.nitrc.org/frs/shownotes.php?release_id=2445) (Whitfield-Gabrieli and Nieto-Castanon, 2012), a functional connectivity toolbox for Matlab (The Mathworks, Natick, MA) that works in conjunction with SPM8 mentioned above. Additional pre-processing under the anatomical component-based noise-correction framework (aCompCor) (Behzadi et al., 2007) included extraction of the first five principle components of the BOLD time-courses from white matter and cerebral spinal fluid (CSF) regions for use as regressors in the first level of analysis of the fMRI data from each individual subject to remove systematic signal variation associated with these non-cortical regions. In addition, the six motion parameters for each session, together with their first derivatives, were regressed out of the voxel time series. Finally, the voxel time series data were band-pass filtered between 0.008 and 0.2 Hz, as recommended by Baria et al. (2011) to minimize contributions from non-physiological BOLD signal fluctuations.

A second level of statistical image analysis was performed across subjects in the standardized MNI framework as described above. MNI coordinates for the 9 regions of interest (ROI) for the cingulo-opercular EF network and additional 9 ROIs in fronto-parietal EF network are listed in Table 1. Functional connectivity between pairs of target regions of interest (ROI) was calculated as the correlation coefficient for the average voxel signal per ROI pair. The time-course data from the normalized ROIs for each network was also used to compute global efficiency as a global network measure for each network and group as described below and illustrated in Figs. 2 and 3.

2.6. Global efficiency measures

Global efficiency (GE) is a measure of the similarity of the time course between each region and those of its neighbors within the network (defined above in Table 1). GE was computed in CONN with the following formula:

$$E = \frac{1}{n}\sum_{i\in N} E_i = \frac{1}{n}\sum_{i\in N}\frac{\sum_{j\in N, j\neq i} d_{ij}^{-1}}{n-1}.$$

where E_i is the efficiency of node i, n is the number of network nodes, N is the set of all network nodes, and ${d_{ij}}^{-1}$ is the inverse shortest path-length between nodes i and j. GE measures were computed for each cognitive control network, containing 9 ROIs each, for each participant in the four groups. We used a significance threshold for network edges of $p < 0.05$ (FDR corrected) to calculate GE values for each network. The average GE value and its standard deviation was also computed for each group, taking the output of CONN for each subject as input to SPSS for calculation of these descriptive statistics and subsequent stages of statistical analysis.

To determine whether age might be a significant factor in the GE measures, we ran a multivariate ANOVA including age as a main effect affecting our results.

To test whether GE values differ between groups for either of the networks tested, we used a two-tailed, two-sample t-test. Significance levels for the t-tests were corrected for 6 comparison in 2 networks; a factor of 12. This factor was added to the correction for the reading measure above (18) for a total Bonferroni correction of 30 to maintain a significance level of $p < 0.05$.

2.7. Correlation of GE with behavioral scores

To test for associations between GE and reading measures, a Pearson correlation between these measures was performed for each network between participants within each group and the reading measures (an overall of 3 correlations per network per group). Data was corrected for multiple comparisons using a Bonferroni correction factor of 24.

Table 1
Target regions of interest with anatomical region listed in the left-hand column and coordinates in the standard Montreal Neurologic Institute framework listed to the right.

	X	Y	Z
Cingulo-opercular network			
Left anterior Prefrontal Cortex [aPFC (L)]	−28	51	15
Right anterior Prefrontal Cortex [aPFC (R)]	27	50	23
Left Lateral anterior Insula/frontal Operculum [Lateral aI fO (L)]	−51	18	13
Right Lateral anterior Insula/frontal Operculum [Lateral aI fO (R)]	45	23	−4
Left Medial anterior Insula/frontal Operculum [Medial aI fO (L)]	−33	24	1
Right Medial anterior Insula/frontal Operculum [Medial aI fO (R)]	33	25	−1
Left anterior Insula/frontal Operculum [aI fO (L)]	−35	14	5
Right anterior Insula/frontal Operculum [aI fO (L)]	36	16	4
Dorsal anterior cingulate/medial superior Frontal Cortex [dACC msFC]	−1	10	46
Fronto-parietal network			
Left dorso-lateral Prefrontal Cortex [dlPFC (L)]	−43	22	34
Right dorso-lateral Prefrontal Cortex [dlPFC (R)]	43	22	34
Left inferior Parietal Lobule [IPL (L)]	−51	−51	36
Right inferior Parietal Lobule [IPL (R)]	51	47	42
Left Intraparietal Sulcus [IPS (L)]	−31	−59	42
Right Intraparietal Sulcus [IPS (R)]	30	−61	39
Left Precuneus [Precuneus (L)]	−9	−72	37
Right Precuneus [Precuneus (R)]	10	−69	39
Mid Cingulate Cortex [mCC]	0	−29	30

3. Results

3.1. Differences in reading ability

Significant differences in reading ability were found among the four subject groups for phonological awareness [$F(3,53) = 9.753$, $p < 0.001$], decoding [$F(3,52) = 8.503$, $p < 0.001$], and orthography [$F(3,53) = 13.697$,$p < 0.001$], shown in Fig. 1. Standard scores from the phonological awareness (CTOPP Ellision subset), decoding (WJ-III letter-word subtest) and orthography (WJ-III word-attack subtest) are reported for all participants in Table 2 (Supplement material), along with demographic information and psychiatric diagnosis. Average reading scores and GE values estimated for each group and network are listed in Table 3 (Supplement material). The dyslexia group differed significantly from each of the other groups on all three reading measures: CTOPP Ellision subset, WJ-III letter-word subtest and WJ-III word-attack subtest at a significance of $p < 0.05$ after Bonferroni correction, as listed in Table 3. The group with mood disorders differed significantly from the control group on the CTOPP measure of phonology. None of the other reading measures differed significantly between groups. The same group ranking of performance was found for each reading measure: relative to healthy controls, children with dyslexia showed the lowest scores, followed by children with mood disorders and then children with behavioral disorders. The percentile scores for each reading measure for each group are displayed graphically in Fig. 1, reflecting the rank ordering of reading performance of the four groups.

3.2. Cingulo-opercular network

Significant differences in GE of the cingulo-opercular network [$F(3,53) = 9.390$, $p < 0.001$; Fig. 2] were found between the four groups as listed in Table 3. In bivariate analysis the group with mood disorders exhibited significantly higher GE in the cingulo-opercular network compared with both the control group and children with dyslexia ($p < 0.05$, corrected). None of the other bivariate comparisons in cingulo-opercular network GE reached significance.

3.3. Fronto-parietal network

Significant group differences for the fronto-parietal network [$F(3,53) = 448.5$, $p < 0.001$; Fig. 3] were also found (see Table 3). In contrast to group differences in the cingulo-opercular network, children with mood disorders showed significantly lower GE scores than children in the three other groups in the fronto-parietal network ($p < 0.001$, corrected). Bivariate comparisons for fronto-parietal GE between other groups did not reach significance after correction for multiple comparisons.

3.4. Influence of age on GE

Multivariate ANOVA including age found no significant main effect of age on GE results $F(5,48) = 0.372$, $p = 0.865$. Therefore we can compare GE between groups without concern about age as a confound in the findings.

3.5. Correlations of phonological awareness and GE of the fronto-parietal network

Children with dyslexia showed typical GE scores in the fronto-parietal network compared with healthy controls, but lower reading scores across all tested measures ($p < 0.001$) while children with mood disorders showed much lower GE in the fronto-parietal network than the other three groups ($F = 448.5$, $p < 0.001$) and low phonological awareness scores ($F = 9.753$, $p < 0.001$). As shown in Fig. 4 and Table 3, both the behavioral disorders group and healthy controls exhibited higher reading measures, and more specifically phonological awareness abilities and comparable GE in the fronto-parietal network. The dyslexia group (blue diamonds in Fig. 4) exhibited lower reading scores but higher GE in the fronto-parietal network while the group with mood disorders groups had both low reading scores and a much lower GE value (red triangles in Fig. 4). We did not detect any significant correlations between other reading measures and GE in the fronto-parietal network in any of the 4 cohorts of subjects tested.

3.6. Correlation of phonological awareness and GE of the cingulo-opercular network

Children with mood disorders displayed significantly higher GE scores in the cingulo-opercular network than children with dyslexia ($t = 4.57$, $p < 0.01$) and health controls ($t = 3.30$, $p < 0.05$). Their CTOPP phonological awareness scores were also lower than the healthy control group ($t = 3.55$, $p < 0.05$) (Table 3 and Fig. 5).

Examining the results of the bivariate correlation analysis, significant correlation was found between the CTOPP Ellision subtest for phonological awareness and the GE in cingulo-opercular executive control network in children with dyslexia ($R = -0.578$, $p < 0.05$). No other correlations between reading measures and network connectivity were approach significant after correction for multiple comparisons.

4. Discussion

As we hypothesized at the outset of this study, children with dyslexia exhibited the most profound deficits in all reading measures (Fig. 1) and these deficits were significantly correlated with reduced functional connectivity in the cingulo-opercular network (Horowitz-Kraus et al., 2017). The observed overall reading deficits in dyslexia have been documented in previous findings (Manis et al., 1993). We also hypothesized that children with mood disorders would display increased cingulo-opercular connectivity and reduced fronto-parietal connectivity. Our findings reported in Table 3 and Figs. 4 & 5 support this hypothesis. However, despite the significant decreased functional connectivity of the fronto-parietal network in the mood disorders group compared to all other groups, the connectivity differences in children with mood disorders were not significantly associated with any of the behavioral reading scores (though these were generally lower for the mood disorders group compared with healthy controls and children with behavioral disorders).

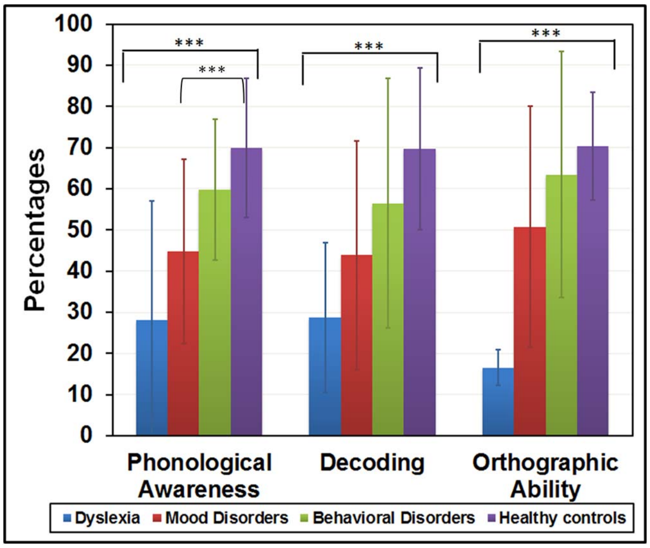

Fig. 1. Differences in reading measures between the four subject groups. ***$p < 0.001$. Healthy controls > behavioral disorders > mood disorders > dyslexia.

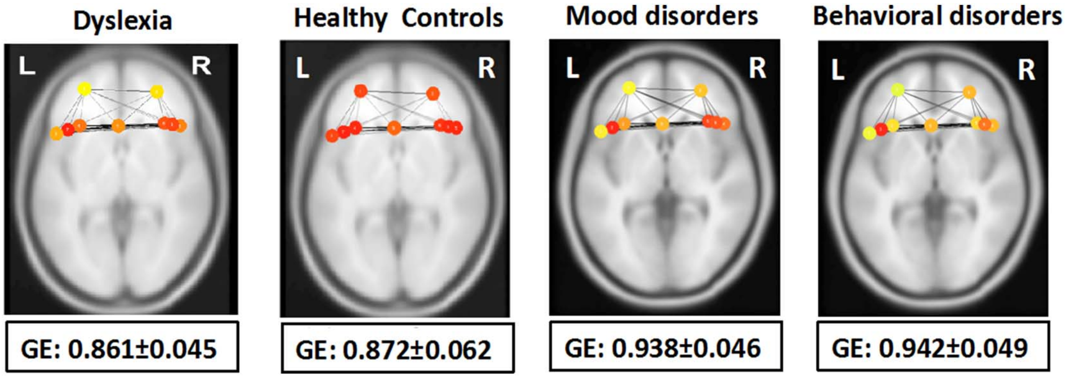

Fig. 2. Functional connectivity of the cingulo-opercular network in four subject groups. GE = average ± standard deviation of global efficiency of all the subjects in each group. The GE per node is the average inverse shortest path length between the given node and all the other nodes. Each node in a given network then has a beta value and a t-score. The beta value of each node is illustrated by the colors in this figure and Fig. 3. A lower beta value is illustrated by a yellow color and a greater beta value is red. Behavioral disorders > mood disorders > healthy controls > dyslexia.

The recent framework of the dual cognitive control network model defines separate roles for each pathway, supporting different attentional demands of reading and provides further identification of differing pathophysiology for reading difficulties from primary (i.e. dyslexia) or secondary sources (i.e. mood disorders). Our findings may also suggest that the GE of the two networks may influence each other as evidenced in the group with mood disorders where the cingulo-opercular GE is increased relative to controls, possibly reflecting a neurological process that is attempting to offset the very low fronto-parietal GE in this group (Table 3). In this case, the compensation mechanism appears to be inadequate and the phonological awareness measure in the group with mood disorders remains below control levels (Fig. 1, Table 3).

4.1. Difficulties in phonological processing related to fronto-parietal network in youth with mood disorders

Our findings further support a network-based pathophysiology related to reading difficulties in youth with mood disorders. Specifically, we have identified markedly reduced GE in the fronto-parietal network in children with mood disorders. Although the GE values in this network do not correlate with the phonological awareness for these children, the greatly reduced connectivity represents a disrupted fronto-parietal network that likely results in decreased attention to reading tasks through an interaction with working memory demands to manipulate parts of a word (Tan et al., 2005). The difficulty imposed by the demands of the CTOPP elision test to pronounce nonsense words by omitting phonemes from real words, may also stress children with mood disorders, known to have an affected limbic system (Pavuluri et al., 2008; Caetano et al., 2005), and reduce their performance even further; thereby explaining the low CTOPP scores in this group relative to healthy controls. Altered activation in regions related to the fronto-parietal network in individuals with bipolar disorder has been previously reported and suggests aberrant activity in the amygdala and dorsolateral prefrontal and cingulate cortices (see review: Drevets, 2000a; Drevets, 2000b). Atypical functional connectivity of the amygdala and regions in the fronto-parietal network was previously related to poorer performance in children with emotional and behavioral dysregulation during a working memory task (Bertocci et al., 2014). These results are complementary to our findings and suggest that the alterations in functional connectivity in the fronto-parietal networks, in conjunction with activation of the amygdala, may have a negative effect on the ability to manipulate sounds within a given word, which may contribute to a working memory overload. Irregular activity in the emotional and EF circuitry in children with mood disorders may also be associated with structural differences that have been identified to explain these deficits (Drevets, 2000a).

Although the GE of the fronto-parietal network in children with mood disorders was lower than that for the other study groups, this might be compensated by the higher GE of the cingulo-opercular network for this patient group. Reduced fronto-parietal and increased cingulo-opercular connectivity in persons with anxiety disorders has been previously proposed (Sylvester et al., 2012), and our findings support a compensation of the cingulo-opercular network in response to reduced fronto-parietal connectivity. This could explain why we did not find a significant association of GE in either network with the phonological awareness measure in this group; even though both the CTOPP score and the GE value in the fronto-parietal network were low.

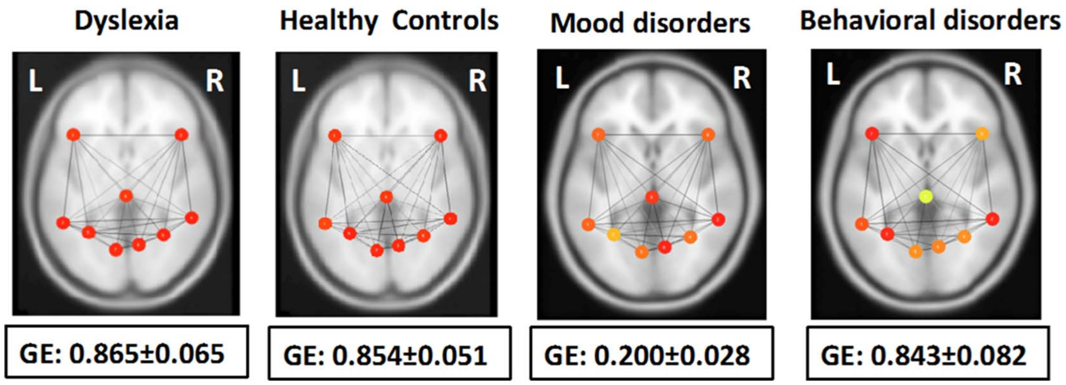

Fig. 3. Functional connectivity of the fronto-parietal network in four subject groups. GE = average ± standard deviation of global efficiency of all the subjects in each group. Dyslexia > healthy controls > behavioral disorders > mood disorders.

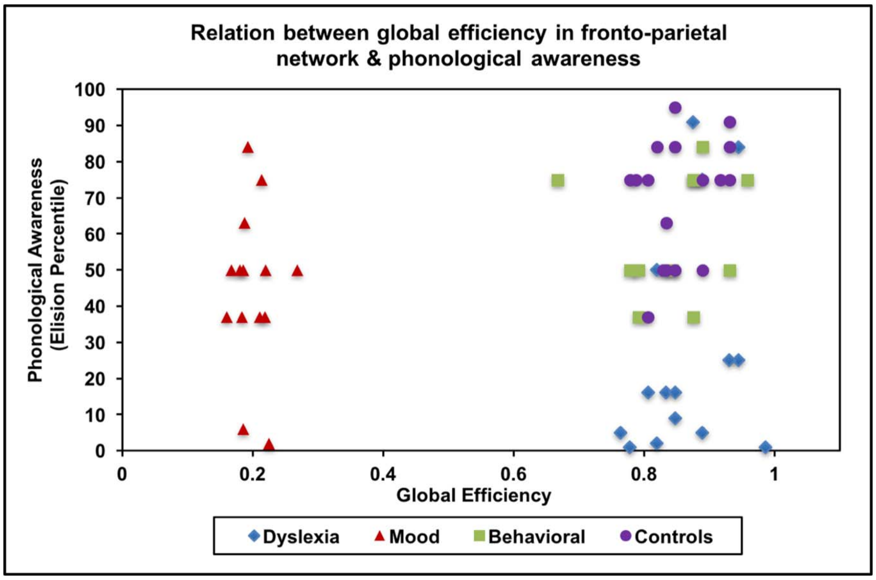

Fig. 4. Relationship between GE of the fronto-parietal networks and phonological processing measures in the four subject groups.

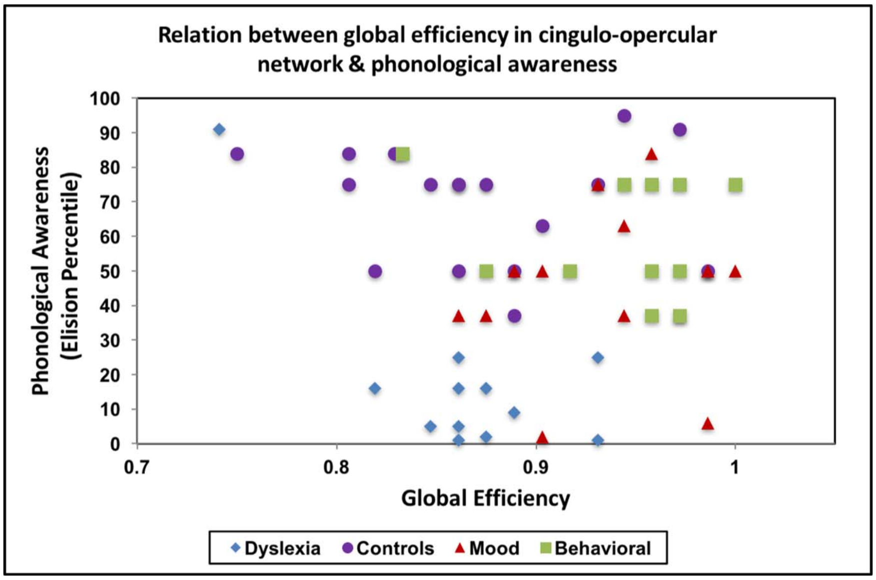

Fig. 5. Relationship between the GE of the cingulo-opercular networks and phonological processing scores in the four subject groups.

4.2. Difficulties in decoding, phonological and orthographical processing are related to cingulo-opercular functional connectivity in youth with dyslexia

Though children with dyslexia are impaired in phonological awareness and all other tested reading measures, they have marginally increased GE of the fronto-parietal network that is slightly greater than healthy controls. This result is in line with previously reported increased functional connectivity of left prefrontal and inferior parietal regions in adolescents with dyslexia (Wolf et al., 2010). However, children with dyslexia also displayed a somewhat lower GE of the cingulo-opercular network compared to healthy controls and children with mood or behavioral disorders. Functionally, recruitment of the cingulo-opercular network with the dorsal attentional network has been shown in young adults for tasks placing demands on phonological and decoding abilities or lexical (orthographical) processes (Ihnen et al., 2015). Reduced executive resources in cingulo-opercular regions also have been shown to increase connectivity of a known phonological processing region (i.e. left angular gyrus) to hippocampal cortex and thalamus as well as with visual processing regions (such as the fusiform gyrus) (Horowitz-Kraus and Holland, 2015) in developmental dyslexia (Wolf et al., 2010). Though the specific alternative connectivity discovered by Wolf and colleagues was not a focus of our specific study, the significant association we discovered between GE in this network and the CTOPP elision subtest scores ($p < 0.05$, corrected) indicates that cingulo-opercular network connectivity is a crucial component in phonological and orthographical processing; and when this connectivity is limited, phonological awareness is impaired. In this case, as seen in our sample, connectivity with alternative regions may permit some degree of compensation.

Schurz et al. (2015) also discovered reduced functional connectivity in cingulo-opercular regions during resting state and reading task conditions in adolescents with dyslexia, relative to typical readers, along with increased functional connectivity of the precuneus – a structure found active in both fronto-parietal and default networks - to regions traditionally related to reading (Schurz et al., 2015). We have previously demonstrated reduced functional connectivity of the cingulo-opercular network that was related to reading difficulties and was strengthened following reading intervention (Horowitz-Kraus et al., 2017; Horowitz-Kraus and Holland, 2015). Despite potential compensation by the fronto-parietal network for reduced integrity in the cingulo-opercular region in children with dyslexia, reduced functional connectivity of this network in children with dyslexia could impair maintenance of phonological representations and lead to weaknesses in phonological awareness and therefore to their inability to store "whole" words in their mental lexicon (i.e. "orthographical processing"). The reduced functional connectivity in the cingulo-opercular may also be related to impaired EFs and more specifically to difficulties in error monitoring and error correction, a crucial ability in learning to read (Horowitz-Kraus et al., 2017). Cingulo-opercular regions like the frontal operculum, have been shown to connect to reading-related regions like the superior temporal gyrus, via the uncinate fasciculus (Friederici, 2009). Tractography analysis also reveals that the uncinate fasciculus, among other white matter tracts, is significantly correlated to phonological decoding in typical readers and children with dyslexia (Odegard et al., 2009). Further studies should explore the morphometry of these areas to see if changes in white and grey matter in these patient populations could support these functional and structural findings.

Although we have focused on the association of the global efficiency of the cingulo-opercular network with decoding, phonological awareness and orthographical processing for children with dyslexia, reduced connectivity of this network also reveals that both EF networks are important in executing other reading domains. Scores on the Letter-Word Identification and Word Attack tests revealed group differences in orthography and decoding, respectively, with the dyslexia group demonstrating weaknesses in both skills. The co-activation of the visual word form area (VWFA) with the dorsal attentional network suggests that attention contributed to orthographic analysis in word recognition (Vogel et al., 2014). Previous studies demonstrated greater functional connectivity between the anterior cingulate cortex, part of the cingulo-opercular network, and the fusiform gyrus (part of the VWFA) in children with dyslexia who showed reading improvement following reading training (Horowitz-Kraus et al., 2015). The cingulo-opercular network, in association with the dorsal attentional network and the VWFA, may thus play a role in the maintenance of orthographic information. Specifically, reduced cingulo-opercular connectivity in children with dyslexia could underlie their orthography deficit by impairing their ability to maintain the orthographical analysis needed to identify words. The same impairment in maintaining attention due to reduced functional connectivity of the cingulo-opercular network could also explain why children with dyslexia struggle with decoding. A future study should examine this point in depth.

4.3. Limitations

The results of this study should be evaluated in the context of the following limitations. First, the resting-state conditions of rsfcMRI indirectly measure activity of brain networks that can be correlated to reading measures but do not assess neural activations during a reading-related task. Another study should consider these same networks during a reading task. Second, due to the small and unequal sample sizes, differences related to sex of participants were not controlled for in this study. Third, as we were specifically focused on the dual networks of cognitive control, we did not consider the role of other cognitive networks involved for these patient populations. Such connections should also be taken into account in a future study. Particularly, GE of the default network should also be explored in the future as the precuneus plays a role in both default and fronto-parietal networks and has been found to have increased connectivity with reading related regions in developmental dyslexia (Schurz et al., 2015). One final limitation of which we are aware relates to the difference in age between the groups of participants we compared. Youth from the LAMS cohorts with mood and behavioral disorders were significantly older than the dyslexia and control groups. Network connectivity is known to change as a function of age and could influence our findings (Dosenbach et al., 2010; Vogel et al., 2010; Karunanayaka et al., 2007). However, within network global efficiency has been reported to stabilize during childhood between 10 and 15 years of age, with functional connectivity estimated to increase by < 20% (Dosenbach et al., 2010; Vogel et al., 2010; Cao et al., 2016) during this age period. Given that the control and dyslexic groups are younger than the groups with behavioral and mood disorders, age dependent increases in GE are not likely to account for the difference we have reported that appear to differentiate children along a continuum of reading disabilities rather than age groups for both reading measures and global efficiency. Note too that the use of standard scores from CTOPP and WJ-III subtests as measures of reading ability already controls for the influence of age on reading measures between groups. Finally, we have included age as a covariate in our multivariate analysis and found that there is not a significant influence of age on our statistical results.

5. Conclusion

Approximately 35% of 4th grade students in the USA read proficiently while up to 32% fail to achieve Basic reading proficiency (U.S. Department of Education, 2015). The results reported here demonstrate that reading difficulties related to a primary reading disorder (i.e., dyslexia) involve abnormalities in neural circuits supporting cognitive control that differ from those associated with reading problems in children with mood disorders and behavioral disorders. Given the comorbidity of reading difficulties with mood and behavioral disorders (Pavuluri et al., 2006; Fristad et al., 1992; Goldston et al., 2007; Arnold et al., 2005; Maughan et al., 2003), this study provides further understanding of specific reading deficits for children with each disorder. Maturation of fronto-parietal cortical structures is shown to relate to the development of EFs like working memory (Tamnes et al., 2013). EF training for processing speed and working memory may prove beneficial to children with mood disorders to strengthen the functional connectivity of the fronto-parietal network. It is possible that stronger functional connectivity in one cognitive control network is used as a compensation strategy to overcome diminished functional connectivity in the other network. This is shown in the increased GE of cingulo-opercular networks for children with mood disorders despite reduced connectivity in the fronto-parietal network, and vice versa for children with dyslexia. These findings may serve as clinical guidance for tailored intervention programs for children suffering from reading difficulties from different sources. More generally, this study supports resting state functional connectivity as a crucial neuroimaging technique for understanding these disorders. It will be important to further delineate the connectivity of children with comorbid dyslexia and mood disorders.

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References

Alvarez, J.A., Emory, E., 2006. Executive function and the frontal lobes: a meta-analytic review. Neuropsychol. Rev. 16 (1), 17–42.

Arnold, E.M., et al., 2005. Severity of emotional and behavioral problems among poor and typical readers. J. Abnorm. Child Psychol. 33 (2), 205–217.

Axelson, D., et al., 2003. A preliminary study of the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children mania rating scale for children and adolescents. J. Child Adolesc. Psychopharmacol. 13 (4), 463–470.

Baria, A.T., et al., 2011. Anatomical and functional assemblies of brain BOLD oscillations. J. Neurosci. 31 (21), 7910–7919.

Behzadi, Y., et al., 2007. A component based noise correction method (CompCor) for BOLD and perfusion based fMRI. NeuroImage 37 (1), 90–101.

Bertocci, M.A., et al., 2014. Behavioral and emotional dysregulation trajectories marked by prefrontal-amygdala function in symptomatic youth. Psychol. Med. 44 (12), 2603–2615.

Birmaher, B., et al., 1997. The Screen for Child Anxiety Related Emotional Disorders (SCARED): scale construction and psychometric characteristics. J. Am. Acad. Child Adolesc. Psychiatry 36 (4), 545–553.

Bush, G., Valera, E.M., Seidman, L.J., 2005. Functional neuroimaging of attention-deficit/hyperactivity disorder: a review and suggested future directions. Biol. Psychiatry 57 (11), 1273–1284.

Caetano, S.C., et al., 2005. Fronto-limbic brain abnormalities in juvenile onset bipolar disorder. Biol. Psychiatry 58 (7), 525–531.

Cao, M., et al., 2016. Toward developmental connectomics of the human brain. Front. Neuroanat. 10, 25.

Castellanos, F.X., Tannock, R., 2002. Neuroscience of attention-deficit/hyperactivity disorder: the search for endophenotypes. Nat. Rev. Neurosci. 3 (8), 617–628.

Cerullo, M.A., et al., 2012. A longitudinal functional connectivity analysis of the amygdala in bipolar I disorder across mood states. Bipolar Disord. 14 (2), 175–184.

Dickstein, S.G., et al., 2006. The neural correlates of attention deficit hyperactivity disorder: an ALE meta-analysis. J. Child Psychol. Psychiatry 47 (10), 1051–1062.

Dosenbach, N.U., et al., 2008. A dual-networks architecture of top-down control. Trends Cogn. Sci. 12 (3), 99–105.

Dosenbach, N.U., et al., 2010. Prediction of individual brain maturity using fMRI. Science 329 (5997), 1358–1361.

Doyle, A.E., et al., 2005. Neuropsychological functioning in relatives of girls with and without ADHD. Psychol. Med. 35 (8), 1121–1132.

Drevets, W.C., 2000a. Functional anatomical abnormalities in limbic and prefrontal cortical structures in major depression. Prog. Brain Res. 126, 413–431.

Drevets, W.C., 2000b. Neuroimaging studies of mood disorders. Biol. Psychiatry 48 (8), 813–829.

Fair, D.A., et al., 2009. Functional brain networks develop from a “local to distributed” organization. PLoS Comput. Biol. 5 (5), e1000381.

Fair, D.A., et al., 2010. Atypical default network connectivity in youth with attention-deficit/hyperactivity disorder. Biol. Psychiatry 68 (12), 1084–1091.

Fleck, D.E., et al., 2012. Functional MRI of sustained attention in bipolar mania. Mol. Psychiatry 17 (3), 325–336.

Friederici, A.D., 2009. Pathways to language: fiber tracts in the human brain. Trends Cogn. Sci. 13 (4), 175–181.

Fristad, M.A., et al., 1992. Depression and learning disabilities in children. J. Affect. Disord. 26 (1), 53–58.

Goldman, L.S., et al., 1998. Diagnosis and treatment of attention-deficit/hyperactivity disorder in children and adolescents. Council on Scientific Affairs, American Medical Association. JAMA 279 (14), 1100–1107.

Goldston, D.B., et al., 2007. Reading problems, psychiatric disorders, and functional impairment from mid- to late adolescence. J. Am. Acad. Child Adolesc. Psychiatry 46 (1), 25–32.

Henin, A., et al., 2007. Can bipolar disorder-specific neuropsychological impairments in children be identified? J. Consult. Clin. Psychol. 75 (2), 210–220.

Horowitz-Kraus, T., 2014. Pinpointing the deficit in executive functions in adolescents with dyslexia performing the Wisconsin card sorting test: an ERP study. J. Learn. Disabil. 47 (3), 208–223.

Horowitz-Kraus, T., Holland, S.K., 2015. Greater functional connectivity between reading and error-detection regions following training with the reading acceleration program in children with reading difficulties. Ann. Dyslexia 65 (1), 1–23.

Horowitz-Kraus, T., Toro-Serey, C., DiFrancesco, M., 2015. Increased resting-state functional connectivity in the cingulo-opercular cognitive-control network after intervention in children with reading difficulties. PLoS One 10 (7), e0133762.

Horowitz-Kraus, T., et al., 2017. Reading related white matter structures in adolescents are influenced more by dysregulation of emotion than behavior. Neuroimage Clin. 15, 732–740.

IBM, 2012. SPSS: Statistical Software for the Social Sciences. IBM Corp., Armonk, NY.

Ihnen, S.K., Petersen, S.E., Schlaggar, B.L., 2015. Separable roles for attentional control sub-systems in reading tasks: a combined behavioral and fMRI study. Cereb. Cortex 25 (5), 1198–1218.

Jacobson, L.A., et al., 2011. Working memory influences processing speed and reading fluency in ADHD. Child Neuropsychol. 17 (3), 209–224.

Karunanayaka, P.R., et al., 2007. Age-related connectivity changes in fMRI data from children listening to stories. NeuroImage 34 (1), 349–360.

Kaufman, J., et al., 1997. Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. J. Am. Acad. Child Adolesc. Psychiatry 36 (7), 980–988.

Kowatch, R.A., et al., 2005. Review and meta-analysis of the phenomenology and clinical characteristics of mania in children and adolescents. Bipolar Disord. 7 (6), 483–496.

Li, F., et al., 2014. Intrinsic brain abnormalities in attention deficit hyperactivity disorder: a resting-state functional MR imaging study. Radiology 272 (2), 514–523.

Manis, F.R., Custodio, R., Szeszulski, P.A., 1993. Development of phonological and orthographic skill: a 2-year longitudinal study of dyslexic children. J. Exp. Child Psychol. 56 (1), 64–86.

Maughan, B., et al., 2003. Reading problems and depressed mood. J. Abnorm. Child Psychol. 31 (2), 219–229.

Neta, M., Schlaggar, B.L., Petersen, S.E., 2014. Separable responses to error, ambiguity, and reaction time in cingulo-opercular task control regions. NeuroImage 99, 59–68.

Odegard, T.N., et al., 2009. Brain connectivity in non-reading impaired children and children diagnosed with developmental dyslexia. Neuropsychologia 47 (8–9), 1972–1977.

Pavuluri, M.N., et al., 2006. Impact of neurocognitive function on academic difficulties in pediatric bipolar disorder: a clinical translation. Biol. Psychiatry 60 (9), 951–956.

Pavuluri, M.N., et al., 2008. An fMRI study of the interface between affective and cognitive neural circuitry in pediatric bipolar disorder. Psychiatry Res. 162 (3), 244–255.

Rubia, K., et al., 1999. Hypofrontality in attention deficit hyperactivity disorder during higher-order motor control: a study with functional MRI. Am. J. Psychiatry 156 (6), 891–896.

Schurz, M., et al., 2015. Resting-state and task-based functional brain connectivity in developmental dyslexia. Cereb. Cortex 25 (10), 3502–3514.

Soares, J.C., Mann, J.J., 1997. The functional neuroanatomy of mood disorders. J. Psychiatr. Res. 31 (4), 393–432.

Strakowski, S.M., Delbello, M.P., Adler, C.M., 2005. The functional neuroanatomy of bipolar disorder: a review of neuroimaging findings. Mol. Psychiatry 10 (1), 105–116.

Sylvester, C.M., et al., 2012. Functional network dysfunction in anxiety and anxiety disorders. Trends Neurosci. 35 (9), 527–535.

Szaflarski, J.P., et al., 2006. A longitudinal functional magnetic resonance imaging study of language development in children 5 to 11 years old. Ann. Neurol. 59 (5), 796–807.

Tamnes, C.K., et al., 2013. Longitudinal working memory development is related to structural maturation of frontal and parietal cortices. J. Cogn. Neurosci. 25 (10), 1611–1623.

Tan, L.H., et al., 2005. Neuroanatomical correlates of phonological processing of Chinese characters and alphabetic words: a meta-analysis. Hum. Brain Mapp. 25 (1), 83–91.

U.S. Department of Education, N.C.f.E.S, 2015. National Assessment of Educational Progress (NAEP), Selected Years, 1992–2015 Reading Assessments.

Versace, Amelia, A, H.E., Bertocci, Michele A., Bebko, Genna, Almeida, Jorge R.C., Perlman, Susan B., Leemans, Alexander, Schirda, Claudiu, Aslam, Haris, Dwojak, Amanda, Bonar, Lisa, Travis, Michael J., Gill, Mary Kay, Demeter, Christine, Diwadkar, Vaibhav, Sunshine, Jeffrey, Holland, Scott K., Kowatch, Robert A., Birmaher, Boris, Axelson, David A., Horwitz, Sarah McCue, Frazier, Thomas, Arnold, Eugene, Fristad, Mary A., Youngstrom, Eric, Findling, Robert L., 2015. White matter structure in youth with behavioral and emotional dysregulation disorders: a probabilistic tractographic study. JAMA Psychiat. 72 (4), 367–376.

Vogel, A.C., Power, J.D., Petersen, S.E., Schlaggar, B.L., 2010. Development of the brain's functional network architecture. Neuropsychol. Rev. 20 (4), 362–375.

Vogel, A.C., Petersen, S.E., Schlaggar, B.L., 2014. The VWFA: it's not just for words anymore. Front. Hum. Neurosci. 8, 88.

Wagner, R.K., Torgesen, J.K., Rashotte, C.A., 1999. Comprehensive Test of Phonological Processing (CTOPP). Pro-Ed, Austin, TX.

Wallis, G., et al., 2015. Frontoparietal and cingulo-opercular networks play dissociable roles in control of working memory. J. Cogn. Neurosci. 27 (10), 2019–2034.

Walshaw, P.D., Alloy, L.B., Sabb, F.W., 2010. Executive function in pediatric bipolar disorder and attention-deficit hyperactivity disorder: in search of distinct phenotypic profiles. Neuropsychol. Rev. 20 (1), 103–120.

Wandell, B.A., Yeatman, J.D., 2013. Biological development of reading circuits. Curr. Opin. Neurobiol. 23 (2), 261–268.

Whitfield-Gabrieli, S., Nieto-Castanon, A., 2012. Conn: a functional connectivity toolbox for correlated and anticorrelated brain networks. Brain Connect. 2 (3), 125–141.

Willcutt, E.G., et al., 2005. Validity of the executive function theory of attention-deficit/hyperactivity disorder: a meta-analytic review. Biol. Psychiatry 57 (11), 1336–1346.

Wolf, R.C., et al., 2010. Functional brain network abnormalities during verbal working memory performance in adolescents and young adults with dyslexia. Neuropsychologia 48 (1), 309–318.

Woodcock, R.W., McGrew, K.S., Mather, N., 2001. Woodcock-Johnson® III Normative Update (NU) Tests of Achievement, Forms A and B, 3rd ed. Houghton Mifflin Harcourt.

Wozniak, J., et al., 2004. The clinical characteristics of unipolar vs. bipolar major depression in ADHD youth. J. Affect. Disord. 82 (Suppl. 1), S59–69.

Youngstrom, E.A., et al., 2008. Developing a 10-item mania scale from the Parent General Behavior Inventory for children and adolescents. J. Clin. Psychiatry 69 (5), 831–839.

Zang, Y.F., et al., 2007. Altered baseline brain activity in children with ADHD revealed by resting-state functional MRI. Brain Dev. 29 (2), 83–91.