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# Reading related white matter structures in adolescents are influenced more by dysregulation of emotion than behavior

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A R T I C L E I N F O

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A B S T R A C T

Mood disorders and behavioral are broad psychiatric diagnostic categories that have different symptoms and neurobiological mechanisms, but share some neurocognitive similarities, one of which is an elevated risk for reading deficit. Our aim was to determine the influence of mood versus behavioral dysregulation on reading ability and neural correlates supporting these skills in youth, using diffusion tensor imaging in 11- to 17-year-old children and youths with mood disorders or behavioral disorders and age-matched healthy controls. The three groups differed only in phonological processing and passage comprehension. Youth with mood disorders scored higher on the phonological test but had lower comprehension scores than children with behavioral disorders and controls; control participants scored the highest. Correlations between fractional anisotropy and phonological processing in the left Arcuate Fasciculus showed a significant difference between groups and were strongest in behavioral disorders, intermediate in mood disorders, and lowest in controls. Correlations between these measures in the left Inferior Longitudinal Fasciculus were significantly greater than in controls for mood but not for behavioral disorders. Youth with mood disorders share a deficit in the executive-limbic pathway (Arcuate Fasciculus) with behavioral-disordered youth, suggesting reduced capacity for engaging frontal regions for phonological processing or passage comprehension tasks and increased reliance on the ventral tract (e.g., the Inferior Longitudinal Fasciculus). The low passage comprehension scores in mood disorder may result from engaging the left hemisphere. Neural pathways for reading differ mainly in executive-limbic circuitry. This new insight may aid clinicians in providing appropriate intervention for each disorder.

## 1. Introduction

### 1.1. Reading difficulties in youth with mood or behavioral disorders

Of U.S. 4th graders, 27%–58% do not achieve basic levels of reading proficiency (The Nation's Report Card, National Center for Education Statistics, see (Donahue et al., 1999)). For approximately 10% of these children, the cause is primarily a deficit in reading mechanisms (i.e., dyslexia (O'Hare, 2010)). For the other 90% (24%–52% of all 4th graders), reading difficulties are secondary to another primary diagnosis. Approximately 30%–40% of youth with either mood or behavioral disorders have comorbid reading difficulties Behavioral disorders include attention deficit hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), and conduct disorder (CD) while mood

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disorders include depressive, bipolar, and anxiety disorders.

Although both mood- and behavioral-disordered youth suffer from severe learning difficulties (Forness and Knitzer, 1992), the neuroimaging literature describes different neural circuits contributing to the difficulties manifested within each group. Mood disorders are thought to be accompanied by neural abnormalities related to the limbic system (greater activation of the amygdala (Davidson et al., 1999; Donegan et al., 2003) and frontal lobe (frontal asymmetries; see Coan and Allen, 2004 for review, Davidson et al., 1999), abnormalities in functional connectivity between the frontal lobe and amygdala (Banks et al., 2007), decreased activation in temporo-parietal (Halari et al., 2009) and parietal regions (Fitzgerald et al., 2008), and decreased functional connectivity in the fronto-parietal and cingulo-opercular networks (Sylvester et al., 2012). In contrast, individuals with behavioral disorders share abnormalities, mainly in neural circuits related to either decreased or altered frontal lobe activation (Spalletta et al., 2001; Brower and Price, 2001, respectively).

Several neuroimaging studies have attempted to characterize neural correlates that can differentiate individuals with mood disorders from those with behavioral disorders, especially using structural-connectivity tools. Fractional anisotropy (FA), a measure related to the diffusivity of white matter water molecules measured by diffusion tensor imaging (DTI), reflects the ratio of axial versus radial diffusivity. Researchers have demonstrated reduced FA values in individuals with mood disorders in white matter tracts in temporal and frontal brain regions (Frazier et al., 2007; Abler et al., 2008), whereas individuals with behavioral disorders had reduced FA values in different tracts, including limbic white matter tracts (van Ewijk et al., 2012; Makris et al., 2008; Konrad et al., 2010; Sarkar et al., 2013). Versace and colleagues recently examined relationships between mood or behavioral dysregulation and white matter structure in three major mood regulation tracts in adolescents (forceps minor, uncinate fasciculus, cingulum). They found that youth with mood dysregulation showed lower FA in these tracts when compared to youth with behavioral dysregulation and with typically developing youth (Versace et al., 2015). They suggested that lower FA in these tracts is associated with altered structural connectivity between the anterior temporal lobe and prefrontal cortex and between the left and right prefrontal cortex, which may represent a neural mechanism of mood dysregulation in youth (Versace et al., 2015). These regions, as well as the parietal regions, which are highly involved in the reading process, are often reported to be abnormal in youth with both mood and behavioral disorders (Horowitz-Kraus et al., 2014a). Because reading relies on most of these anatomical regions, the existence of reading difficulties in youth with mood and behavioral disorders is not surprising.

### 1.2. Neural circuits related to reading (phonological processing, orthographical processing and reading comprehension)

Reading is one of the most complex cognitive human abilities; it generally engages orthographic, phonological, and semantic processors simultaneously (Parallel Distributed Processing model; Seidenberg and McClelland, 1989). The most traditional neuroimaging model for reading suggests that neural circuits related to reading include the Occipito-temporal Ventral Stream, Angular Gyrus, and Inferior Parietal Lobule (in proximity to Wernicke's area), as well as the Inferior Frontal Gyrus (including Broca's Area) corresponding to these three processors, especially in the left hemisphere (Shaywitz, 2003). Whereas the left hemisphere has been primarily related to phonological and orthographic processing at the word level, the right hemisphere has been related to reading comprehension (Horowitz-Kraus et al., 2014b). The Arcuate Fasciculus (AF) and the Superior Longitudinal Fasciculus (SLF) connect the frontal and the temporo-parietal regions (Makris et al., 2005), whereas the Inferior Longitudinal Fasciculus (ILF) connect the temporal and occipital regions (Uddin et al., 2010), and the inferior fronto-occipital fasciculus (IFOF) connect the frontal-occipital regions (Makris et al., 2009). Interestingly, greater FA values in the right AF and a greater functional connectivity between regions generated in the sentence comprehension task in 17-year-old typical readers have been correlated with higher passage comprehension scores from the Woodcock-Johnson III battery (WJ-III) (Horowitz-Kraus et al., 2014b). This correlation was evident primarily in the anterior part of the AF, emphasizing right hemispheric contributions to reading-comprehension performance. An association of higher reading-comprehension scores with greater functional and structural connectivity in the right hemisphere was also evident in 7- to 9-year-old typical readers (Horowitz-Kraus et al., 2015b).

The advancing field of neuroimaging has revealed that the reading process involves more than the classical phonological, orthographic, and semantic regions. Additional processors include the engagement of executive functions and control networks, such as the fronto-parietal and cingulo-opercular networks (Horowitz-Kraus et al., 2015a; Horowitz-Kraus et al., 2014a; Horowitz-Kraus et al., 2014c; Vogel et al., 2014). The involvement of regions related to error monitoring (Anterior Cingulate Cortex; Horowitz-Kraus et al., 2014a; Horowitz-Kraus and Breznitz, 2014), executive functions (Dorsolateral Prefrontal Cortex; Horowitz-Kraus et al., 2014a), and visual attention (Precuneus; Vogel et al., 2014; Vogel et al., 2013) are all part of a dual cognitive control network (Dosenbach et al., 2008), indicating these regions are critical for intact reading.

Literature points at behavioral evidence of reading impairments and general differences in FA values in different white matter tracts in individuals with mood or behavioral disorders (Pavuluri et al., 2006). However, there is still a gap in knowledge on differences in sub-domains of reading (i.e., phonology vs orthography vs reading comprehension) and neural circuits related to these reading components between the two groups. Recruiting from a multisite longitudinal study of youth with mood or behavioral dysregulation, the Longitudinal Assessment of Manic Symptoms (LAMS) study (Horwitz et al., 2010), the current exploratory study investigated different effects of mood and behavioral disorders on reading ability. According to Frith's model for reading development and for an intact reading comprehension, phonology and orthography should be mastered (Frith, 1985). Therefore in the current study, ewe focused on phonemic awareness (i.e., phonological processing), orthographical processing (i.e., word recognition), and reading comprehension (i.e., passage comprehension) to identify differences between mood and behavioral disorders in FA values that correlate with these abilities in white matter tracts known to be involved in reading ability. Based on studies described above, this study examined several bilateral white matter tracts as regions of interest (ROIs): AF, ILF, SLF, and IFOF We hypothesized that, due to evidence of lower activation and structural connectivity in these neural circuits related to reading as well as impairments in the limbic circuitry (involving the frontal regions) in youth with mood disorders, greater reading difficulties would be observed in mood disorders than in behavioral disorders. We also postulated that youth with mood disorders would exhibit lower FA values in frontal portions of reading-related tracts compared to youth with behavioral disorders.

## 2. Results

### 2.1. Behavioral data

Differences in IQ between the groups were not significant [full scale IQ for mood disorders $M = 114.57$, $SD = 17.06$; for behavioral disorders $M = 105.59$, $SD = 12.34$; for controls $M = 110.85$, $SD = 12.77$ [$F(2,36) = 1.25$, $p = 0.3$].

ANOVAs for the three groups (mood disorders, behavioral disorders, and controls) and three reading measures (phonemic awareness, orthographical ability, and reading comprehension) indicated significant differences between the groups for phonological awareness and reading comprehension. Post-hoc independent *t*-tests revealed that youth with

**Table 1**
Phonological awareness, orthographical abilities, and reading comprehension (in percentiles) in youth with mood (M) disorders, youth with behavioral disorders (B) and control (C) participants.

| Ability | Measure in percentile | Mood *M* (*SD*) | Behavior *M* (*SD*) | Control *M* (*SD*) | *F* *p* values | Statistics contrast *t* |
|---|---|---|---|---|---|---|
| Phonological awareness | Elision subtest (CTOPP) | 43.29 (22.50) | 60.08 (18.70) | 64.62 (11.29) | $F(2,36) = 5.13$ $p < 0.05$ | C > M −2.07* |
| Orthographical abilities | Letter-word (WJ-III) | 50.79 (29.20) | 63.45 (28.34) | 60.28 (22.41) | $F(2,35) = 0.78$ $p = 0.466$ | C > M −3.14** |
| Reading comprehension | Passage comprehension (WJ-III) | 36.08 (20.08) | 49.74 (27.23) | 61.75 (28.91) | $F(2,32) = 3.26$ $p = 0.05$ | C > M −2.56* |

*F*, results from the ANOVA test; *t*, results from *t*-test analyses; CTOPP, Comprehensive Test of Phonological Processing; WJ-III, Woodcock-Johnson III battery.
* $p < 0.05$.
** $p < 0.01$.

mood disorders, but not behavioral disorders, had significantly lower scores in these measures than control participants (Table 1) despite IQ being at least as high.

### 2.2. Correlation of reading measures

The three reading scores across the combined groups were all significantly and positively correlated (phonemic awareness and reading comprehension, $r = 0.44$, $p < 0.01$; phonemic awareness and orthographic processing, $r = 0.55$, $p < 0.01$; orthographical processing and reading comprehension, $r = 0.35$, $p < 0.05$).

### 2.3. Imaging data

#### 2.3.1. Group composites

There was no main effect of group upon FA in the four bilateral tracts: AF, ILF, SLF, IFOF. Post-hoc *t*-tests also yielded no significant results.

#### 2.3.2. Correlation of FA values in the selected ROIs with reading measures

Because there was a significant main effect of group on phonological awareness and reading comprehension, we correlated these measures with FA values in the bilateral ROIs. The four separate ANCOVAs revealed significant results in all four ROIs ($p < 0.05$ after FDR correction); higher phonological awareness scores were associated with higher FA values in all chosen ROIs (Table 2 and Fig. 1).

To determine if there are group differences in correlation of FA values with reading ability for the four selected ROIs, a Group FA × Reading ability interaction was checked using each reading measure separately. Higher phonological awareness scores were positively correlated with FA values in the left AF in youth with behavioral disorders; this correlation was significantly greater than in youth with mood disorders. A similar correlation (phonological awareness with FA) in the anterior portion of the left ILF was greater in youth with mood disorders (but not behavioral disorders) than in control participants ($p < 0.05$, FDR corrected; Table 3 and Fig. 2 for Behavioral disorders > Mood disorders, and Fig. 3 for Controls > Mood disorders).

#### 2.3.3. Correlation of reading comprehension scores and FA measures in the selected ROIs

The four separate ANCOVAs revealed significant results in all chosen ROIs ($p < 0.05$, FDR-corrected). Higher reading comprehension scores were associated with higher FA values for all ROIs (Table 4 and Fig. 4).

To determine if there were group differences in FA values for the four selected ROIs, a Group FA × Reading ability interaction was checked using each reading measure separately. Higher reading comprehension scores were positively correlated with FA values in the left AF, and the correlation was significantly higher in youth with mood disorders than in the control group ($p < 0.05$, FDR-corrected; Table 5 and Fig. 5).

**Table 2**
White matter tracts and nearest gray matter points from the significant correlation between phonological awareness scores and FA measures in the selected regions of interest (using ANOVA) ($p < 0.05$, FDR corrected). Regions were defined using the Harvard-Oxford atlas in FSL.

| Tract | Nearest gray matter | BA |
|---|---|---|
| L AF | Precuneus | 7 |
| | Central opercular cortex | 44 |
| | Insular cortex | 13 |
| R AF | Precuneus | 7 |
| | Cingulate cortex | 23/24 |
| L ILF | Middle temporal gyrus, | 21 |
| | Superior temporal gyrus | 22 |
| | Heschl's gyrus | 41 |
| | Planum temporale | 42 |
| | Lateral occipital cortex | 18/19 |
| | Middle temporal gyrus | 21 |
| | Angular gyrus | 39 |
| R ILF | Middle temporal gyrus | 21 |
| | Superior temporal gyrus | 22 |
| | Parietal operculum | 40 |
| | Planum temporale | 42 |
| L SLF | Precentral gyrus | 4/6 |
| | Postcentral gyrus | 1 |
| | Inferior frontal gyrus | 9/5/44/46 |
| | Central opercular cortex | 44 |
| | Insular cortex | 13 |
| R SLF | Central opercular cortex | 44 |
| | Insular cortex | 13 |
| | Precentral gyrus | 4/6 |
| | Postcentral gyrus | 1 |
| L IFOF and R IFOF | Heschl's gyrus | 41 |
| | Insular cortex | 13 |
| | Planum polare | 22 |
| | Planum temporale | 42 |

BA, Brodmann area according to the Harvard-Oxford atlas implemented in FSL; L, left; R, right; AF, Arcuate Fasciculus; ILF, Inferior Longitudinal Fasciculus; SLF, Superior Longitudinal Fasciculus; IFOF, Inferior Frontal-Occipital Fasciculus.

## 3. Discussion

Psychiatric disorders in youth is generally divided into behavioral disorders involving some emotional dysregulation (including attention deficit/hyperactivity disorder, disruptive behavior disorders, conduct disorder, and oppositional defiant disorder) and mood disorders involving some behavioral problems (including depressive disorder, bipolar spectrum disorder, and anxiety disorder). This study examined potential behavioral and structural differences related to three reading measures-phonemic awareness, orthography, and reading comprehension-in youth with mood disorders and those with behavioral disorders compared to age-matched control participants. As postulated, youth with mood disorders had the lowest reading scores (despite the nominally highest IQ (9 points above behavioral disorders and 4 points above controls, not significant for this small sample size). More specifically, youth with mood disorders showed lower phonology and

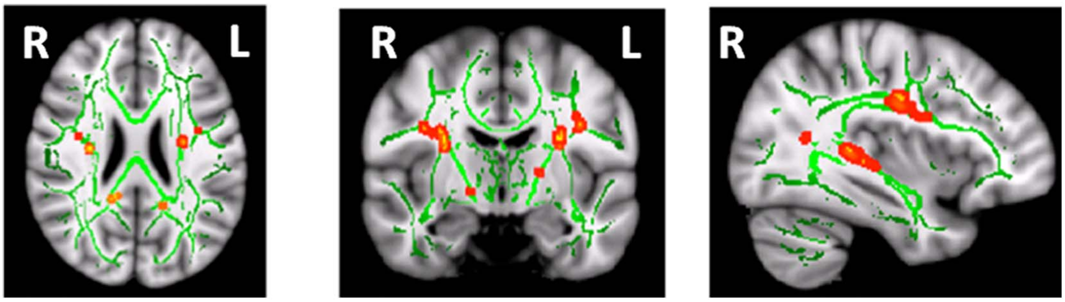


**Fig. 1.** Comparison of youth with mood disorders, those with behavioral disorders, and control participants: ANCOVA for fractional anisotropy (FA) values for four brain regions using phonological awareness percentage as a covariate. Three-dimensional tractography results demonstrating the significant positive correlation of FA values with percentages for the phonological awareness subtest from the CTOPP battery ($p < 0.05$, FDR-corrected). Axial (left panel), coronal (middle panel), and sagittal (right panel) views of the MNI-152 (1 mm) template and the white matter skeleton (green) are shown (left portion of image = right hemisphere, right portion of image = left hemisphere). Hotter color represents a greater correlation between the FA values and the behavioral measure.

**Table 3**
Post-hoc *t*-tests of < < is something missing here? > > using the phonological awareness measure as a covariate of interest ($p < 0.05$, FDR-corrected).

| Tract | Statistics contrast | Nearest gray matter | BA | Figure |
|---|---|---|---|---|
| L AF | B > M | Lateral occipital cortex | 18/19 | 3 |
| | | Inferior temporal gyrus | 20 | |
| | | Middle temporal gyrus | 21 | |
| L ILF | M > C | Inferior temporal gyrus | 20 | 4 |
| | | Fusiform gyrus | 37 | |
| | | Parahippocampal gyrus | 27/34/35 | |

BA, Brodmann area according to the Harvard-Oxford atlas implemented in FSL atlas; L, left; AF, Arcuate Fasciculus; B, youth with behavioral disorders; M, youth with mood disorders; ILF, Inferior Longitudinal Fasciculus; C, control participants.

reading comprehension scores than those with behavioral disorders. Youth with behavioral disorders showed greater left AF correlation of FA with phonological awareness than youth with mood disorders. Those with behavioral disorders also showed an overall decreased reading performance compared to controls. Youth with mood disorders showed greater correlation of left ILF FA values with phonological awareness than control participants. Correlation of reading comprehension with FA values in the left AF was higher in youth with mood disorders than in control participants. Since only two children in the group with mood disorders also had behavioral disorders, the results do reflect the differences between children with mood disorders vs those with behavioral disorders.

### *3.1. Greater phonemic awareness deficit in youth with mood disorders compared to youth with behavioral disorders*

Youth with mood disorders experienced greater deficits in phonemic awareness and reading comprehension than youth with behavioral disorders. As noted, there are several neuronal differences between mood and behavioral disorders. The former exhibit impairment not only in frontal neural circuits, but also in the limbic system (Davidson et al., 1999; Donegan et al., 2003), the fronto-limbic (Banks et al., 2007) and tempo-parietal circuits (Halari et al., 2009), and in reduced gray matter in the Angular Gyrus and Superior Temporal Gyrus in the parietal and temporal lobes, respectively (Mak et al., 2009). Altered activation of the limbic system, together with frontal system disturbance, may cause a greater deficit in orienting attention to phonological stimulation (which, in this case, was not intuitive). Atypical activation of the tempo-parietal circuits, associated with phonological processing (Shaywitz, 2003), may contribute to phonemic awareness deficit in youth with mood disorders.

Another possibility is that lower performance in the phonological awareness task in youth with mood disorders than in youth with behavioral disorders may depend on task characteristics. In the ‘Elision’ task used for the current study, individuals were requested to delete a sound in the beginning, middle, or end of a spoken word and to create a new word from the remaining sounds. This manipulation is not intuitive and relies not only on phonology, but also on working memory (Kroese et al., 2000), which, in turn, is related primarily to frontal and also parietal lobe activation (Tamnes et al., 2013). Since youth with mood disorders suffer from a disruption not only in frontal regions but also in mood regulation controlled by the limbic system, the need to read nonsense words when their phonological ability is impaired may be more stressful than for youth with behavioral disorders, resulting in lower performance. A follow-up assessment involving self-reports of the youth's perception of this task is needed. Qualitative interviewing might be useful for this.

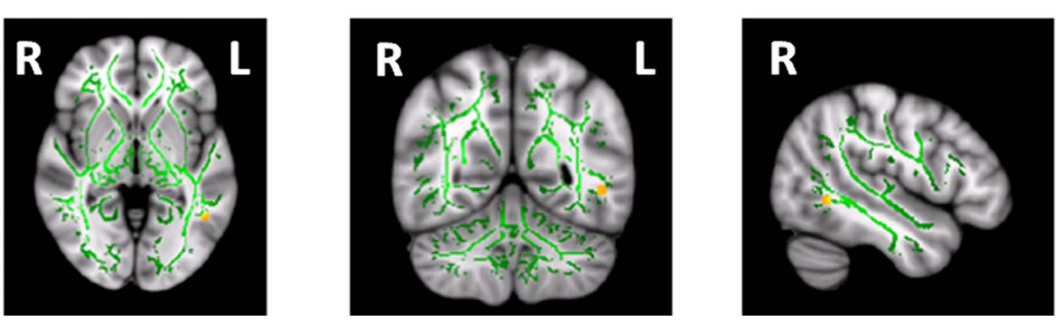


**Fig. 2.** Comparison of youth with either mood or behavioral disorders: independent *t*-test for fractional anisotropy (FA) values for the left Arcuate Fasciculus (AF) using phonemic awareness percentage as a covariate. Three-dimensional tractography results demonstrating the significant positive correlation of FA values of the left AF with percentages for the phonemic awareness subtest from the CTOPP battery ($p < 0.05$, FDR-corrected). Axial (left panel), coronal (middle panel), and sagittal (right panel) views of the MNI-152 (1 mm) template and the white matter skeleton (green) are shown (left portion of image = right hemisphere, right portion of image = left hemisphere). Yellow color indicates the region of greater FA values for youth with mood versus those with behavioral disorders; the left AF.

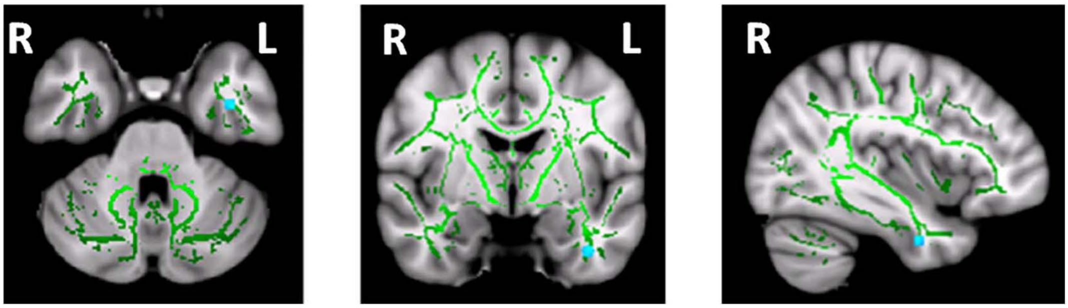


**Fig. 3.** Comparison of youth with mood disorders and control participants: independent *t*-test for fractional anisotropy (FA) values for the left Inferior Longitudinal Fasciculus (ILF) using phonological awareness percentage as a covariate. Three-dimensional tractography results demonstrating the significant positive correlation of FA values of the left ILF with percentages for the phonological awareness subtest from the CTOPP battery ($p < 0.05$, FDR-corrected). Axial (left panel), coronal (middle panel), and sagittal (right panel) views of the MNI-152 (1 mm) template and the white matter skeleton (green) are shown (left portion of image = right hemisphere, right portion of image = left hemisphere). Blue color indicates the region of greater FA values for youth with mood disorders versus controls; the left Inferior Longitudinal Fasciculus. MNI, Montreal Neurological Institute.

**Table 4**
White matter tracts and nearest gray matter points from the significant correlation between reading comprehension scores and FA measures in the selected ROIs (ANCOVA) ($p < 0.05$, FDR corrected). Regions were defined using the Harvard-Oxford atlas in FSL.

| Tract | Nearest gray matter | BA |
|---|---|---|
| L AF | Precuneus | 7 |
| | Cingulate cortex | 23/24 |
| | Central opercular cortex | 44 |
| R AF | Precuneus | 7 |
| L ILF | Planum temporale | 42 |
| | Superior temporal gyrus | 22 |
| R ILF | Planum temporale | 42 |
| L SLF | Central opercular cortex | 44 |
| | Precentral gyrus | 4/6 |
| | Inferior frontal gyrus (pars opercularis) | 44 |
| R SLF | Precentral gyrus | 4/6 |
| | Middle frontal gyrus | 6/8/9/10 |
| | Inferior frontal gyrus (pars opercularis) | 44 |
| | Central opercular cortex | 44 |
| L IFOF | Insular cortex | 13 |
| | Heschl's gyrus | 41 |
| R IFOF | Planum temporale | 42 |
| | Insular cortex | 13 |

BA, Brodmann area according to the Harvard-Oxford atlas implemented in FSL atlas; L, left; R, right; AF, Arcuate Fasciculus; ILF, Inferior Longitudinal Fasciculus; SLF, Superior Longitudinal Fasciculus; IFOF, Inferior Frontal-Occipital Fasciculus.

### 3.2. *Difficulties in reading comprehension in youth with mood disorders compared to youth with behavioral disorders*

Study results highlight the critical role of the frontal and limbic systems as well as fronto-parietal circuits in reading comprehension.

**Table 5**
Results from the post-hoc *t*-tests using the reading comprehension measure as a covariate of interest.

| Tract | Statistics contrast | Nearest gray matter | BA | Figure |
|---|---|---|---|---|
| L AF | M > C | Insular cortex | 13 | 5 |
| | | Central opercular cortex | 44 | |

L, left; AF, Arcuate Fasciculus; M, youth with mood disorders; C, control participants; BA, Brodmann area according to the Harvard-Oxford atlas implemented in FSL atlas.

Reading comprehension engages the right hemisphere in typical readers (Horowitz-Kraus et al., 2014b; Horowitz-Kraus et al., 2015b), especially the frontal region (Horowitz-Kraus et al., 2014b). Whereas the right hemisphere previously has been related primarily to metaphors, humor, and sarcasm (see Johns et al., 2008 for a review), it also has been related to mood state (see Gainotti, 2012 for a review). Therefore, we suggest that youth with mood disorders, who share difficulties in mood regulation and demonstrate an overall altered activation of the right hemisphere (Yurgelun-Todd et al., 2000; Foland et al., 2008; Killgore et al., 2008; Strakowski et al., 2011; Liu et al., 2012; Najt and Hausmann, 2014), will also have altered right hemisphere function supporting reading comprehension (Prat et al., 2012). In support of this hypothesis and the involvement of the right hemisphere in children with intact reading comprehension (Horowitz-Kraus et al., 2015b), we found a greater correlation of reading comprehension scores with white matter tracts in the left hemisphere in youth with mood disorders as opposed to our previous observation of a right-lateralized correlation with this measure in both children (Horowitz-Kraus et al., 2015b) and adolescents (Horowitz-Kraus et al., 2014b).

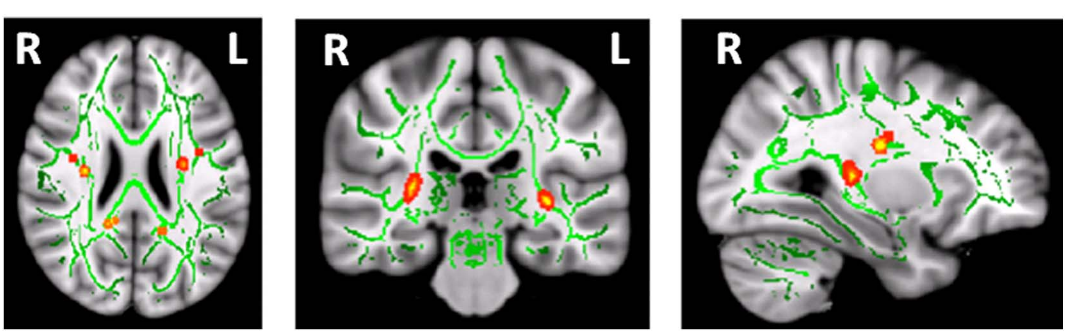


**Fig. 4.** Comparison of youth with mood disorders, those with behavioral disorders, and control participants: ANCOVA for fractional anisotropy (FA) values for four brain regions using reading comprehension percentage as a covariate. Three-dimensional tractography demonstrating the significant positive correlation of FA values with percentages for the reading comprehension subtest from the Woodcock-Johnson III battery ($p < 0.05$, FDR-corrected). Axial (left panel), coronal (middle panel), and sagittal (right panel) views of the MNI-152 (1 mm) template and the white matter skeleton (green) are shown (left portion of image = right hemisphere, right portion of image = left hemisphere). Hotter color represents a greater correlation between the FA values and the behavioral measure.

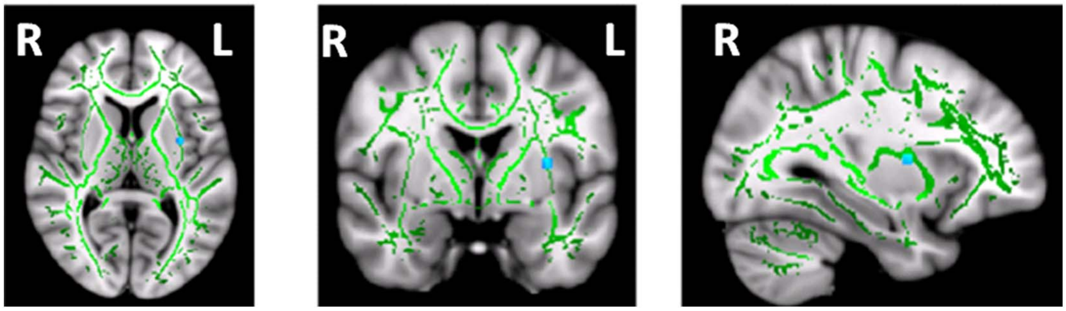


**Fig. 5.** Comparison of youth with mood disorders and control participants: independent *t*-test for fractional anisotropy (FA) values for the left Inferior Longitudinal Fasciculus using reading comprehension percentage as a covariate. Three-dimensional tractography demonstrating the significant positive correlation of FA values with percentages for the reading comprehension subtest for passage comprehension ($p < 0.05$, FDR-corrected). Axial (left panel), coronal (middle panel), and sagittal (right panel) views of the MNI-152 (1 mm) template and the white matter skeleton (green) are shown (left portion of image = right hemisphere, right portion of image = left hemisphere). Blue color indicates the region of greater FA values for youth with mood disorders versus controls; the left Inferior Longitudinal Fasciculus. MNI, Montreal Neurological Institute.

### *3.3. Involvement of cognitive control in reading among youth with mood or behavioral disorders*

Another critical component in reading is intact executive functions (Horowitz-Kraus, 2014), such as working memory (de Jong, 1998), speed of processing (Breznitz and Misra, 2003), and switching/shifting attention and cognitive control (Houde et al., 2010). Cognitive control abilities recently were related to two cognitive-control/executive-function networks with different neuroanatomical correlates (Dosenbach et al., 2008): 1) the rapid adaptive control network, which allocates attention to a cue and involves a frontal-parietal circuit; and 2) the set-maintenance network, which maintains task goals, sustains adjustments for feedback control, monitors errors, and involves a cingulo-opercular circuit. Connectivity within these networks increases throughout development in healthy controls (Dosenbach et al., 2008), and both networks are engaged during reading (Ihnen et al., 2013). Our results suggest a positive correlation between the FA values in the left AF and reading comprehension scores that was greater in mood disorders than in controls. This implies that greater reading comprehension scores were correlated with greater FA in parts of the cingulo-opercular network in youth with mood disorders compared to control participants. This finding suggests an altered involvement of neural circuits related to cognitive control processes related to this network, specifically monitoring and conflict-resolution processes (Dosenbach et al., 2008), which has been suggested previously (Sylvester et al., 2012) and may be one of the causes for reading comprehension deficit in individuals with mood disorders. Another possibility is dysfunction in functional connectivity of the fronto-parietal network in youth with mood disorders (Sylvester et al., 2012), and more specifically, the right fronto-parietal network (Tamnes et al., 2013; Najt et al., 2013), which also is involved in working memory and phonological processing (Tamnes et al., 2013). Because both the cingulo-opercular and fronto-parietal networks can be easily identified during rest (Dosenbach et al., 2008), a future study involving a resting-state functional connectivity analysis, complementing to the current structural connectivity study and focusing specifically on these networks and their association with reading scores, is needed to confirm this point. These results also demonstrate the greater disruption in cognitive control networks in individuals with mood disorders (Shanmugan et al., 2016; Sylvester et al., 2012), which, due to the central role of cognitive control in reading proficiency, may be one of the reason for the greater reading deficit in children with mood disorders.

### *3.4. The absence of differences in orthographical abilities between children with mood disorder and children with behavioral disorders*

According to the reading acquisition model (Frith, 1985), orthographical ability is an important component in reading development. Each of these abilities sought to map different neural circuits. Therefore, when exploring reading challenges, it is important to examine both phonology and orthography. The absence of differences in orthographical abilities observed between children with mood vs behavioral disorders is intriguing and may be related to different alteration these groups have in cognitive control and other networks supporting reading and therefore differences in compensation pathways these two populations may take. Children with mood disorders may suffer from impairments related to the cingulo-opercular related to cognitive control (Sylvester et al., 2012), which was previously shown to be related to increased orthographic abilities in children with reading difficulties (Horowitz-Kraus and Holland, 2015). Also, the dorsal attention network which was reported to show altered functional connections in individuals with mood disorders (Sylvester et al., 2012) is functionally connected with the visual word form area related to orthographic abilities (Vogel et al., 2012). On the other hand, children with behavioral disorders show hypoactivation in regions in the fronto-parietal network, the thalamus, and the cerebellum (Shanmugan et al., 2016) which participate in orthographic tasks as well (Horowitz-Kraus et al., 2014a). We therefore suggest that children with mood disorders may compensate for these neural alterations in ways different from those with behavioral disorders which may be inefficient since both show relatively lower orthographic ability than controls. However, since this study did not directly examine the neural circuits related to orthographic ability using an orthographic task, a future in-depth study is needed to examine children participating in an orthographic processing task (i.e. lexical decision).

### *3.5. Limitations of the study*

These results should be considered with the following limitations: 1) the sample was small and, although it was selected to be representative of the entire LAMS longitudinal cohort (N = 685), had limited power to detect statistically significant differences; 2) due to the small sample size, the study did not control for a possible sex effect on reading ability; therefore, a future study enrolling more participants should control for sex; 3) although this study used a correlation approach between FA values in selected white matter tracts with reading scores, using a specific task to examine neural circuits that directly support reading may deepen our understanding; and 4) the groups of youth with mood or behavioral disorders had varying mood and behavior disorders. In fact, one of the participants in the mood-disorder group had anxiety rather than depression or bipolar disorder. A future study should verify observed differences in FA correlations with reading measures for more specific disorder subgroups.

### *3.6. Conclusions and significance*

These results revealed differences in neural correlates for reading difficulties in youth with mood disorders compared to youth with behavioral disorders. Differences suggest there may be a need to revise interventions for reading difficulties in these populations. If youth with mood disorders who have an altered activation of the right hemisphere have trouble in reading comprehension due to right hemispheric issues, specific training could facilitate compensation for this deficit. For example, integrating other right-hemisphere elements, such as training in metaphors and semantics, as a "warm-up" for training in reading comprehension may be helpful for youth with mood disorders. Executive-function training designed to improve frontal lobe function, and more specifically, cognitive abilities related to the fronto-parietal and cingulo-opercular cognitive control networks (Dosenbach et al., 2008) also might have a positive effect on reading abilities in youth with mood disorders and those with behavioral disorders. Our results did not show significant differences between FA values in the selected white matter tracts between controls and the youth with behavioral disorders. However, we did note a trend of lower reading comprehension between the groups (youth with mood disorders had the lowest reading comprehension scores vs the highest in controls). Therefore, interventions involving higher order thinking (related to the cognitive control networks mentioned above) also may be beneficial for the latter group who suffers from atypical frontal activation (Spalletta et al., 2001; Brower and Price, 2001).

## 4. Methods and materials

### 4.1. Participants

Data for the current study were drawn from a subsample of participants in a multisite study of youth enrolled in a longitudinal study of behavioral and emotional dysregulation during development, the Longitudinal Assessment of Manic Symptoms (LAMS) study (Horwitz et al., 2010). The LAMS study recruited 9-18 year-old children visiting 9 outpatient mental health clinics associated with the four university partners. A subsample of these youth was invited to participate in the neuroimaging component of the study. 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 as described by Versace et al. (2015). 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).

Fourteen LAMS youth with mood disorders (mean age = 15.47 ± 1.79 years; 5 females; 2 of which had behavioral disorders as well), 12 LAMS youth with behavioral disorders (mean age = 14.96 ± 1.96 years; 3 females) and 13 healthy control participants (mean age = 13.91 ± 2.33; 5 females) who did not meet criteria for the mood or behavioral disorders participated in the current study. No significant difference in age was determined among the three groups [$F(2,36) = 2.032$, $p = 0.146$]. None of the participants had any neurological impairment or neurological trauma. Youth signed assents and parents provided signed consents for participation in the study, for which participants were compensated. The study was approved by the Institutional Review Boards at Cincinnati Children's Hospital Medical Center, University of Pittsburgh Medical Center and Case Western Reserve University.

### 4.2. Neurocognitive testing

All participants received the Wechsler Abbreviated Scale of Intelligence test (Wechsler, 1999) for full-scale IQ scores; an Analysis of Variance revealed no significant differences in IQ between the groups. Reading and reading-related measures included: 1) Phonemic awareness using the 'Elision' subtest from the Comprehensive Test of Phonological Processing (CTOPP) battery (Wagner et al., 1999); 2) orthographical processing using the 'Letter-Word' subtest (WJ-III) (Woodcock and Johnson, 1989); and 3) reading comprehension using the 'Passage Comprehension' subtest (WJ-III). For the 'Elision' subtest, participants were required to orally manipulate sounds in the beginning, middle, or end of a given word. For the 'Letter-Word' subtest, participants were asked to read a list of letters followed by a list of words, at their comfortable reading rate. For the 'Passage Comprehension' subtest, participants were asked to read a sentence or paragraph and provide a missing word implied by the context of the passage. All participants completed the same test forms (Form A) for both the CTOPP and WJ-III subtests.

### 4.3. Image acquisition

Data were collected at three sites. At Cincinnati Children's Hospital Medical Center. DTI data were acquired using a single-shot spin-echo, echo-planar imaging (SE-EPI) sequence on a Philips Achieva 3T MRI scanner with Dual Quasar gradients and transmit/receive quadrature head coil (Philips Medical Systems, Best, The Netherlands). Acquisition parameters were: TR/TE = 9900/98 ms, acquisition matrix = 128 × 128, field of view = 256 × 256 (in-plane resolution = 2 × 2 mm), and slice thickness = 2 mm with no gap. Diffusion images were acquired using gradient encoding applied in 61 non-colinear directions and $b = 1000\ s/mm^2$, and seven non-diffusion weighted (T2-weighted, $b = 0\ s/mm^2$) uniformly interspersed reference images were denoted by $b_0$. At University of Pittsburgh Medical Center and Case Western Reserve University, DTI data were acquired using Siemens 3T MRI systems with identical imaging protocols and quality-assurance procedures. Quality control and intersite variability measures were used as covariates of no-interest to control for differences between the different sites contributing imaging data for this study (Versace et al., 2015).

### 4.4. Data analyses

#### 4.4.1. Reading data analysis

To verify our hypothesis that overall differences between the groups primarily would be in phonological awareness and reading comprehension, three separate Analyses of Variance (ANOVA) were performed, one for each reading measure: 1) phonological awareness, 2) orthography, and 3) reading comprehension, in the three groups. Post-hoc $t$-tests identified the source for the difference among the three groups. Results were corrected for multiple comparisons using a Bonferroni correction.

#### 4.4.2. DTI data analysis

Images were pre-processed, including correction for eddy current and head motion (Jenkinson and Smith, 2001). Tensor decomposition was performed to generate FA indices. Tract-Based Spatial Statistics (TBSS) (Smith et al., 2006) was then used to prepare the individual diffusion maps for voxel-based group analysis by performing the following steps: All FA images were nonlinearly registered to a template of averaged FA images (FMRIB-58) in Montreal Neurological Institute (MNI) space using FNIRT (FMRIB, Oxford, UK) (Rueckert et al., 1999). After transformation into MNI space, a cohort mean FA image was created and thinned to generate a cohort mean FA skeleton of the white matter tracts. Each subject's aligned FA image was then projected onto the cohort mean FA skeleton by filling it with FA values from the

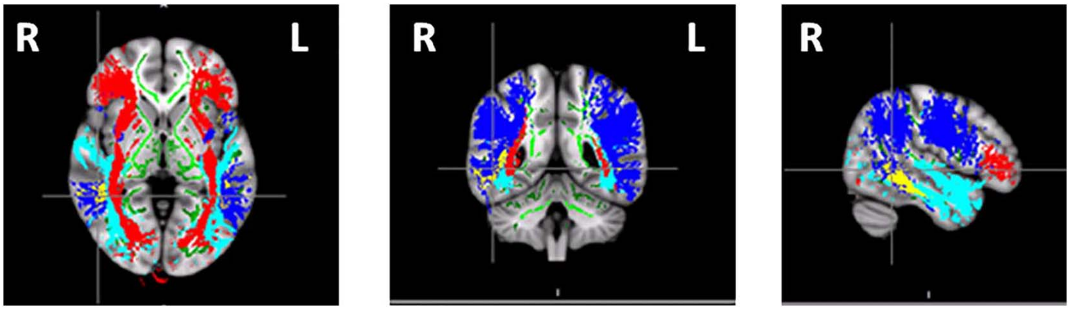


**Fig. 6.** White matter tracts included in the analysis. Axial (left panel), coronal (middle panel), and sagittal (right panel) views of the four white matter tracts that were included in the regions of interest used in the Tract-Based Spatial Statistics analysis: Arcuate Fasciculus (yellow), Inferior Longitudinal Fasciculus (light blue), Superior Longitudinal Fasciculus (dark blue), and Inferior Fronto Occipital Fasciculus (red) overlaying the MNI-152 (1 mm) template and the white matter skeleton (green). All white matter tracts were selected bilaterally. MNI, Montreal Neurological Institute.

nearest relevant tract center, achieved by searching perpendicular to the local skeleton structure for maximum value. A second localized coregistration step was used to alleviate alignment problems (see Horowitz-Kraus et al., 2014b for details) as well as for the spatial smoothing (Smith et al., 2009).

Four major masks were created using the JHU atlas (Mori, 2007) in the region of Arcuate Fasciculus (AF), Inferior Longitudinal Fasciculus (ILF), Superior Longitudinal Fasciculus (SLF), and Inferior Fronto Occipital Fasciculus (IFOF), the reading-related bilateral white matter tracts (Wandell and Yeatman, 2013). Four skeletonized masks were then derived by the intersection of these ROIs and the TBSS white matter skeleton (Fig. 6). Finally, between-group comparisons and correlation analyses were performed at voxel-based brain level using the four skeletonized masks, using four separate randomized analyses (i.e., four separate ANCOVAs) (Nichols and Holmes, 2002) with the Threshold-Free Cluster Enhancement (TFCE) (Smith et al., 2007). Level of significance was set at $p < 0.05$ and corrected for false discovery rate (FDR-corrected).

#### 4.4.3. *Group differences*

To determine the relationships between the different reading measures, three Pearson correlation analyses were performed (one for each reading measure) for the entire sample. To determine the main effect of group upon FA, four parallel ANCOVAs were performed at brain level using the four ROIs (bilateral AF, ILF, SLF, and IFOF). To identify the source for FA differences among the three groups (pending significance), three post-hoc pair-wise *t*-tests were performed at brain level, using the same ROIs ($p < 0.05$, FDR corrected).

#### 4.4.4. *Correlation of FA values in the selected ROIs with reading measures*

To determine the relationships between FA and reading ability measures that resulted in significant differences among groups, four separate Analyses of Covariance (ANCOVA) were performed at brain level using the same four ROIs and the demeaned values of reading ability (e.g., phonological) scores as a covariate of interest. The interaction of Group FA × Reading ability for each ROI using the same threshold ($p < 0.05$, corrected) was used.

## Compliance with ethical standards

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### Conflict of interest

Dr. Fristad receives royalties from Guilford Press, American Psychiatric Press and Child & Family Psychological Services. Dr. Arnold has received research funding from Curemark, Forest, Lilly, Neuropharm, Novartis, Noven, Shire, and YoungLiving (as well as NIH and Autism Speaks) and has consulted with or been on advisory boards for Gowlings, Neuropharm, Novartis, Noven, Organon, Otsuka, Pfizer, Roche, Seaside Therapeutics, Sigma Tau, Shire, and Tris Pharma and received travel support from Noven. In the last 24 months, Dr. Findling receives or has received research support, acted as a consultant and/or served on a speaker's bureau for Alcobra, American Academy of Child & Adolescent Psychiatry, American Physician Institute, American Psychiatric Press, Bracket, CogCubed, Cognition Group, Coronado Biosciences, Dana Foundation, Elsevier, Forest, Guilford Press, Ironshore, Johns Hopkins University Press, Jubilant Clinsys, KemPharm, Lundbeck, Merck, NIH, Neurim, Novartis, Otsuka, Oxford University Press, Pfizer, Physicians Postgraduate Press, Purdue, Rhodes Pharmaceuticals, Roche, Sage, Shire, Sunovion, Supernus Pharmaceuticals, Transcept Pharmaceuticals, Tris, Validus, and WebMD. Dr. Youngstrom has consulted with Otsuka and Lundbeck. Drs. Horwitz, Horowitz-Kraus, Holland, Versace, Bebko, Almeida, Travis, Gill, Bonar, Schirdar, Diwadkar, Sunshine, Brimaher, Axelson, Taylor, Horwitz, Fraizer, Bertocci, Perlman and Philips reported no biomedical financial interests or potential conflicts of interest.

### Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

### Informed consent

Informed consent was obtained from all individual participants included in the study.

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## References

Abler, B., Hofer, C., Viviani, R., 2008. Habitual emotion regulation strategies and baseline brain perfusion. Neuroreport 19 (1), 21–24.
Versace, Amelia, Acuff, H., Bertocci, Michele A., Bebko, Genna, Almeida, Jorge R.C., Perlman, Susan B., Leemans, Alexander, Schirda, Claudiu, Amanda, Haris Aslam, Bonar, Dwojak 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.
Banks, S.J., et al., 2007. Amygdala-frontal connectivity during emotion regulation. Soc. Cogn. Affect. Neurosci. 2 (4), 303–312.
Breznitz, Z., Misra, M., 2003. Speed of processing of the visual-orthographic and auditory-phonological systems in adult dyslexics: the contribution of “asynchrony” to word recognition deficits. Brain Lang. 85 (3), 486–502.
Brower, M.C., Price, B.H., 2001. Neuropsychiatry of frontal lobe dysfunction in violent and criminal behaviour: a critical review. J. Neurol. Neurosurg. Psychiatry 71 (6), 720–726.
Coan, J.A., Allen, J.J., 2004. Frontal EEG asymmetry as a moderator and mediator of emotion. Biol. Psychol. 67 (1–2), 7–49.
Davidson, R.J., et al., 1999. Regional brain function, emotion and disorders of emotion. Curr. Opin. Neurobiol. 9 (2), 228–234.
Donahue, P.L., Voelkl, K.E., Campbell, J.R., Mazzeo, J., 1999. The NAEP 1998 Reading Report Card for the Nation and the States (NCES 1999-500). U.S. Department of Education, Washington, DC.
Donegan, N.H., et al., 2003. Amygdala hyperreactivity in borderline personality disorder: implications for emotional dysregulation. Biol. Psychiatry 54 (11), 1284–1293.
Dosenbach, N.U., et al., 2008. A dual-networks architecture of top-down control. Trends Cogn. Sci. 12 (3), 99–105.
van Ewijk, H., et al., 2012. Diffusion tensor imaging in attention deficit/hyperactivity disorder: a systematic review and meta-analysis. Neurosci. Biobehav. Rev. 36 (4), 1093–1106.
Fitzgerald, P.B., et al., 2008. A meta-analytic study of changes in brain activation in depression. Hum. Brain Mapp. 29 (6), 683–695.
Foland, L.C., et al., 2008. Evidence for deficient modulation of amygdala response by prefrontal cortex in bipolar mania. Psychiatry Res. 162 (1), 27–37.
Forness, S.R., Knitzer, J., 1992. A new proposed definition and terminology to replace ‘serious emotional disturbance’ in Individuals with Disabilities Education Act. Sch. Psychol. Rev. 21 (1), 12.
Frazier, J.A., et al., 2007. White matter abnormalities in children with and at risk for bipolar disorder. Bipolar Disord. 9 (8), 799–809.
Frith, U., 1985. Beneath the surface of developmental dyslexia. In: Patterson, K.E., Marshall, J.C., Coltheart, M. (Eds.), Surface Dyslexia. Erlbaum, London, pp. 301–330.
Gainotti, G., 2012. Unconscious processing of emotions and the right hemisphere. Neuropsychologia 50 (2), 205–218.
Halari, R., et al., 2009. Reduced activation in lateral prefrontal cortex and anterior cingulate during attention and cognitive control functions in medication-naive adolescents with depression compared to controls. J. Child Psychol. Psychiatry 50 (3), 307–316.
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., Breznitz, Z., 2014. Can reading rate acceleration improve error monitoring and cognitive abilities underlying reading in adolescents with reading difficulties and in typical readers? Brain Res. 1544, 1–14.
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. http://dx.doi.org/10.1007/s11881-015-0096-9.
Horowitz-Kraus, T., et al., 2014a. Reading acceleration training changes brain circuitry in children with reading difficulties. Brain Behav. 4 (4).
Horowitz-Kraus, T., et al., 2014b. Involvement of the right hemisphere in reading comprehension: a DTI study. Brain Res. 1582, 34–44.
Horowitz-Kraus, T., et al., 2014c. Greater utilization of neural-circuits related to executive functions is associated with better reading: a longitudinal fMRI study using the verb generation task. Front. Hum. Neurosci. 8, 447.
Horowitz-Kraus, T., DiFrancesco, M., Kay, B., Wang, Y., Holland, S.K., 2015a. Increased functional connectivity of specific brain networks after reading training in dyslexic children. Clin. Neuroimage 8, 619–630.
Horowitz-Kraus, T., et al., 2015b. Right is not always wrong: DTI and fMRI evidence for the reliance of reading comprehension on language-comprehension networks in the right hemisphere. Brain Imaging Behav. 9 (19). http://dx.doi.org/10.1007/s11682-014-9341-9.
Horwitz, S.M., et al., 2010. Longitudinal Assessment of Manic Symptoms (LAMS) study: background, design, and initial screening results. J. Clin. Psychiatry 71 (11), 1511–1517.
Houde, O., et al., 2010. Mapping numerical processing, reading, and executive functions in the developing brain: an fMRI meta-analysis of 52 studies including 842 children. Dev. Sci. 13 (6), 876–885.
Ihnen, S.K., Petersen, S.E., Schlaggar, B.L., 2013. Separable roles for attentional control sub-systems in reading tasks: a combined behavioral and fMRI study. Cereb. Cortex 25 (5), 1198–1218. http://dx.doi.org/10.1093/cercor/bht313. (November 24).
Jenkinson, M., Smith, S., 2001. A global optimisation method for robust affine registration of brain images. Med. Image Anal. 5 (2), 143–156.
Johns, C.L., Tooley, K.M., Traxler, M.J., 2008. Discourse impairments following right hemisphere brain damage: a critical review. Lang Ling Compass 2, 1038–1062.
de Jong, P.F., 1998. Working memory deficits of reading disabled children. J. Exp. Child Psychol. 70 (2), 75–96.
Killgore, W.D., Gruber, S.A., Yurgelun-Todd, D.A., 2008. Abnormal cortico striatal activity during fear perception in bipolar disorder. Neuroreport 19, 1523–1527.
Konrad, A., et al., 2010. Disturbed structural connectivity is related to inattention and impulsivity in adult attention deficit hyperactivity disorder. Eur. J. Neurosci. 31 (5), 912–919.
Kroese, J.M., Hynd, George W., Knight, Deborah F., Hiemenz, Jennifer R., Hall, Josh, 2000. Clinical appraisal of spelling ability and its relationship to phonemic awareness (blending, segmenting, elision, and reversal), phonological memory, and reading in reading disabled, ADHD, and normal children. Read. Writ. 13 (1–2), 105–131.
Liu, J., Blond, B.N., van Dyck, L.I., Spencer, L., Wang, F., Blumberg, H.P., 2012. Trait and state cortico striatal dysfunction in bipolar disorder during emotional face processing. Bipolar Disord. 14, 432–441.
Mak, A.K., et al., 2009. Gray matter reduction associated with emotion regulation in female outpatients with major depressive disorder: a voxel-based morphometry study. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 33 (7), 1184–1190.
Makris, N., et al., 2005. Segmentation of subcomponents within the superior longitudinal fascicle in humans: a quantitative, in vivo, DT-MRI study. Cereb. Cortex 15 (6), 854–869.
Makris, N., et al., 2008. Attention and executive systems abnormalities in adults with childhood ADHD: a DT-MRI study of connections. Cereb. Cortex 18 (5), 1210–1220.
Makris, N., et al., 2009. Delineation of the middle longitudinal fascicle in humans: a quantitative, in vivo, DT-MRI study. Cereb. Cortex 19 (4), 777–785.
Mori, S.a.v.Z.P., 2007. Human white matter atlas. Am. J. Psychiatry.
Najt, P., Hausmann, M., 2014. Atypical right hemispheric functioning in the euthymic state of bipolar affective disorder. Psychiatry Res. 220 (1–2), 315–321.
Najt, P., Bayer, U., Hausmann, M., 2013. Right fronto-parietal dysfunction underlying spatial attention in bipolar disorder. Psychiatry Res. 210 (2), 479–484.
Nichols, T.E., Holmes, A.P., 2002. Nonparametric permutation tests for functional neuroimaging: a primer with examples. Hum. Brain Mapp. 15 (1), 1–25.
O'Hare, A., 2010. Dyslexia: what do paediatricians need to know? Paediatr. Child Health 20 (7), 338–343.
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.
Prat, C.S., Mason, R.A., Just, M.A., 2012. An fMRI investigation of analogical mapping in metaphor comprehension: the influence of context and individual cognitive capacities on processing demands. J. Exp. Psychol. Learn. Mem. Cogn. 38 (2), 282–294.
Rueckert, D., et al., 1999. Nonrigid registration using free-form deformations: application to breast MR images. IEEE Trans. Med. Imaging 18 (8), 712–721.
Sarkar, S., et al., 2013. Frontotemporal white-matter microstructural abnormalities in adolescents with conduct disorder: a diffusion tensor imaging study. Psychol. Med. 43 (2), 401–411.
Seidenberg, M.S., McClelland, J.L., 1989. A distributed, developmental model of word recognition and naming. Psychol. Rev. 96 (4), 523–568.
Shanmugan, S., Wolf, D.H., Calkins, M.E., Moore, T.M., Ruparel, K., Hopson, R.D., Simon, B.A., et al., 2016. Common and dissociable mechanisms of executive system dysfunction across psychiatric disorders in youth. Am. J. Psychiatry 173, 517–526.
Shaywitz, S.E., 2003. Overcoming Dyslexia: A New and Complete Science-based Program for Reading Problems at Any Level. A.A. Knopf.
Smith, S.M., et al., 2006. Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. NeuroImage 31 (4), 1487–1505.
Smith, S.M., et al., 2007. Acquisition and voxelwise analysis of multi-subject diffusion data with tract-based spatial statistics. Nat. Protoc. 2 (3), 499–503.
Smith, S.M., et al., 2009. Correspondence of the brain's functional architecture during activation and rest. Proc. Natl. Acad. Sci. U. S. A. 106 (31), 13040–13045.
Spalletta, G., et al., 2001. Prefrontal blood flow dysregulation in drug naive ADHD children without structural abnormalities. J. Neural Transm. 108 (10), 1203–1216.
Strakowski, S.M., et al., 2011. Functional magnetic resonance imaging brain activation in bipolar mania: evidence for disruption of the ventrolateral prefrontal-amygdala emotional pathway. Biol. Psychiatry 69 (4), 381–388.
Sylvester, C.M., et al., 2012. Functional network dysfunction in anxiety and anxiety disorders. Trends Neurosci. 35 (9), 527–535.
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.
Uddin, L.Q., et al., 2010. Dissociable connectivity within human angular gyrus and intraparietal sulcus: evidence from functional and structural connectivity. Cereb. Cortex 20 (11), 2636–2646.
Vogel, A.C., et al., 2012. The putative visual word form area is functionally connected to the dorsal attention network. Cereb. Cortex 22 (3), 537–549.
Vogel, A.C., et al., 2013. Functional network architecture of reading-related regions across development. Brain Lang. 125 (2), 231–243.
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.
Wandell, B.A., Yeatman, J.D., 2013. Biological development of reading circuits. Curr. Opin. Neurobiol. 23 (2), 261–268.
Wechsler, D., 1999. Wechsler Intelligence Scale for Children — Third Edition (WISC-III). The Psychological Corporation, New York.
Woodcock, R.W., Johnson, M.B., 1989. Woodcock-Johnson Psycho-Educational Battery-Revised (WJ-R). Developmental Learning Materials: Allen, TX.
Yurgelun-Todd, D.A., et al., 2000. fMRI during affect discrimination in bipolar affective disorder. Bipolar Disord. 2 (3 Pt 2), 237–248.