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Behav Brain Res. Author manuscript; available in PMC 2021 March 02.

Published in final edited form as:

Behav Brain Res. 2020 March 02; 381: 112382. doi:10.1016/j.bbr.2019.112382.

Frontal volume as a potential source of the comorbidity between attention-deficit/hyperactivity disorder and reading disorders

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Abstract

Prefrontal volume reductions commonly are demonstrated in ADHD, but the literature examining prefrontal volume in reading disorders (RD) is scant despite their also having executive functioning (EF) deficits. Furthermore, only a few anatomical studies have examined the frontal lobes in comorbid RD/ADHD, though they have EF deficits similar to RD and ADHD. Hence, we examined frontal gyri volume in children with RD, ADHD, RD/ADHD and controls, as well as their relationship to EF for gyri found to differ between groups. We found right inferior frontal (RIF) volume was smaller in ADHD, and smaller volume was related to worse behavioral regulation. Left superior frontal (LSF) volume was larger in RD than ADHD, and its size was negatively related to basic reading ability. Left middle frontal (LMF) volume was largest in RD/ADHD overall. Further, its volume was not related to basic reading nor behavioral regulation but was related to worse attentional control, suggesting some specificity in its EF relationship. When examining hypotheses on the etiology of RD/ADHD, RD/ADHD was commensurate with ADHD in RIF volume and both RD and ADHD in LSF volume (being midway between the groups), consistent with the common etiology hypothesis. Nevertheless, they also had an additional gyrus affected: LMF, consistent with the cognitive subtype hypothesis in its specificity to RD/ADHD. The few other frontal *a*MRI studies on RD/ADHD supported both hypotheses as well. Given this, future research should continue to focus on frontal morphology in its endeavors to find neurobiological contributors to the comorbidity between RD and ADHD.

Keywords

Reading disorders; ADHD; comorbid RD/ADHD; MRI; children; frontal lobe

1.0 Introduction

Reading disorder (RD) and ADHD have a 20–40% comorbidity (Boada, Willcutt, & Pennington, 2012; Shaywitz, Fletcher, & Shaywitz, 1995), which is greater than the base

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Disclosures: All authors report no conflicts of interest.

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rate of either disorder. Unfortunately, there is a dearth of research on the neurologic contributors to this comorbidity, despite emerging literature on various genetic and environmental contributors (Gialluisi et al., 2014; Neale et al., 2008; Willcutt et al., 2010; Willcutt et al., 2014). A potential source of the comorbidity may be atypical frontal lobe structure due to the executive functioning (EF) deficits found in both RD and ADHD (Castellanos & Proal, 2012; Langer, Benjamin, Becker, & Gaab, 2019; Moura, Simões, & Pereira, 2015; Nigg, 2005). Although numerous studies have examined frontal lobe structure in ADHD, the literature on the frontal lobes in RD is more sparse. Moreover, few studies have examined the comorbidity of ADHD and RD using structural MRI, and none were found that manually traced the frontal lobes by gyrus. Hence, the primary aim of this project was to examine frontal lobe gyrus volume as a potential source of the comorbidity between RD and ADHD, and in so doing determine whether our data are consistent with one of two competing hypotheses on the etiology of RD/ADHD: the common etiology hypothesis and the cognitive subtype hypothesis. We also sought to determine frontal-behavioral relationships for the gyri identified as being different between groups.

Within the cognitive/neuropsychological literature there are two commonly cited hypotheses as to the causes of RD/ADHD comorbidity: common etiology and cognitive subtype. The cognitive subtype hypothesis states RD/ADHD may be a unique subtype distinct from RD and ADHD (Rucklidge & Tannock, 2002). For example, poor rapid automatized naming and reaction time were shown to be worse in RD/ADHD than in RD only and ADHD only by these authors. Taking this position, one might expect a frontal region(s) to be specially affected in RD/ADHD versus RD and ADHD. Others suggest RD/ADHD is an additive combination of RD and ADHD (common etiology hypothesis; Willcutt et al., 2001). For example, all three groups- RD, ADHD, and RD/ADHD – have been shown to have processing speed deficits (McGrath et al., 2012). Taking this position, one may expect the frontal regions affected in RD and ADHD to be affected in RD/ADHD, without additional areas being affected in RD/ADHD. As noted above, we examined these positions in relation to our frontal data.

A valuable contribution of this study is its focus on the frontal gyri in ‘native space’. Most prior research on RD and ADHD has assessed the frontal lobes in larger blocks when using tracing, or it used automated/semi-automated voxel-based morphometry (VBM)- or parcellation-based methods. VBM findings are affected by the choices made during pre-processing, and the method is more sensitive to motion artifacts than tracing. Furthermore, most automated/semi-automated methods require morphing the scan data into a ‘common space’. Given the heterogeneity of the tertiary brain regions across individuals, including prefrontal, it is unknown what effect this morphing process has on the MRI data. Hence, we manually traced each frontal gyrus to determine which gyri are affected in children with ADHD and/or RD. No other comprehensive tracing study of this nature was found in either the RD or ADHD literature. Because the methods used may affect findings, a second aim of this study was to determine how complementary VBM and tracing methods are when analyzing largely the same sample. VBM was used on a subset of this data (N = 106) as more MRI scans had to be omitted from it due to motion artifacts (Jagger-Rickels, Kibby, & Constance, 2018). Results will be compared between the two studies in the discussion.

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1.1 ADHD

Children with ADHD frequently present with executive dysfunction, likely due to poor frontal-striatal functioning (Casey, Castellanos, Giedd, & Marsh, 1997; Castellanos, 1997). While EF may be spared in some children with ADHD (Castellanos, Sonuga-Barke, Milham, & Tannock, 2006; Kibby & Cohen, 2008; Nigg, Willcutt, Doyle, & Sonuga-Barke, 2005; Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005), a large body of research suggests that children with ADHD typically have impairment in at least one aspect of EF including response inhibition (especially in individuals with hyperactivity/impulsivity), WM, vigilance, and fluency (Barkley, 1997; Castellanos & Proal, 2012; Kibby, 2012; Martinussen, Hayden, Hogg-Johnson, & Tannock, 2005; Martinussen & Tannock, 2006; Nigg, 2005; Shallice et al., 2002; Tucha et al., 2005). Findings on problem-solving/set-shifting as measured by the Wisconsin Card Sorting Test are divergent (Houghton et al., 1999; Pineda, 1998; Schmitz et al., 2002; Weyandt, Rice, Linterman, Mitzlaff, & Emert, 1998). Planning may be spared when measured with Tower tasks (Ozonoff & Jensen, 1999; Sonuga-Barke, Dalen, Daley, & Remington, 2002; Weyandt et al., 1998).

When examining frontal structures in ADHD, dorsolateral prefrontal cortex (DLPF) frequently has been shown to be atypical in size versus controls (Castellanos & Proal, 2012; De La Fuente, Xia, Branch, & Li, 2013; Kasparek, Theiner, & Filova, 2015; Makris et al., 2015; Moreno-Alcázar et al., 2016; Ranta et al., 2009; Seidman, 2006, 2011), consistent with the cognitive EF deficits found in this group. Inferior frontal cortex (IF) commonly is implicated also (de Mello et al., 2013; Depue et al., 2010; Jagger-Rickels, Kibby, & Constance, 2018; Kasparek et al., 2015; Lim et al., 2013; Pironti et al., 2014; Sowell et al., 2003; van ‘t Ent et al., 2007), and size of the right IF may be related to poor response inhibition/behavioral regulation (Aron & Poldrack, 2005; Depue et al., 2010). Orbitofrontal (OF; De La Fuente et al., 2013; Hesslinger et al., 2002; Jagger-Rickels et al., 2018; Makris et al., 2015; Seidman et al., 2011; van ‘t Ent et al., 2007), superior frontal (SF) (De La Fuente et al., 2013; Hill et al., 2003; Jagger-Rickels et al., 2018; Seidman et al., 2006; Seidman et al., 2011), middle frontal (MF) (Jagger-Rickels et al., 2018; Villemonteix et al., 2015) and/or precentral volume (PC) (Carmona et al., 2005; Villemonteix et al., 2015) may be affected as well. When using tracing, Kibby and colleagues (Kibby, Kroese, Krebbs, Hill, & Hynd, 2009) found smaller right pars triangularis length in children with ADHD, and when the total sample was used right anterior ascending ramus length was related to attention problems. Despite frontal findings being common in single studies, only ventromedial/OF findings were supported by a meta-analysis on structural MRI findings in ADHD (Norman et al., 2016, erratum in 2019), and others did not find any frontal atypicalities in their meta-analyses (Frodl & Skokauskas, 2012, Samea et al., 2019). This may be due to single-study results varying as to whether the areas found are larger or smaller in ADHD versus controls, as well as peaks being scattered within the gyri across studies, which likely are related to age of the sample, heterogeneity of the disorder, and/or measurement (e.g., VBM, parcellation) and preprocessing methods used.

1.2 Reading Disorders

Of the various aspects of EF, WM is the best studied in RD. Deficits in WM are commonly found (Baddeley & Hitch, 1994; Booth, Boyle, & Kelly, 2010; de Jonge & de Jonge, 1996;

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Kibby, 2012; Smith-Spark & Fisk, 2007; Swanson, 2006), and verbal WM likely plays a role in the reading process (Kibby, 2009a, 2009b; Kibby & Cohen, 2008; Kibby, Marks, Morgan, & Long, 2004; Swanson & Ashbaker, 2000). Other aspects of EF have not been as well studied. Based upon the limited research conducted, children with RD may have deficits in problem-solving, planning, fluency, set-shifting and organization, but behavioral regulation may be spared (Asbjørnsen, Helland, Obrzut, & Boliek, 2003; Langer et al., 2019; Moura, Simões, & Pereira, 2015; Reiter, Tucha, & Lange, 2005; Smith-Spark, Henry, Messer, Edvardsdottir, & Zięcik, 2016; Willcutt et al., 2001). Hence, their deficit(s) may be specific to cognitive EF.

Most 'whole-brain' MRI studies on RD have found the temporoparietal and/or occipitotemporal structures to be atypical in size, although findings have been disparate due to different measurement/preprocessing techniques, varying operational definitions and severities of RD, and lack of control for age, gender, handedness, SES, and/or IQ (Jagger-Rickels et al., 2018; Pennington, 2009; Richlan, Kronbichler, & Wimmer, 2013; Williams, Juranek, Cirino, & Fletcher, 2018). Less research has been conducted on the frontal lobes specifically despite cognitive EF deficits being found in this population. Of that conducted, the pars triangularis has been implicated when using tracing (Eckert, 2003), and its size correlated with verbal WM, rapid naming, and phonological processing (Eckert, 2003; Kibby et al., 2009). When using automated/semi-automated methods, RD and control groups differ in volume of the left OF and bilateral IF, SF, MF, SMA and/or PC gyri (Brown et al., 2001; Eckert, Berninger, Vaden, Gebregziabher, & Tsu, 2016; Jagger-Rickels et al., 2018; Jednoróg, Gawron, Marchewka, Heim, & Grabowska, 2014; Krafnick, Flowers, Luetje, Napoliello, & Eden, 2014; Patael et al., 2018; Richlan et al., 2013; Tamboer, Scholte, & Vorst, 2015; Vinckenbosch, Robichon, & Eliez, 2005; Xia, Hoeft, Zhang, & Shu, 2016). Further, PC volume may be related to phonological processing, with left IF being related to basic reading ability and right SF to rapid naming and auditory attention shifting (Jednoróg et al., 2014). Bilateral DLPF may be related to comprehension (Patael et al., 2018). Nevertheless, in large sample studies, only areas outside of the frontal lobes have been found (Eckert et al., 2017; Jednorog et al., 2015). In addition, similar to what was found with ADHD, few regions have been replicated in meta-analyses on structural MRI studies in RD. Regions that have been found were not in the frontal lobes (Linkersdorfer et al., 2012, Richlan, Kronbichler, & Wimmer, 2013), and one study did not find any significant clusters, including non-frontal areas, when controlling for total brain/intracranial volume (Eckert et al., 2016). Reasons for the null frontal findings likely are similar to those mentioned for ADHD.

1.3 Comorbid RD/ADHD

Research on comorbid RD/ADHD frequently reveals deficits consistent with both disorders. For example, children with RD often have poor phonological processing and verbal WM, whereas children with ADHD often have poor inhibitory control; those with RD/ADHD tend to have both sets of problems (Kibby & Cohen, 2008; Moura et al., 2017; Roodenrys et al., 2001; Rucklidge & Tannock, 2002; Willcutt, Pennington, Olson, Chhabildas, & Hulslander, 2005). Moreover, children with RD/ADHD have been shown to have deficits in WM, set-shifting, response inhibition, and interference control (Korkman & Pesonen, 1994; Langer et

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al., 2019; Moura et al., 2017; Rucklidge & Tannock, 2002; Willcutt et al., 2010) based upon the limited EF literature available on this group. Furthermore, all three groups, RD, ADHD, and RD/ADHD, have been shown to have deficits on EF tasks when examined within the same study (Langer et al., 2019; Närhi & Ahonen, 1995), consistent with this project's aim of determining whether atypical frontal structure may be a shared contributor. Hence, much of the EF literature on RD/ADHD supports the common etiology hypothesis.

Only three studies were found that addressed the frontal lobes using structural MRI in RD/ADHD. Kibby and colleagues (2009) demonstrated smaller right pars triangularis size in ADHD irrespective of RD status (it was comparably reduced in RD and RD/ADHD). Using VBM, Jagger-Rickels and colleagues (2018) revealed reductions in right SF, left medial frontal, and left MF gyri in RD/ADHD. Moreover, all three groups, RD, ADHD, and RD/ADHD, had smaller right SF clusters versus controls in this study, being a potential source of shared etiology. When analyzing cortical thickness, Langer and colleagues (2019) found a reduction in left IF in RD and RD/ADHD. The RD group also had a reduction in left SF. It should be noted that the first author of the current project conducted the pars triangularis study on RD and ADHD using a different database (Kibby et al., 2009). The Jagger-Rickels and colleagues' study (2018) was conducted with a subset of this sample, as noted earlier.

1.4 Purpose and Hypotheses

Based upon the literature reviewed, poor cognitive EF may be a potential source of shared etiology between ADHD and RD, whereas poor behavioral regulation may be specific to ADHD, contributing to RD and ADHD being separable but overlapping disorders. Thus, the purpose of this study was to determine whether atypical frontal lobe volume may be a potential source of the RD/ADHD comorbidity. Consistent with this, there are multiple, bilateral prefrontal regions that deviate from controls in both RD and ADHD at the single-study level, as illustrated above. Through analyzing the scant research available that studied the three groups, RD, ADHD, and RD/ADHD (Jagger-Rickels et al, 2018; Kibby et al., 2009; Langer et al., 2019), it was hypothesized that right SF volume would be affected in both RD and ADHD, whereas right IF volume would be affected in ADHD and left IF volume would be affected in RD. Although Jagger-Rickels and colleagues found left medial and left MF clusters in the RD/ADHD group but not the RD nor ADHD groups, children with RD/ADHD were not expected to have additional frontal gyri affected beyond those affected in RD and in ADHD based upon the EF literature reviewed in total, as the medial and middle frontal clusters found in the Jagger-Rickels et al. study were not large. Hence, it was hypothesized that our data would be consistent with the common etiology hypothesis, finding shared areas but no unique areas to RD/ADHD, based upon the bulk of the neuropsychological literature on this topic. A related purpose of this project was to examine brain-behavioral relationships for gyri found to differ between groups.

2.0 Materials and Methods

2.1 Participants

Participants included 151 children with RD (24), ADHD (63), RD/ADHD (24), and controls (40), ages 8–12 years. They represent a community sample recruited through larger, NIH-

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funded projects focused upon the neurobiological contributors to ADHD and RD. Only children with MRI scans were included in this study. The four groups were comparable in age, gender, race/ethnicity, SES (maternal education), handedness, and total brain volume (TBV) (*p*s > .10). They differed in nonverbal IQ [$F_{3, 147} = 8.67$, $p < .001$], such that the clinical groups had a lower mean IQ than controls (*p*s < .01) but were comparable to each other. Nevertheless, all groups had average intellect overall, and IQ was minimally correlated with the brain variables (*r*s < .2, *p*s > .10), so it was not used as a covariate. Groups differed in inattention, hyperactivity/impulsivity, and reading ability where expected (*p*s < .001). As it is a community sample, sample severity is mild. See Table 1 for descriptive data.

2.2 Clinical Diagnosis

Children were diagnosed by a licensed, clinical-child neuropsychologist. Diagnostic criteria are more thoroughly described in previous studies using this database (Jagger-Rickels et al., 2018; Kibby et al., 2015). In brief, ADHD was diagnosed using DSM-IV criteria, the current edition during data collection. The Behavior Assessment System for Children, Second Edition (BASC-2) (Reynolds & Kamphaus, 2004) questionnaire, Attention Problems and Hyperactivity/Impulsivity scales, were used during the diagnostic process to determine whether symptom severity was above average and symptoms appeared across home and school settings. The ADHD group included 51% with Predominately Inattentive type and 49% with Combined type. The RD/ADHD group included 62% with Predominately Inattentive type and 38% with Combined type. This difference was not significant, $X^2(2) = 1.32$, $p = .51$. Neither group included children with Predominately Hyperactive/Impulsive type, as this subtype is rare post early childhood (Barkley, 2003).

Children were diagnosed with an RD in basic reading following the guidelines of Pennington (Pennington, 2009). He noted that whether children are classified as poor readers (reading ability below average; IQ is irrelevant provided the child is not intellectually disabled similar to the DMS-5) or identified by way of a discrepancy definition (such as that used by the DSM-IV), both groups share the core deficit in RD: poor phonological processing. Thus, both definitions have merit and should be utilized. Using both definitions aids generalization as well, as some prior research used the discrepancy definition and some used the poor reader definition. For this study, a poor reader was defined as reading a standard deviation below the mean in basic reading. For the discrepancy definition we utilized the regression formula of the State of Washington which controlled for the correlation between the achievement and IQ measures. For both definitions, the child had to be struggling with reading academically. To be diagnosed with RD, a child only had to meet one of the two definitions. Most children with RD met the criteria for both definitions, performing below average in basic reading and having an IQ/achievement discrepancy (58%). Twenty-three percent were poor readers without an IQ discrepancy, and nineteen percent met the discrepancy criteria but had basic reading standard scores at or above 85. Basic reading ability had to be below a 100 standard score to be included in the discrepancy group. Children with RD/ADHD met criteria for both disorders: RD and ADHD.

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Controls did not meet criteria for either disorder. Further, all participants had to meet the following criteria. Measured intelligence had to be greater than 79. In addition, children could not have a history of significant perinatal complications (e.g., prematurity, toxemia), medical or neurological disorder that may affect cognition (e.g., prolonged high fever, traumatic brain injury), or severe environmental stressor (e.g., recent parental divorce, child abuse).

2.3 Measures

All participants within this study underwent a neuropsychological evaluation and a structural MRI scan. Various EF and reading measures were administered as part of the neuropsychological battery. Verbal working memory was assessed with the Children's Memory Scale (CMS) (Cohen, 1997) Sequences subtest. Visual Attention from the NEPSY (Korkman, Kirk, & Kemp, 1998) was used to measure selective attention, and its Off Task Behaviors raw score was used to assess more general attentional control. The Woodcock-Johnson Tests of Achievement, Third Edition (Woodcock, 2001) was used to assess word identification (Letter-Word Identification) and decoding (Word Attack). These measures are described in the Appendix.

2.4 General Procedures

Parents provided written informed consent, and children provided written informed assent before data were collected. For their participation, parents received a free neuropsychological report on their child, and children received a free T-shirt. The study was approved by SIU's Human Subjects Committee prior to its instigation as well as throughout data collection.

2.5 MRI Protocol and Procedures

Children underwent a 3D, T1-weighted MRI scan on a Philips Intera 1.5T scanner: TE = 4.6ms, TR = 30ms, flip angle = 35; FOV = 256 X 256. Images included 200 axial slices, 1.6mm thick, .8mm apart. Children's heads were stabilized during the scan to reduce motion artifact.

After aligning the scan through the three planes and segmenting gray and white matter via Analyze software, each of the following gyri were manually traced using the article by Crespo-Facorro and colleagues (Crespo-Facorro et al., 1999) as a guide: PC, SF, MF, IF, and OF. In brief, the longitudinal fissure and cingulate, central, PC, SF and IF sulci served as boundaries, and gyri were traced throughout their entirety. See Figure 1 for a sample slice. Inter- and intra-rater reliabilities were high (rs > .90). Inter-rater reliability was attained through two individuals tracing a gyrus on 10 consecutive MRI scans (each gyrus had two individuals tracing it). Each slice was included in the correlation analysis as opposed to one total volume for the gyrus. Intra-rater used a similar procedure, but with one individual tracing the gyrus at two different times. This procedure was followed for each gyrus, and the co-authors SD, SL, and MS, were the people conducting the tracing.

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3.0 Results

3.1 Group differences

A 2 (ADHD or not) by 2 (RD or not) MANCOVA was used with TBV as the covariate. The omnibus equations were not significant (RD: $\lambda = .94$, $F_{10, 137} = 0.91$, $p = .53$, $\eta p^2 = .06$; ADHD: $\lambda = .92$, $F_{10, 137} = 1.26$, $p = .26$, $\eta p^2 = .08$; RD X ADHD: $\lambda = .92$, $F_{10, 137} = 1.21$, $p = .29$, $\eta p^2 = .08$). Nevertheless, sample size was small for the analysis; with the effect sizes found, 194 (based on ADHD ES) - 255 (based on RD ES) children would be needed for a power of .80. Given the large number of variables for the sample size, scant *a*MRI research on RD/ADHD, and minimal research on the frontal lobes comparing the three clinical groups, the univariate results are presented to guide future research. Many prior studies in this area have had similar problems due to small cell size resulting from the high cost of MRI scans. For the univariate main effects of RD and ADHD, as well as the interaction terms, see Table 2. Here it is noted that right IF is smaller in ADHD versus no-ADHD, and left SF is larger in RD versus no-RD. When reviewing the means, it also is noted that RD had the largest mean on left SF of the four groups and ADHD the smallest, which likely contributed to this variable's univariate significance. Thus, this difference was tested: $t_{85} = 2.25$, $p = .03$. In terms of the RD X ADHD interaction terms, only left MF was significant at the univariate level. See Figure 2 for a depiction of the four groups' mean left MF volumes to aid in understanding of the interaction.

3.2 Frontal/Behavioral relationships

To determine whether group differences were supported by brain-behavioral relationships in the total sample, hierarchical regression was used. Because right IF volume was smaller in ADHD at the univariate level, the BASC-2 Attention Problems and Hyperactivity scales were used to determine whether right IF volume was related to the inattention and/or hyperactivity/impulsivity dimensions of ADHD. TBV was entered in the first step, with right IF volume being entered into the second step to predict either Attention Problems or Hyperactivity. The equation predicting Attention Problems was not significant, adjusted $R^2 = .01$, $F_{2,147} = 1.38$, $p = .26$, R^2 change = .01, Beta = −.11, $p = .20$, but the equation predicting Hyperactivity was significant, adjusted $R^2 = .04$, $F_{2,147} = 3.69$, $p = .03$, R^2 change = .05, Beta = −.23, $p = .007$. This shows smaller RIF volume is related to greater hyperactivity/impulsivity levels.

As basic RD diagnosis was associated with larger left SF volume, WJ-III Letter-Word Identification (LWI) and Word Attack (WA) were used to determine whether left SF volume was related to word identification and decoding in the total sample. TBV was entered in the first step, with left SF volume being entered into the second step to predict either LWI or WA. The equation predicting LWI was significant, adjusted $R^2 = .08$, $F_{2,148} = 7.50$, $p = .001$, R^2 change = .05, Beta = −.25, $p = .005$. The equation predicting WA was as well, adjusted $R^2 = .09$, $F_{2,148} = 7.95$, $p = .001$, R^2 change = .05, Beta = −.26, $p = .004$. Because verbal WM is related to both basic reading ability and dorsolateral prefrontal cortex functioning based upon prior research and may account for their relationship, Sequences was entered into both regressions in Step 1 along with total brain volume, to determine whether it accounted for the relationship between left SF volume and basic reading ability. This was

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the case. For LWI, Sequences was significant (Beta = .60, $p < .000$), but left SF volume no longer was (Beta = −.09, $p = .24$). For WA, Sequences was significant (Beta = .56, $p < .000$), but left SF volume no longer was (Beta = −.11, $p = .16$).

Because left MF volume was significant for the RD/ADHD interaction term only (not RD or ADHD main effects), first it was verified that left MF volume was not related to basic reading ability or hyperactivity, as left SF and right IF were, respectively. Neither of these hierarchical equations controlling for total brain volume was significant, ps > .10. Next Visual Attention and Visual Attention Off Task Behaviors were examined in relation to left MF volume. TBV was entered into the first block, with LMF volume being entered into the second block to predict Visual Attention or its Off Task Behaviors. Left MF volume was not related to Visual Attention (adjusted $R^2 = -.004$, $F_{2,139} = 0.74$, $p = .48$, R^2 change = .002, Beta = −.05, $p = .63$), but it was related to Off Task Behaviors, adjusted $R^2 = .09$, $F_{3,138} = 5.42$, $p = .001$, R^2 change = .07, Beta = .30, $p = .001$. The latter equation controlled for age as well, as Off Task Behaviors is measured in raw scores. This analysis suggests larger left MF volume is associated with worse endogenous attention control. To determine whether Off Task Behaviors' relationship with left MF volume was specific, right IF and left SF volumes were examined in relation to the two Visual Attention measures using the same covariates that were used with left MF volume. None of these equations were significant, ps > .10.

4.0 Discussion

The aims of this study were to determine whether frontal morphology may be a potential contributor to the comorbidity between RD and ADHD and to examine corresponding structure-function relationships for gyri that differed between groups. It also sought to determine whether the common etiology or cognitive subtype hypothesis was a better fit with the data. The lack of significant RD X ADHD interaction terms for the two variables suggests children with RD/ADHD have volumes commensurate with ADHD and with RD in terms of right IF and left SF, respectively. Finding shared atypicalities between RD/ADHD and ADHD or RD is consistent with the common etiology hypothesis and our study's hypothesis. Finding shared frontal structure atypicalities between RD or ADHD and RD/ADHD is commensurate with prior whole-brain research as well (Jagger-Rickels et al., 2018; Langer et al., 2019). Nevertheless, the regions identified differed across studies, with Jagger-Rickels implicating the right SF and Langer and colleagues implicating the left IF as shared areas. In addition, we found an RD X ADHD interaction for left MF at the univariate level; this specificity to RD/ADHD is consistent with the cognitive subtype hypothesis. A rather surprising finding was that left SF was affected in RD and in ADHD but in opposite directions, with RD/ADHD having an intermediate value closer to RD. Thus, left SF may be a potential source of differentiation between RD and ADHD diagnosis. Taken together, this study replicated one area previously shown to be atypical in ADHD: right IF, along with generating two areas for future comorbidity research: left SF and left MF.

Although we did not find left IF to be affected in RD as hypothesized, right IF was smaller in ADHD at the univariate level. These findings are quite similar to what was shown when tracing the pars triangularis using a different database (Kibby et al., 2009), suggesting they

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are not dependent upon sample or tracing technique. The finding of smaller right IF in ADHD also is consistent with results from different researchers using other methods (de Mello et al., 2013; Depue et al., 2010; Langer et al., 2019; Lim et al., 2013; Pironti et al., 2014; Sowell et al., 2003; van ‘t Ent et al., 2007). Furthermore, the current study demonstrated smaller right IF volume is related to worse behavioral regulation, consistent with prior research in this area (Aron & Poldrack, 2005; Depue et al., 2010). Hence, our findings, along with previous work, suggest right IF size is associated with a core symptom of ADHD: hyperactivity/impulsivity. Thus, the right IF region should continue to be examined when investigating neurobiological markers of ADHD.

Our finding of left SF being larger in RD than ADHD is novel. The study using VBM on this data found a cluster in the left SF that was smaller in ADHD than controls (Jagger-Rickels et al., 2018), suggesting the current study’s finding on ADHD is not spurious. Other studies have demonstrated smaller left SF size in ADHD as well using different methods (Makris et al., 2015; Ranta et al., 2009; Seidman, 2006; Seidman et al., 2011). In contrast, few have found left SF to be affected in RD, except Langer and colleagues (2019) who found it to be smaller when using cortical thickness. When SF is implicated in RD, it is typically right SF (Jagger-Rickels et al., 2018; Jednoróg et al., 2014; Patael et al., 2018; Williams et al., 2018). Nevertheless, we found left SF volume to be negatively correlated with both aspects of basic reading ability in the current study, suggesting the RD finding is not spurious. Some suggest SF is affected in RD because of the SMA which is important for response inhibition (Langer et al., 2019). However, it could be due to the DLPF area given our regression results showing verbal WM accounted for the relationship between left SF volume and basic reading ability, as verbal WM is commonly associated with the DLPF region in functional studies (e.g., Narayanan et al., 2005; Smith, Jonides, Marshuetz, & Koeppe, 1998; Veltman, Rombouts & Dolan, 2003). Future research segmenting the SF into posterior and anterior regions is indicated to determine which region(s) is driving this finding and whether the relationship between left SF volume and basic reading ability is mediated by verbal WM. Further research is needed to determine whether the RD versus ADHD difference can be replicated as well. If so, it has important implications for the dissociation between the two disorders given the current debate as to the sources of the comorbidity versus sources of their uniqueness.

The discovery of left MF being larger in RD/ADHD overall based on the RD X ADHD interaction term is a novel finding also. In addition, larger left MF volume was related to worse attention control. This relationship was specific, in the sense that left MF was not related to basic reading ability nor behavioral regulation, like left SF and right IF were, respectively. Also, left SF and right IF were not related to attention control. Worthy of note, the Jagger-Rickels and colleagues study found a small left MF cluster in RD/ADHD but not in RD or ADHD, being unique to RD/ADHD. The opposing sizes (smaller in VBM and larger in tracing) likely are due to the methods used, as the cluster identified with VBM was quite anterior and a small part of the total gyrus, whereas tracing found the gyrus as a whole to be bigger. Taken together, these findings suggest left MF volume may be larger for some children with RD/ADHD versus those with RD or ADHD, and this morphology difference may be related to attentional control. Further, finding a gyrus that is differentially affected in RD/ADHD versus RD and ADHD supports the cognitive subtype hypothesis, as noted

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above. Thus, future research should determine whether these findings can be replicated. In so doing it should separate anterior from posterior regions to determine what is driving the left MF findings.

Another interest of this study was to determine how much overlap there is between VBM and tracing in terms of their findings. Similar to what Eckert and colleagues (2005) demonstrated, we believe the two methods are complementary. We found left SF and right IF to be smaller in ADHD with both methods. Left MF was affected in RD/ADHD using both methods, but in opposite directions. Left SF was shown to be affected in RD with tracing only. With VBM it is possible to take a whole brain approach, and many more areas were identified through this method across the cerebrum in the clinical groups. In addition to the VBM findings discussed above, we found a smaller left PC cluster in RD and right MF cluster in ADHD of the frontal areas identified (Jagger-Rickels et al., 2018). Both Jagger and colleagues and Langer and colleagues (2019) found right SF to be affected in all three clinical groups being a potential source of the comorbidity between RD and ADHD, although Langer and colleagues used *f*MRI to show right SF atypicality. Fewer findings were revealed with tracing in the present study, but this may be related to the larger size of the areas studied (whole gyri as opposed to voxels). Tracing also may be less susceptible to potentially spurious findings given its reduced sensitivity to motion artifact and its use of native space. Hence, continued research using both methods is warranted.

A major limitation of this study is sample size. Low power affected our omnibus results for the MANCOVA. Nonetheless, this is not an uncommon limitation in MRI studies. Because of sample size we were unable to analyze subtypes of ADHD, as the RD/ADHD sample would be too small if broken down by subtype. For the same reason, we were unable to analyze subtypes or operational definitions of RD (poor reader versus discrepancy). Hence, further research is warranted in these areas. In addition, this project focused upon RD in basic reading; hence, future research is warranted focused upon children with RD in reading comprehension.

Another limitation is that we had a community sample of mild severity. Additional and/or differing results may be found if a clinic sample were used. Nonetheless, use of a community sample aids in generalization to the population of children with RD and/or ADHD at large, ages 8–12 years. Future research should compare findings using clinic versus community samples.

In conclusion, left SF volume was larger in RD than ADHD and was negatively related to basic reading ability. This relationship was accounted for by verbal WM, which is commensurate with previous research demonstrating verbal WM is related to basic reading ability (Kibby & Cohen, 2008; Kibby, 2009a,b) and the DLPF region is involved with verbal WM (Narayanan et al., 2005; Smith et al., 1998; Veltman et al., 2003). If these findings are replicated, it may help guide early diagnosis in the future. Smaller right IF size was revealed in ADHD (including RD/ADHD) and was correlated with behavioral regulation, being a potential biomarker of ADHD. Finding shared regions between RD/ADHD and ADHD or RD in this study, our VBM study, our 2009 study, and the only other *a*MRI study found in this area (Langer et al., 2019) is commensurate with the common etiology hypothesis of RD/

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ADHD. Nevertheless, we also found larger left MF size was specific to RD/ADHD and was related to attentional control. Further, all but the 2009 study also found various areas unique to RD/ADHD, consistent with the cognitive subtype hypothesis. Hence, RD/ADHD may have both shared and unique contributors from RD and ADHD. Based upon our prior VBM study and Langer and colleagues' research, smaller right SF may be a shared deficit.

As multiple studies have supported the common etiology hypothesis, both neuroimaging and cognitive, current treatment of RD/ADHD should include both the standard treatments for RD (educational interventions) as well as the standard treatments for ADHD (behavioral treatment and psychopharmacology) (Langer et al., 2019). Moreover, treatment should be studied further to determine whether additional or modified treatments for RD/ADHD are needed because of the cognitive subtype hypothesis's support in the neuroimaging literature.

Acknowledgements

Funding for data collection was provided by grants from NIH/NICHD [R03 HD048752, R15 HD065627]. The views expressed in this manuscript may not reflect NIH/NICHD's views. We would like to thank Lucinda Trusty, Sarah Vadnais, and Jacqueline Klaver who contributed to this project in its early stages.

Appendix

Measures Used

CMS Sequences	On some items the examinee is asked to say specific sequences from memory (e.g., days of the week). Then the examinee is asked to say them in reverse order. On some items they are asked to generate number sequences (e.g., count by 6s). This test yields age-based standard scores.
BASC-2	The Attention Problems scale corresponds with symptoms on the inattention dimension of ADHD (e.g., poor sustained attention, distractibility); the Hyperactivity scale corresponds with the hyperactivity/impulsivity dimension of ADHD (overactive and impulsive symptoms). Both scales yield age- and sex-based T-scores, with higher scores representing worse symptoms.
NEPSY Visual Attention OTB	Visual Attention measures selective attention to target stimuli which are in the presence of distractor items. This measure is timed and yields age-based standard scores. Off Task Behaviors (OTB) records, in raw scores, how frequently the participant is off task during this measure. It was used as a measure of attention control because when such behaviors occur on this task, they are due to a lapse in endogenous attention.
WJ-III LWI	Letter-Word Identification measures word identification in our age range. The measure is untimed and yields age-based standard scores.
WJ-III Word Attack	Word Attack measures pseudoword decoding. The measure is untimed and yields age-based standard scores.

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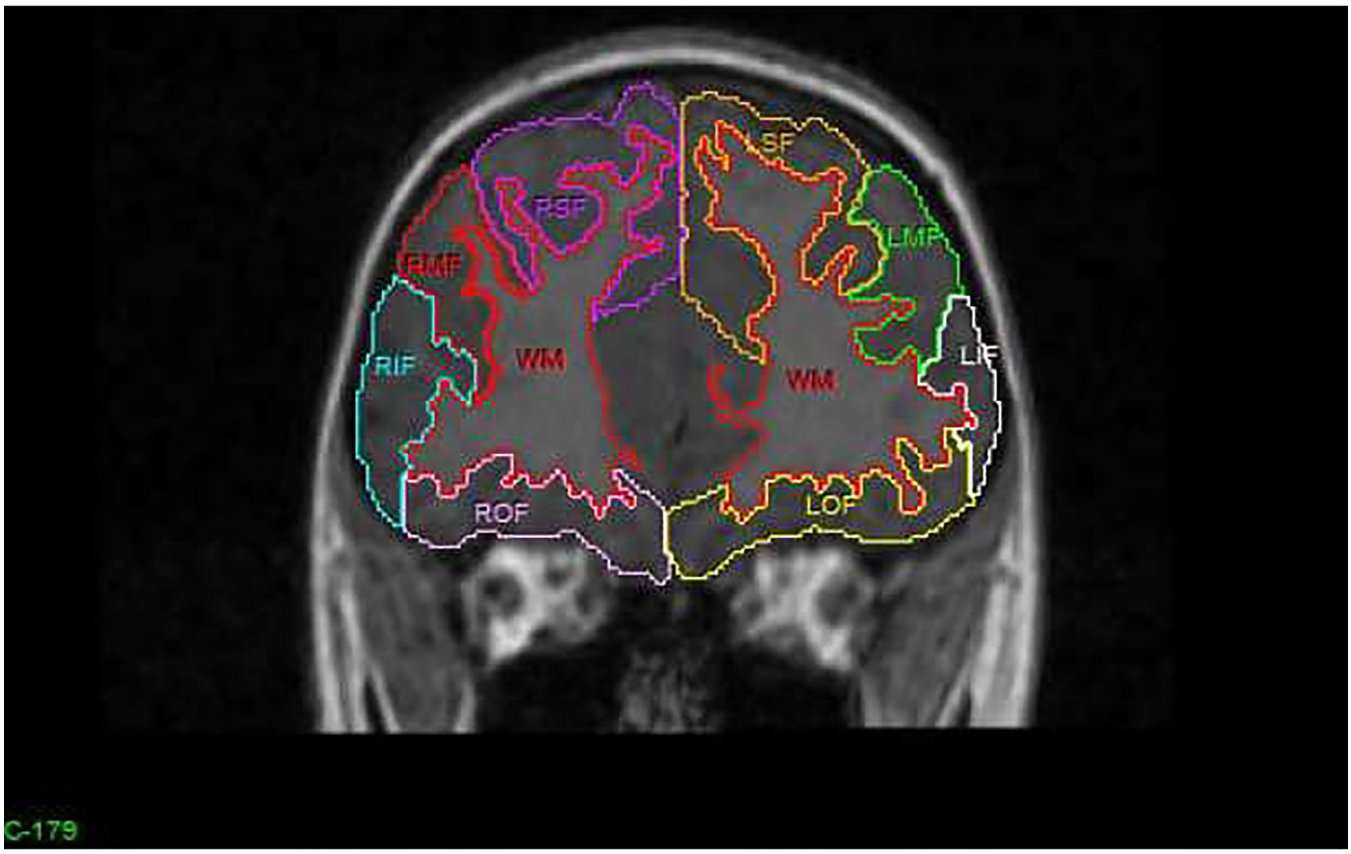


Figure 1.

Depiction of manual tracing of the frontal lobe

RSF = Right Superior Frontal; LSF = Left Superior Frontal; RMF = Right Middle Frontal; LMF = Left Middle Frontal; RIF = Right Inferior Frontal; LIF = Left Inferior Frontal; ROF = Right Orbital Frontal; LOF= Left Orbital Frontal; WM = White Matter

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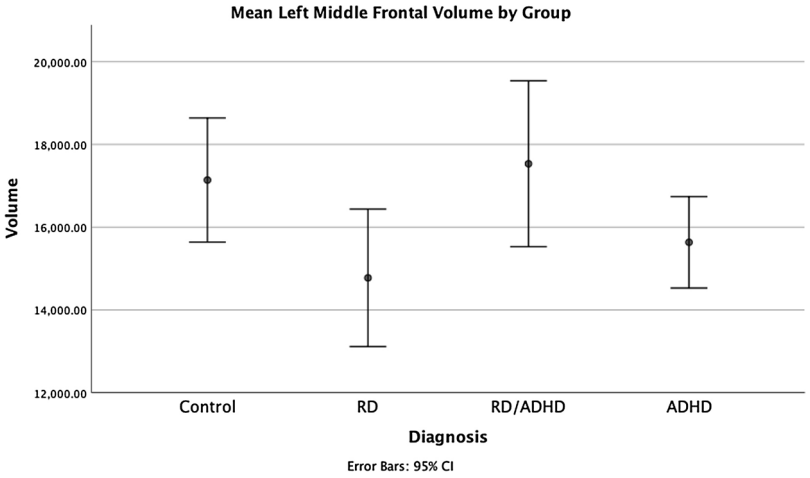


Figure 2.

Means of left middle frontal gyrus volume are represented by dots, with the 95% confidence interval being represented by the error bars. Means are in mm^3.

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Table 1

Descriptive Data on Participants

Variable	**Control Mean(SD) or % n = 40**	**RD Mean(SD) or % n = 24**	**ADHD Mean(SD) or % n = 63**	**RD/ADHD Mean(SD) or % n = 24**	**Statistics (*F* or X^2, df, *p*)**
Gender (Male)	19(48%)	14(58%)	30(48%)	13(54%)	$X^2(3)=1.07$, $p=.78$
Race (Caucasian)	34(85%)	23(96%)	58(92%)	19(79%)	$X^2(12)=10.42$, p=.58
Age (years)	9.60(1.30)	9.38(1.38)	9.60(1.34)	9.21(1.50)	$F(3,147)=0.63$, $p=.60$
Maternal Education	5.49(1.07)	5.57(0.95)	5.53(1.07)	5.25(1.23)	$F(3,144)=0.46$, $p=.71$
Edinburgh	87.75(20.57)	82.08(23.95)	80.32(28.17)	92.50(7.37)	$F(3,144)=1.96$, $p=.12$
TONI IQ	108.25(10.46)	100.88(7.83)[a]	99.75(11.39)[a]	95.38(9.72)[a]	$F(3,147)=8.67$, $p<.001$
WJ-III LWI	106.03(11.72)	79.29(9.12)[a,b]	102.43.10(9.56)	82.83(8.99)[a,b]	$F(3,147)=57.71$, $p<.001$
WJ-III Word Attack	105.78(10.44)	84.75(6.96)[a,b]	102.06(8.60)	89.21(8.27)[a,b]	$F(3,147)=40.48$, $p<.001$
Inattention	49.05(9.29)	51.78.(7.92)	68.17(6.25)[a,c]	67.50(4.70)[a,c]	$F(3,146)=75.28$, $p<.001$
Hyperactivity/Imp.	45.90(7.31)	49.30(6.85)	62.89(12.64)[a,c]	60.04(12.11)[a,d]	$F(3,146)=12.51$, $p<.001$
Total Brain Volume (mm^3)	1244333.67 (184958.96)	1161959.55 (138884.25)	1197166.71 (156578.62)	1219982.41 (183727.42)	$F(3,147)=1.38$, $p=.25$

Note. TONI = Test of Nonverbal Intelligence; WJ-III = Woodcock-Johnson Tests of Achievement, 3rd Ed.; LWI = Letter-Word Identification subtest. Inattention was measured with the BASC-2 Parent report Attention Problems scale; Hyperactivity/Imp. was measured with the BASC-2 Parent report Hyperactivity/Impulsivity Scale. The Edinburgh was used to measure handedness in percent right handed. Maternal Education was measured using a modified Hollingshead scale, 5 = some college.

[a] group differs from controls at $p < .001$.

[b] group differs from ADHD at $p < .001$.

[c] group differs from RD at $p < .001$.

[d] group differs from RD at $p < .01$

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Table 2

Descriptive Data on Frontal Volumes (mm^3) and Univariate Findings

Frontal Gyrus	Controls MM(SE)	RD MM(SE)	ADHD MM(SE)	RD/ADHD MM(SE)	2 X 2 Analyses	F(1,46)	p	ηp^2
R Prefrontal	14454.17 (447.06)	14992.36 (576.90)	14310.34 (354.20)	14178.28 (573.64)	RD or not	0.17	.68	.001
					ADHD or not	0.94	.34	.006
					RD X ADHD	0.45	.50	.003
L Prefrontal	13676.37 (424.30)	13760.56 (547.54)	13818.05 (336.17)	13140.01 (544.44)	RD or not	0.40	.53	.003
					ADHD or not	0.26	.61	.002
					RD X ADHD	0.64	.42	.004
R Orbitofrontal	11915.00 (280.36)	12410.20 (361.79)	12043.06 (222.13)	11857.60 (359.75)	RD or not	0.25	.62	.002
					ADHD or not	0.47	.50	.003
					RD X ADHD	1.18	.28	.008
L Orbitofrontal	11661.19 (259.67)	12116.26 (335.09)	11918.02 (205.73)	11434.34 (333.19)	RD or not	0.00	.97	.000
					ADHD or not	0.54	.47	.004
					RD X ADHD	2.59	.11	.017
R Superior Frontal	19732.63 (448.35)	20191.64 (578.57)	19782.86 (355.23)	20798.85 (575.30)	RD or not	2.19	.14	.015
					ADHD or not	0.44	.51	.003
					RD X ADHD	0.31	.58	.002
L Superior Frontal	18441.67 (406.90)	20117.94 (525.08)	18340.95 (322.39)	18916.20 (522.11)	RD or not	6.20	.01	.041
					ADHD or not	2.09	.15	.014
					RD X ADHD	1.46	.23	.010
R Middle Frontal	16296.01 (579.52)	16060.88 (747.84)	15527.35 (459.15)	15899.85 (743.61)	RD or not	0.01	.92	.000
					ADHD or not	0.53	.47	.004
					RD X ADHD	0.22	.64	.002
L Middle Frontal	16762.18 (657.90)	15245.83 (848.98)	15742.50 (521.25)	17406.01 (844.18)	RD or not	0.01	.92	.000
					ADHD or not	0.61	.44	.004
					RD X ADHD	4.66	.03	.031
R Inferior Frontal	18149.34 (502.02)	18813.52 (647.83)	17347.91 (397.75)	17370.89 (644.17)	RD or not	0.38	.54	.003
					ADHD or not	4.07	.04	.027
					RD X ADHD	0.33	.57	.002
L Inferior Frontal	17889.30 (462.17)	17798.54 (596.40)	17388.79 (366.17)	17758.00 (593.03)	RD or not	0.07	.79	.001

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Frontal Gyrus	Controls MM(SE)	RD MM(SE)	ADHD MM(SE)	RD/ADHD MM(SE)	2 X 2 Analyses	F(1,46)	p	ηp^2
					ADHD or not	0.28	.60	.002
					RD X ADHD	0.20	.64	.002

Note. Marginal means (MM) and standard errors (SE) are controlling for total brain volume, as are the univariate statistics. R = Right; L = Left.