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# Neural Alterations Influencing Skilled Reading In Adhd: A Task-Based Fmri Study

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**NEURAL ALTERATIONS INFLUENCING SKILLED READING IN ADHD: A TASK-BASED FMRI STUDY**

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**DEDICATION**

To my family

and to my students,

past, present, and future.

“We are all faced with a series of great opportunities brilliantly disguised as impossible situations.” - Charles R. Swindoll

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# CHAPTER 1

## INTRODUCTION

### 1.1 Prevalence and symptomatology in ADHD

#### 1.1.a Diagnosis of ADHD

Attention-deficit/Hyperactivity Disorder (ADHD) is one of the most common childhood, neuropsychiatric disorders, occurring in about 5-10% of the population (APA, 2000; Carroll, Maughan, Goodman, & Meltzer, 2005; Faraone, Sergeant, Gillberg, & Biederman, 2003; Polanczyk, Willcutt, Salum, Kieling, & Rohde, 2014). ADHD is a complex neurodevelopmental disorder with a high rate of comorbidity (Barnard-Brak, Sulak, & Fearon, 2011; DuPaul, Gormley, & Laracy, 2013; Willcutt & Pennington, 2000; Willcutt et al., 2001), symptoms persisting into adulthood (Biederman, Petty, Evans, Small, & Faraone, 2010; Faraone, Biederman, & Mick, 2006), and increased risk of developing other disorders such as antisocial, mood, anxiety and substance use disorders (Elia, Ambrosini, & Berrettini, 2008; Spencer, Biederman, & Mick, 2007). Broadly speaking, those with ADHD have symptoms of poor impulse control, excessive motor activity, and short attention span (APA, 2000; Barkley, 1997). The high prevalence presents a significant public health concern, since increased academic problems from an early age produce an increased societal and economic burden (Fried et al., 2013; Sciberras et al., 2014), including poorer career achievement and productivity (Preston, Heaton, McCann, Watson, & Selke, 2009; Snow & Biancarosa, 2003).

ADHD has a heterogeneous symptomatology (Castellanos, Sonuga-Barke, Milham, & Tannock, 2006; Durston, van Belle, & de Zeeuw, 2011; Nigg, Willcutt, Doyle, &

Sonuga-Barke, 2005; Sonuga-Barke, 2003; Spencer et al., 2007), which may change over time (Willcutt et al., 2012) and includes a wide range of possible cognitive impairments (Castellanos et al., 2006; Nigg et al., 2005). Three clusters of symptoms have traditionally been identified as subtypes in the DSM-IV-TR (APA, 2000) and presentations in the DSM-5 (APA, 2013). These clusters are referred to as ADHD-Combined, ADHD-Predominantly Inattentive, and ADHD-Hyperactive, with ADHD-Combined being the most prevalent (e.g., Elia et al., 2008; Froehlich et al., 2007). Other sub-categorizations have been hypothesized based on common co-morbidities, such as Conduct Disorder or Oppositional Defiant Disorder, or based upon other shared characteristics such as cognitive impairments or affective dysregulation (Castellanos et al., 2006; Nigg & Casey, 2005; Willcutt, Pennington, Olson, Chhabildas, & Hulslander, 2005). Despite investigations seeking to distinguish etiologies between the subgroups, much speculation remains as to the neural impairments producing the different phenotypes (Nigg et al., 2005). However, the unifying feature in the vast majority of ADHD cases is an inability to maintain focus as compared with similarly aged counterparts (Lalonde, Turgay, & Hudson, 1998).

**1.2 Sustained attention deficits in ADHD**

The inability to sustain attention is arguably the core executive function deficit in ADHD, which subserve other common dysfunctions, including working memory, planning, and inhibition (Durston, 2008; Martinussen & Tannock, 2006; van Lieshout, Luman, Buitelaar, Rommelse, & Oosterlaan, 2013). Sustained attention is a specific construct within attention that refers to the ability to maintain focus and response readiness to a given task (Barkley, 1997; Langner & Eickhoff, 2013). Sustained attention is mediated by frontoparietal and frontostriatal networks, as demonstrated through lesion and functional neuroimaging studies (Fig. 1, Corbetta & Shulman, 2002; Häger et al., 1998; Ogg et al., 2008). Within these networks, structural and biochemical neuroimaging studies have identified differences in neurodevelopmental trajectories in ADHD compared with typically developing controls (TDC; Posner & Petersen, 1990). Specifically, Stanley *et al.* (2008) have shown a lack of progressive maturation in the prefrontal cortex of children with ADHD. Multiple volumetric studies have found decreased caudate volume in ADHD (Carrey et al., 2012; Castellanos et al., 2002; Shook et al., 2010), and some cortical thickness measures suggest delayed, if not permanently altered, development of the prefrontal cortex (Shaw et al., 2006). Though functional neuroimaging studies have consistently implicated frontostriatal and frontoparietal dysfunction in ADHD (Banich et al., 2009; Burgess et al., 2010; Durston et al., 2003; Epstein et al., 2007), it remains unclear whether the neural dysfunctions are similar for children with ADHD across subtypes or co-morbidities.

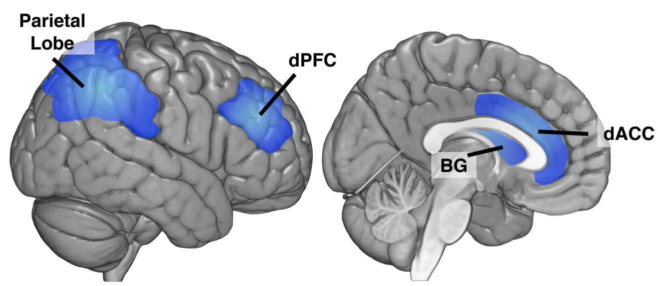



**Fig. 1** Four, predominant areas related to attention processes are depicted. The frontostriatal and frontoparietal networks have been implicated in ADHD pathology. dPFC = dorsal prefrontal cortex, BG = basal ganglia, dACC = dorsal anterior cingulate cortex

Versions of the Continuous Performance Task (CPT, Rosvold, Mirsky, Sarason, Bransome, & Beck, 1956) have often been used to assess cognitive aspects of sustained attention (Conners, Epstein, Angold, & Klaric, 2003) and have been adapted for neuroimaging (e.g., Weissman, Roberts, Visscher, & Woldorff, 2006). The CPT has also been assessed as a possible, diagnostic tool for ADHD, but lacks high specificity for the diagnosis versus other potential co-morbidities or disorders. Specifically, ADHD and learning disabled populations perform categorically worse than controls, but may not differ from each other (Aaron, Joshi, & Phipps, 2004; Advokat, Martino, Hill, & Gouvier, 2007; Epstein et al., 2009). Two groups (Kofler et al., 2013; Miranda et al., 2012) recently explored subtleties in the Conners' CPT-II scoring and suggest that children with ADHD have a characteristic pattern of highly variable response times and poorer overall performance during a CPT. Neurally, ADHD functional neuroimaging studies have implicated activation differences in the right hemisphere prefrontal cortex (PFC), parietal lobe (PL), basal ganglia (BG), and cerebellum in ADHD children responding to tasks similar to the CPT, including the go/no-go, Stroop, and stop-signal tasks (Banich et al., 2009; Burgess et al., 2010; Durston et al., 2003; Epstein et al., 2007).

**1.3 Inattention is associated with reading problems**

<u>1.3.a Cognitive and neuroimaging data suggest an association between inattention and poor reading skills</u>

Since attention may play a large role in other executive functions (van Lieshout et al., 2013), it is unsurprising that more severe attention impairments have been associated with greater academic problems (Alloway, Gathercole, & Elliott, 2010; Schmiedeler & Schneider, 2013; Sciberras et al., 2014). Likewise, compelling evidence shows an important relationship between attention and reading skills (Aaron, Joshi, Palmer, Smith, & Kirby, 2002; Jaeger, 2003; Rogers, Hwang, Toplak, Weiss, & Tannock, 2011; Semrud-Clikeman, 2012; Willcutt et al., 2005), and an ADHD child with inattentive subtype is more likely to have a co-occurring RD diagnosis (Carroll et al., 2005; Levy, Young, Bennett, Martin, & Hay, 2013; Mayes & Calhoun, 2007; Willcutt et al., 2003). In regard to performance on the CPT, distinguishing ADHD-Predominantly Inattentive subtype from those with Reading Disabilities can be extremely difficult (Aaron et al., 2002). In general, impaired attention has been implicated in RD (Carroll et al., 2005; Rogers et al., 2011; Willcutt & Pennington, 2000) and linked with poorer literacy skills at various stages of development (Sims & Lonigan, 2013). Thus, while reading requires integration of numerous cognitive abilities (Richards et al., 2006; Vidyasagar & Pammer, 2010; Zumberge, Baker, & Manis, 2007), the association between inattention and phonological processing remains one of the prominent focuses in RD and ADHD research (de Jong et al., 2009; Martinussen & Tannock, 2006; McGrath et al., 2011; Paloyelis, Rijsdijk, Wood, Asherson, & Kuntsi, 2010; Purvis & Tannock, 2000; Rucklidge & Tannock, 2002; Willcutt et al., 2001).

<u>1.3.b ADHD has a high co-occurrence with Reading Disability (RD)</u>

Boys with ADHD are highly susceptible to Reading Disability (RD), evidenced by upwards of 50% of a community-based cohort (Yoshimasu et al., 2010) or 45% in broader studies qualifying for a diagnosis of co-occurring ADHD and RD (Del'Homme, Kim, Loo, Yang, & Smalley, 2007; DuPaul et al., 2013; Pennington, Groisser, & Welsh, 1993; Willcutt & Pennington, 2000). RD is characterized by poor reading skills, particularly related to phonological processing, but is only diagnosed if a person shows impaired skill in spite of adequate education, opportunity to receive instruction and exposure to text, and mental capacity (Pugh et al., 2001; B. A. Shaywitz, Fletcher, Holahan, & Shaywitz, 1992; Snowling, 2001). For those affected, the co-occurring disorders (ADHD/+RD) produce significant behavioral and educational challenges, often requiring substantial remediation in the education system (Sexton, Gelhorn, Bell, & Classi, 2012). Remediation techniques driven by neurocognitive and neuroimaging RD studies have previously shown promise for normalizing functional activation and structural areas in children with RD (Aylward et al., 2003; Keller & Just, 2009; B. A. Shaywitz et al., 2004; Simos et al., 2002; Temple et al., 2003); however, without knowledge of the neural circuitry affected by ADHD/+RD, it is unclear whether the techniques sufficiently address the dysfunctional patterns in the sizable population with ADHD/+RD.

**1.4 Cognitive impairments shared by ADHD and RD**

<u>1.4.a A brief survey of hypotheses regarding the presentation of ADHD/+RD</u>

Most of the extant knowledge about the two disorders is from neuropsychological studies examining common cognitive, behavioral, or genetic factors. Numerous hypotheses have been put forward as investigators have sought to determine whether the two disorders are truly dissociable or have common, shared impairments. One of the first, prominent postulations, called the phenocopy hypothesis, addressed the difficulty of disentangling the chief contributors to academic troubles in RD or ADHD (Hinshaw, 1992; Pennington et al., 1993). In short, the hypothesis stated that inattention in ADHD may produce difficulty acquiring reading skills and, conversely, poor reading skills may present as inattentive behaviors. Thus, a student may appear to have both disorders, but ultimately the presentation was due to the severity of one of the disorders. Despite considerable face validity, neuropsychological support has not been overwhelming for the phenocopy hypothesis. Other, competing hypotheses related to poor auditory (Franceschini, Gori, Ruffino, Pedrolli, & Facoetti, 2012; Raschle, Stering, Meissner, & Gaab, 2014) or visual (Chouake, Levy, Javitt, & Lavidor, 2012; Livingstone, Rosen, Drislane, & Galaburda, 1991; Vidyasagar & Pammer, 2010) integration have also been proposed to explain the higher incidence of co-occurring disorders. However, there is inconsistent evidence for these impairments predicting reading abilities (Heim et al., 2010; McLean, Stuart, Coltheart, & Castles, 2011), and the hypotheses have not sufficiently described how attention and phonologic impairments may be related (Goswami, 2014). Studies investigating executive dysfunctions contributing to RD or ADHD/-RD have identified several candidate processes that may be shared by both disorders, including working memory, processing speed, and attention (Christopher et al., 2012; Levy et al., 2013; Martinussen, Hayden, Hogg-Johnson, & Tannock, 2005; Mayes & Calhoun, 2007; McGrath et al., 2011; Rogers et al., 2011; Rucklidge & Tannock, 2002; Steele, Karmiloff-Smith, Cornish, & Scerif, 2012; Willcutt & Pennington, 2000). Given that those with ADHD/+RD show a non-additive combination of ADHD/-RD and RD neurocognitive deficits (Bental & Tirosh, 2007; de Jong et al., 2009; Germanò, Gagliano, & Curatolo, 2010), the evidence currently points to a multiple deficit hypothesis (Pennington, 2006; Shanahan et al., 2006) as the most plausible explanation for the co-occurring disorders (Sexton et al., 2012).

1.4.b The multiple deficit hypothesis of ADHD/+RD

The multiple deficit hypothesis has gained wide acceptance and outlines that co-occurring ADHD/+RD comes about through a combination of cognitive and reading impairments (Pennington, 2006). Children with ADHD/+RD often show decreased processing speed, verbal working memory, planning, and attention performance (Willcutt et al., 2005). Furthermore, those with ADHD/+RD may be more affected, as compared with ADHD/-RD or RD alone, on any of these cognitive domains (de Jong et al., 2009; Germanò et al., 2010; Katz, Brown, Roth, & Beers, 2011). Specifically with respect to inattention, there is some evidence that children with ADHD/+RD perform more poorly compared to ADHD/-RD on some aspects of CPTs, specifically including reaction time variability (McGee, Clark, & Symons, 2000; Miranda et al., 2012; Tamm et al., 2014; Willcutt et al., 2001). However, given the paucity of neuroimaging studies investigating differences between ADHD/+RD and ADHD/-RD, it is unclear whether corresponding neural dysfunctions are more exaggerated, or even unique, between the two ADHD subgroups.

1.4.c Theoretical implications for inattention in phonological processes

Phonological processing encompasses the ability to convert written graphemes, basic combinations of letters, into phonemes, the simplest auditory units of language (Ramus et al., 2003). The process of grapheme-to-phoneme conversion is referred to as decoding or, more colloquially, sounding out words (for review, Carreiras, Armstrong, Perea, & Frost, 2014). As with the co-occurring diagnosis, several hypotheses have been proffered for the causes of RD, including a magnocellular/attention (Chouake et al., 2012; Livingstone et al., 1991; Pammer, Hansen, Holliday, & Cornelissen, 2006; Vidyasagar & Pammer, 2010) and cerebellar/rhythm theory (Fawcett, 2011; Nicolson, Fawcett, Brookes, & Needle, 2010). However, the phonological deficit hypothesis remains the most empirically supported and commonly accepted (Eden & Vaidya, 2008; Ramus et al., 2003; S. E. Shaywitz & Shaywitz, 2008;

Snow & Biancarosa, 2003; Snowling, 2001), stating that someone with a clinical RD diagnosis is characterized by poor ability to manipulate phonologic stimuli (Pugh et al., 2001; S. E. Shaywitz, Morris, & Shaywitz, 2008).

The process of reading - visualizing letters, forming logical combinations, manipulating the sounds, and then subvocally stating a word - unsurprisingly requires executive functions, including attention (Berninger, Raskind, Richards, Abbott, & Stock, 2008; Levy et al., 2013; Mayes & Calhoun, 2007; Rogers et al., 2011; Samuels, 2002; Steele et al., 2012; Willcutt & Pennington, 2000). Thus, the association between inattention and phonological problems is intuitive and has been demonstrated in ADHD broadly, RD (Preston et al., 2009; Semrud-Clikeman, 2012; Zumberge et al., 2007), and non-affected (Dittman, 2013; Pham, Fine, & Semrud-Clikeman, 2011) populations of children. This association across diagnoses illustrates the complex, dimensional nature of attention and phonological ability may need to be investigated as such, rather than based purely on a diagnosis. However, given the paucity of neuroimaging studies addressing ADHD/+RD, diagnostic-based grouping is an important first step to determining the possible neural underpinnings of poor attention and reading abilities.

**1.5 Frontostriatal alterations and attentional impairment**

In light of the associations between inattention and phonological impairments, the striatum may play a key role in ADHD/+RD. The striatum receives corticostriatal afferents from many regions, leading to its integrative role (Calzavara, Mailly, & Haber, 2007; Haber & Calzavara, 2009). As such, the striatum is likely involved in many executive functions, including attention (Draganski et al., 2008). Accordingly, ADHD/+RD subjects have shown transiently improved reading scores when given methylphenidate over placebo (Hale et al., 2011; Keulers et al., 2007). Little is currently known about the extent of striatal differences between ADHD/+RD and ADHD/-RD, though cortical and sub-cortical structures in frontostriatal and frontoparietal attention networks play a significant role in ADHD pathology.

As previously noted, multiple volumetric studies have found decreased caudate volume in ADHD (Carrey et al., 2012; Castellanos et al., 2002; Shook et al., 2010). Additionally, genetic association has been intimated between poorer attention (Bidwell et al., 2011; Luca et al., 2007; Willcutt, Pennington, Olson, & DeFries, 2007), lower reading ability (Cornish, Savage, Hocking, & Hollis, 2011), and smaller caudate volume (Durston et al., 2008; Paloyelis et al., 2010). Neuroimaging ADHD studies have also reported abnormally thinner cortex in the parietal and frontal lobes (Shaw et al., 2006) and abnormal activation of frontoparietal (Halperin & Schulz, 2006; Petersen & Posner, 2012) and frontostriatal networks in response to attention (Hart, Radua, Nakao, Mataix-Cols, & Rubia, 2012; Makris et al., 2008; Posner & Petersen, 1990; Sarter, Gehring, & Kozak, 2006; Sarter, Givens, & Bruno, 2001) compared with TDC. The impact of ADHD/+RD in these studies is unclear, since RD was not an exclusionary criterion. However, the relative degree of impairment suggests that increased dysfunction in the frontostriatal attention network may differentiate ADHD/+RD from ADHD/-RD from a neural perspective.

**1.6 The dual subnetwork hypothesis of reading and reading fluency**

Anatomical (for review, Wandell, 2011) and lesion-based studies (Price et al., 2003) support the existence of two, left-lateralized subnetworks for language-related

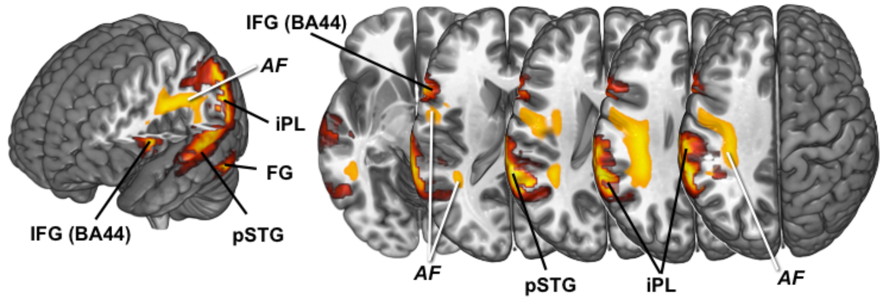



**Fig. 2** The dorsal reading subnetwork is responsible for phonologic processing. Cortical areas and white matter tracts (italics) depicted are based on probabilistic masks within FSL.

processing. Dual subnetwork models of language and reading, including the Dual Route Cascade (Coltheart, Rastle, Perry, Langdon, & Ziegler, 2001) and Connectionist Dual Process (Perry, Ziegler, & Zorzi, 2007; Ziegler et al., 2008) computational models, provide a framework for the development of fluent reading skills through the two subnetworks that operate in conjunction with one another and may be under executive control (Hickok, 2009; Hickok & Poeppel, 2004; Ziegler et al., 2008), as alluded to earlier. In short, the models state that reading is accomplished through the cooperation of two routes, or subnetworks, engaging at different levels based on the familiarity of a word to an individual (Binder, Medler, Desai, Conant, & Liebenthal, 2005; Brennan, Cao, Pedroarena-Leal, McNorgan, & Booth, 2012; Harm & Seidenberg, 2004). Novel or unfamiliar words are decoded by occipital, parietal, and temporal cortical areas connected by the arcuate fasciculus (Hickok:2009dt; Blackmon et al., 2010; Hickok & Poeppel, 2007; Sandak et al., 2004, Fig. 2) and will be referred to as the *dorsal decoding subnetwork*. As word familiarity increases through exposure to text, word recognition becomes of the less effortful and primary strategy. Word recognition is accomplished through cortical areas within the occipital, temporal, and frontal cortices connected by the extreme capsule and inferior longitudinal fasciculus to the IFG (Saur et al., 2008, Fig. 3). Collectively, these areas will be termed the *ventral recognition subnetwork* for this study. A few studies have indicated that the ventral recognition subnetwork also reorganizes itself as fluency develops - familiar words preferentially recruit the anterior IFG and FG compared with letter strings (Binder et al., 2003; Bokde, Tagamets, Friedman, & Horwitz, 2001; Mechelli et al., 2005; Pammer et al., 2004). Therefore, neural impairments in either subnetwork or executive dysfunctions affecting automaticity and cognitive flexibility may have important implications for the development of RD within ADHD.

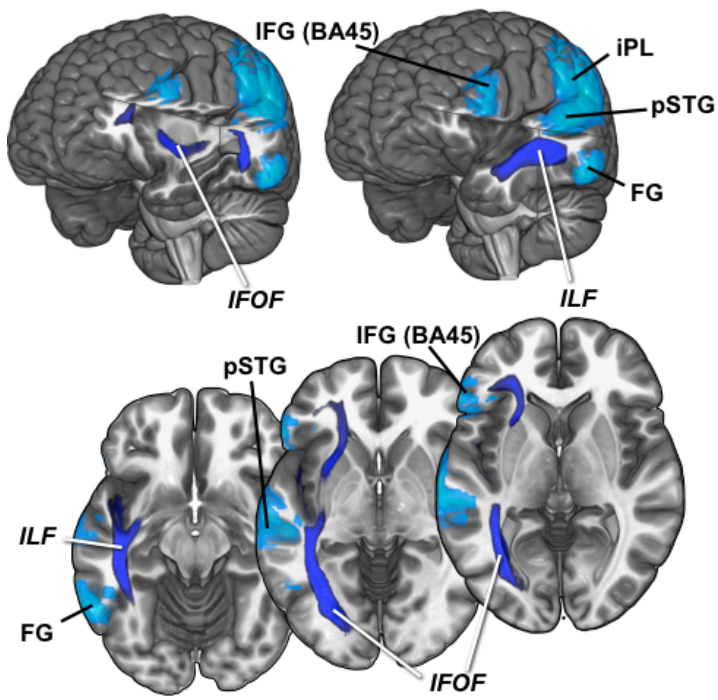



**Fig. 3** Orthographic processing requires the ventral reading subnetwork. Cortical areas and white matter tracts (italics) depicted are based on probabilistic masks within FSL.

Impairments within the dorsal decoding subnetwork have been associated most closely with RD. Specifically, the posterior superior temporal gyrus (pSTG; BA 22) and inferior parietal lobe (iPL; BA 40) typically show decreased activation in RD compared with controls (Q. Cao et al., 2008; Hoeft et al., 2007; S. E. Shaywitz & Shaywitz, 2008; Temple et al., 2001). Functional studies have also demonstrated that decreased phonological abilities correspond with more elaborated processing in the broadly defined, bilateral inferior frontal gyrus (IFG; BA 44/45; Simos et al., 2002; Temple et al., 2001). Neuropsychological studies show greater deficits in reading fluency measures, particularly phonologic awareness (e.g., pseudoword decoding), in ADHD/+RD compared to ADHD/-RD and typically developing controls (TDC; Willcutt et al., 2001). Functional activation of the dorsal decoding subnetwork in response to a phonologically-based task has not previously investigated for ADHD/+RD. However, phonologic deficits are not apparent in ADHD/-RD (Purvis & Tannock, 2000; Rucklidge & Tannock, 2002; Willcutt et al., 2010), suggesting that dorsal decoding subnetwork dysfunctions distinguish ADHD/+RD from ADHD/-RD.

### 1.7 Current questions and scope

Neuropsychological data indicates that those with ADHD/+RD have more severe cognitive impairments than those with either disorder (Willcutt et al., 2005); yet, questions remains about the etiology of ADHD/+RD and whether there is a double dissociation between the disorders from the perspective of neuroimaging. To begin addressing this question, the current study was designed to investigate specifically whether there are additional, neural differences in ADHD/+RD relative to ADHD/-RD. Two manipulations of a sustained attention task were used to assess functional alterations in attention-related areas in response to 1) non-linguistic and 2) phonologic stimuli. The distinction provides insight from a neural perspective into whether attention deficits exist generally or in response to reading-oriented tasks for ADHD/+RD. The phonologic condition also provides evidence to address the degree to which ADHD/+RD and ADHD/-RD inherently differ in functional activation of reading-related, cortical areas. Thus, the first half of this project aims to characterize alterations within the attention and reading networks that may contribute to ADHD/+RD.

The first study, Chapter 2, was conducted to provide insight into attention network activation differences between the ADHD subgroups under non-linguistic conditions. Several investigations using tasks similar to the CPT have demonstrated that right hemispheric frontoparietal and frontostriatal areas play a key role in initiating, directing, and sustaining attention (Petersen & Posner, 2012; Sarter et al., 2001; 2006). Unfortunately, ADHD neuroimaging studies often lack exclusion criteria for RD and use linguistic tasks (i.e., Stroop interference) to assess attention or inhibition. Given the inconsistent exclusion criteria and generally small sample sizes, it is uncertain how ADHD/+RD and ADHD/-RD may differ in functional activation of attention network areas. It was hypothesized that ADHD/+RD would show decreased functional activation relative to ADHD/-RD along attention-related, frontostriatal areas in the right hemisphere.

The primary goal of the second study, Chapter 3, is to investigate potential differences in the functional activation between ADHD/+RD and ADHD/-RD in response to a novel phonologically-based, sustained attention task. The task was developed to stress phonological processing within the dorsal decoding subnetwork. However, the prolonged attentional component was also initially part of the design, so that comparisons between linguistic and non-linguistic tasks could be made. Thus, there were two hypothesis related to the second study. First, ADHD/+RD would demonstrate significantly decreased activation of posterior, cortical areas within areas associated with reading. Second, given the association between inattention and poor phonology, even greater dysfunction in the frontostriatal attention network would be evident in ADHD/+RD.

The results from the first two studies brought about a conceptual shift in the analysis strategy, which is elaborated in remaining chapters. The rationale behind the shift and the quantitation for a novel metric based on cognitive performance during reading tasks is introduced in Ch. 4. Psychological characterizations of the groups defined by the new metric are explored in Ch. 5. Results from testing predictions about the neural underpinnings for the groups during orthographic and phonologic lexical decision tasks are presented in Ch. 6. Finally, Ch. 7 gives a broad overview of the findings with suggestions for future directions.

# CHAPTER 2

## NON-LINGUISTIC, NUMERIC ATTENTION PARADIGM REVEALS FUNCTIONAL DIFFERENCES BETWEEN ADHD/+RD AND ADHD/-RD

As mentioned in Chapter 1, right hemispheric frontostriatal and frontoparietal attention networks are consistently implicated in ADHD pathology. Though ADHD children and adolescents have shown functional hypoactivation in frontostriatal and frontoparietal network areas during attention and response inhibition (go/no-go; Durston et al., 2003; Epstein et al., 2007), working memory (N-Back) and error monitoring (Stroop naming tasks; Banich et al., 2009; Burgess et al., 2010), relatively few fMRI studies have applied a CPT paradigm to ADHD populations (for review, Hart, Radua, Nakao, Mataix-Cols, & Rubia, 2012). Also, due to the limited power of smaller sample sizes, use of linguistic stimuli in the paradigms, or lack of formal screening or exclusion for a co-occurring reading disability (for review, Paloyelis, Mehta, Kuntsi, & Asherson, 2007), it remains unclear whether altered attention networks in ADHD/-RD are also present in ADHD/+RD to a similar extent relative to controls during non-linguistic sustained attention tasks.

Frontal regions, including the dorsal prefrontal cortex (dPFC), are largely responsible for top-down control of attention (for review, Baluch & Itti, 2011; Katsuki & Constantinidis, 2014). The inferior frontal gyrus (IFG), striatum, insula, and dorsal anterior cingulate (dACC) are associated with monitoring responses and re-engaging attention after a lapse during sustained attention (Weissman & Prado, 2012; Weissman, Roberts, Visscher, & Woldorff, 2006). The superior and inferior parietal lobe (iPL) have multiple functions related to orienting and sustaining attention

(Corbetta & Shulman, 2002; Häger et al., 1998; Ogg et al., 2008). While the networks logically are tied to each other, there is also some room for specialization of (dys)function.

This study employed a non-linguistic, numeric CPT (n-CPT), adapted for fMRI, to identify neural alterations in frontoparietal and frontostriatal attention network areas that might distinguish ADHD/+RD from ADHD/-RD and TDC as a critical first step. Specifically, it is important to establish whether those with ADHD/+RD show impaired activation patterns compared with ADHD/-RD or controls during a monotonous task with non-letter, numeric stimuli termed the n-CPT. The Conners' CPT-II computerized assessment (Conners, Epstein, Angold, & Klaric, 2003) was also completed to characterize the behavioral ramifications of functionally impaired attention areas during a more difficult task, involving both prolonged attention and rapid letter identification. In view of behavioral symptomatology and cognitive scores implicating attention in ADHD/+RD, the hypothesis was more extensive hypoactivation in frontostriatal attention areas relative to both ADHD/-RD and TDC groups. Further, consistent poorer performance in attention during both the n-CPT and the Conners' CPT-II was hypothesized for ADHD/+RD compared with either group.

**2.1 Sample Characteristics for the Numeric CPT**

Seventeen controls, sixteen boys meeting criteria for DSM-IV-TR ADHD/-RD, and twelve boys with co-occurring ADHD/+RD were included in this first study. As noted in Table 4, six subjects (3 TDC, 2 ADHD/-RD, and 1 ADHD/+RD) completed the paradigm prior to inclusion of the WIAT-III assessment and do not have scores. However, these subjects were retained to maintain reasonable sample size given that the verbal IQ scores were within normal limits (range: 87-106) and the discrepancy between Performance and Verbal IQ was less than 1.5 standard deviations for all but the ADHD/+RD subject. The ADHD/-RD group was composed of ten combined subtype and six inattentive subtype; co-morbidities included four subjects with conduct disorder, one with anxiety, and none with oppositional defiant disorder. Fourteen of the sixteen ADHD/-RD subjects were currently on a stable dose of psychostimulants (maintained for at the current dose for six months). Seven of the ADHD/+RD group had combined subtype, five were predominately inattentive; three subjects had comorbid conduct disorder. Six of the twelve ADHD/+RD subjects were receiving stable doses of psychostimulants. All subjects were free of psychostimulant medication for at least a 24-hour period prior to the MR examination and Conners' CPT-II testing.

**2.2 Numeric Continuous Performance Task (n-CPT)**

All subjects received verbal instructions along with a 1min:15s training version of the n-CPT on a computer outside of the scanning room, prior to the MRI examination. During the n-CPT, visual tokens were presented serially in 90-second attention blocks and followed by 30-second, control condition, fixation blocks (Fig. 4). There were three repetitions of alternating attention and fixation blocks. Tokens were single digits for the first block, double digits for the second and third blocks, and static pound characters for the fixation blocks. In contrast to response inhibition paradigms, like the Conners' CPT and Sustained-Attention-to-Response task, visual tokens were presented in a pseudorandom order and at a ratio of three non-target tokens for every target token (i.e., with a duration of 250 msec and an inter-stimulus interval of 1 sec).

Thus, the present study engaged sustained attention processing preferentially by using less frequent target-to-non-targets ratio and extended block lengths, which are much longer than the typical 15 sec to 30 sec block lengths reported in task-based fMRI studies. During attention blocks, subjects were instructed to press a button with the right index finger when the target token was shown. During fixation blocks, subjects passively viewed one or two pound characters (i.e., "##"). Responses to non-targets, false alarms, were compared with hits to determine group differences in Sensitivity (d'). Sensitivity accounts for tradeoffs between strategy and accuracy (e.g., pressing the button for each stimulus produces both high hit and false alarm rates, resulting in poor sensitivity). Due to technical issues with the response box, the behavioral performance measures during the n-CPT were missing from two participants (one TDC and one ADHD/+RD).

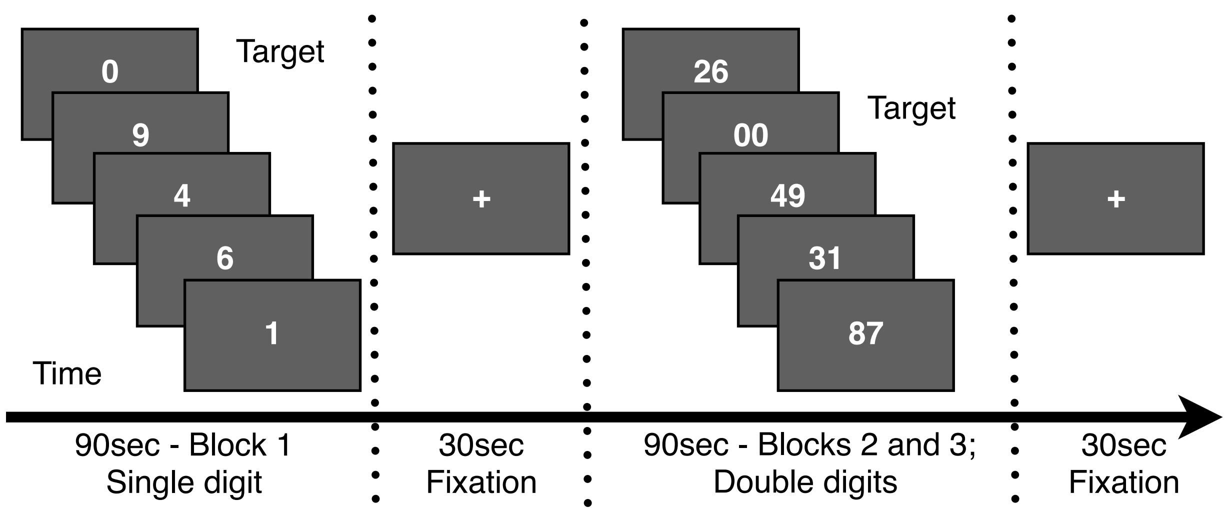



**Fig. 4** A diagram of the n-CPT. Numeric stimuli are presented serially for 90 sec. attention blocks. First-level analyses contrast attention and fixation blocks.

<u>Imaging and processing protocol for the wr-CPT</u>

The total task duration for the n-CPT is 6min:27s. Details for the gradient echo planar functional and Magnetization Prepared Rapid Gradient Echo anatomical acquisition sequences are in Appendix D. Functional images underwent pre-processing and motion correction as outlined in Appendix E. First-level analyses, reflecting greater functional activation during the sustained attention condition compared to the fixation condition, were generated for each subject and carried forward into the second-level analysis. The second-level analysis modeled group effects across all three groups in an ANCOVA design with age and d' as covariates of no interest. Regions associated with attention processing based on the literature, including the middle and inferior frontal gyri [MFG (BA 9 & 46) and IFG (BA 44 & 45)], insular cortex, dorsal anterior cingulate cortex [dACC (BA 24 & 32)], striatum (caudate and putamen), thalamus, and the superior and inferior parietal lobe [sPL (BA 5 & 7) and iPL (BA 40)], were examined.

Specific Behavioral Analysis

Group differences in age, FSIQ, and reading assessment scores between ADHD/+RD, ADHD/-RD, and TDC subjects were assessed using ANOVA. To characterize diagnostically-based group performance during the n-CPT fMRI scan, mean Hit RT, Hit RT SE, and Sensitivity (d') were chosen as behavioral performance metrics. Main effects were assessed for each of the behavioral metrics using an ANCOVA with age as a covariate and depicted in Fig. 5. Conners' CPT-II (see Appendix F for description) scores were unavailable for five subjects (2 TDC and 3 ADHD/+RD). Those available were assessed using ANCOVA with age as a covariate and reported in Table 3.

## 2.3 Results

2.3.a **Demographics, Symptoms and Reading Ability**

The three groups, ADHD/+RD, ADHD/-RD, and TDC, did not differ in age ($F_{2,45}$ = .67; $p$ = .51) or FSIQ ($F_{2,45}$ = .49; $p$ = .62). ADHD subgroups did not differ on the Conners' Cognitive Problems/Inattention subscale ($F_{1,27}$ = .10, $p$ = .75) or Hyperactivity ($F_{1,27}$ = .007, $p$ = .93). Reading performance differentiated ADHD/+RD from both of the other groups in Word Reading ($F_{2,45}$ = 5.8, $p$ = .006; Tukey's HSD ADHD/+RD < ADHD/-RD, $p$ = .011; ADHD/+RD < TDC, $p$ = .015) and Pseudoword Decoding ($F_{2,45}$ = 12.1, $p$ < .001; Tukey's HSD ADHD/+RD < ADHD/-RD, $p$ < .001; ADHD/+RD < TDC, $p$ < .001). Table 1 gives an overview of the demographics results.

**Table 1. Demographics for non-linguistic, n-CPT**

| | TDC | ADHD/-RD | ADHD/+RD | Group *p*-value | Tukey's HSD *post-hoc* |
|---|---|---|---|---|---|
| n (completed WIAT-III) | 18 (15) | 16 (14) | 12 (11) | | |
| Age in years | 11.8 (1.6) | 12.4 (2.1) | 11.8 (1.9) | 0.51 | |
| Full Scale IQ | 111 (16) | 106 (15) | 109 (13) | 0.62 | |
| Conners' Cognitive Problems and Inattention | - | 58 (12) | 57 (13) | 0.75 | |
| Conners' Hyperactivity | - | 65 (17) | 67 (21) | 0.93 | |
| WIAT-III Word Reading, Normed | 104 (9) | 104 (10) | 90 (15) | 0.006 | a, *p* = .015; b, *p* = .011 |
| WIAT-III Pseudoword Decoding, Normed | 105 (8) | 109 (9) | 86 (19) | <.001 | a, *p* < .001; b, *p* < .001 |

Note: Standard deviations are bracketed. a = ADHD/+RD < TDC; b = ADHD/+RD < ADHD/-RD. See methods for RD diagnostic criteria.

2.3.b **Conners' CPT-II Behavioral Performance**

Results from the computerized attention task showed group differences on multiple outcome measures related to inattention, including Hit RT SE ($F_{2,40}$ = 5.4, $p$ = .009) and Variability ($F_{2,40}$ = 6.4, $p$ = .004). Tukey's HSD *post-hoc* results showed significant impairments in ADHD/+RD relative to controls in Hit RT SE ($p$ = .0093) and Variability of Hit RT SE ($p$ = .0093, Cohen's $d$ = 1.29). ADHD/-RD also evidenced decreased scores compared with TDC in Variability ($p$ = .017, Cohen's $d$ = 1.11). Variability of Hit RT SE did not differ significantly between ADHD/+RD and ADHD/-RD due to a small effect size (Cohen's $d$ = .21). Other key measures from the Conners' CPT-II are reported in Table 3.

2.3.c **n-CPT Behavioral Performance during the fMRI**

Reaction times (RT) for correctly identified target tokens, termed hits, were used to calculate mean Hit RT and Hit RT Standard Error (SE; Fig. 5). After covarying for age, there were no significant group differences on the key measurements mean Hit RT ($F_{3,43}$ = .28, $p$ = .76), Hit RT SE ($F_{3,43}$ = .47, $p$ = .63), or d' scores ($F_{3,43}$ = .55, $p$ = .58; see Fig. 5).

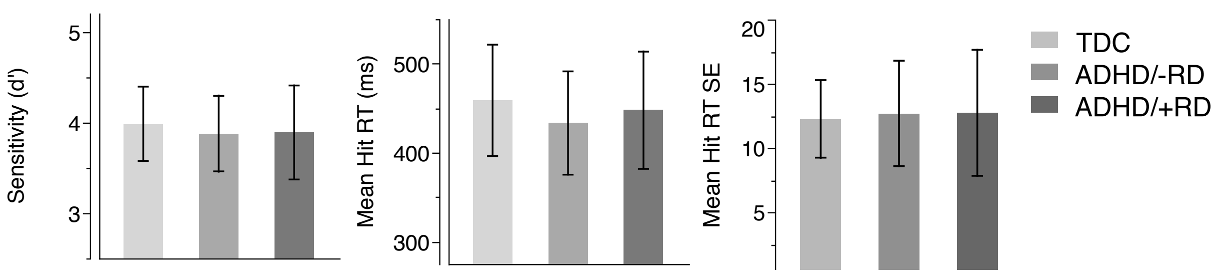



**Fig. 5** No group differences were detected the numeric continuous performance task conducted in the scanner, as exemplified by sensitivity (**a**), mean hit RT (**b**), or mean hit RT SE (**c**). Error bars are SD. RT = reaction time, SE = standard error

2.3.d **fMRI activations**

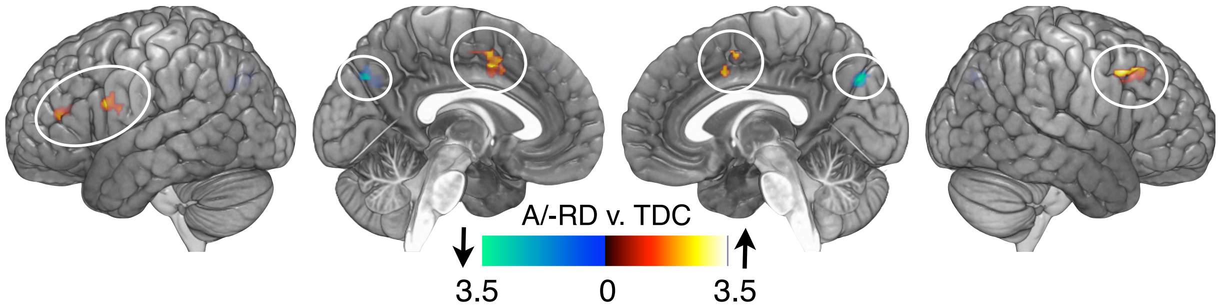



**Fig. 6** Functional activation differences between ADHD/-RD and TDC in response to sustained attention to serially presented, numeric tokens. ADHD/-RD shows increased activation in the left IFG (BA 6 and 45), left dACC (BA 24), and right MFG (BA 9). Hypoactivation of bilateral, medial parietal cortex (BA 7) was also observed in ADHD/-RD compared with TDC. dACC = dorsal anterior cingulate cortex, IFG = inferior frontal gyrus, MFG = middle frontal gyrus

Based on cluster-level corrections, hyperactivation in the left IFG (BA 45), left dACC (BA 24), and right MFG (BA 9) was observed in ADHD/-RD relative to TDC. Additionally, bilateral hypoactivation by ADHD/-RD compared with TDC was seen in the medial sPL (BA 7). These group differences are detailed in Fig. 6 and Table 2. Functional activation within the masked, attention areas did not differ significantly between ADHD/+RD and TDC. Extracted parameters estimates from clusters that differed significantly between ADHD/-RD and TDC provide further evidence that ADHD/+RD did not differ significantly from TDC in attention areas (Fig. 8). However, compared to ADHD/+RD, ADHD/-RD showed greater activation in the left iPL (BA 40), right dACC (BA 32), and right caudate as depicted in Fig. 7 and noted in Table 2.

**Table 2. Functional activation differences in response to a simple, numeric CPT**

| | Hemisphere | Region | BA | Cluster Extent | Peak t-score | MNI coordinates x | y | z |
|---|---|---|---|---|---|---|---|---|
| ADHD/-RD > TDC | | | | | | | | |
| | Left | IFG | 45 | 140 | 3.71 | -42 | 39 | 13 |
| | | IFG | 6 | 135 | 2.91 | -58 | 2 | 16 |
| | | dACC | 24 | 358 | 3.08 | -9 | 3 | 37 |
| | Right | MFG | 9 | 215 | 3.61 | 51 | 15 | 40 |
| ADHD/-RD < TDC | | | | | | | | |
| | Left | sPL | 7 | 137 | 3.31 | -20 | -66 | 31 |
| | Right | sPL | 7 | 173 | 3.31 | 6 | -75 | 34 |
| ADHD/+RD < ADHD/-RD | | | | | | | | |
| | Left | iPL | 40 | 196 | 3.26 | -51 | -30 | 34 |
| | Right | dACC | 32 | 136 | 2.95 | 8 | 42 | 9 |
| | | dACC | 32 | 259 | 4.21 | 16 | 9 | 37 |
| | | Caudate | | 136 | 4.06 | 14 | 18 | 9 |

dACC = dorsal anterior cingulate cortex, MFG = middle frontal gyrus, IFG = inferior frontal gyrus, sPL = superior parietal lobe, iPL = inferior parietal lobe

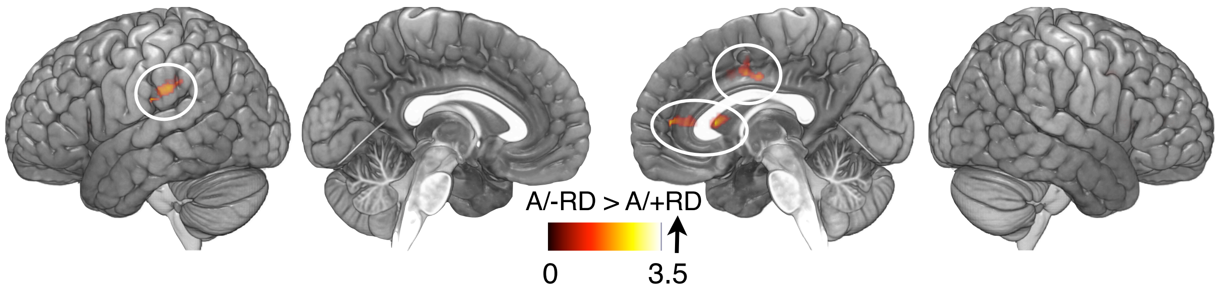



**Fig. 7** Functional activation differences between ADHD/+RD and ADHD/-RD in response to the numeric CPT. Hyperactivation of the left inferior parietal lobe (BA 40), right dorsal anterior cingulate cortex (BA 32), and right caudate was evident in ADHD/-RD relative to ADHD/+RD.

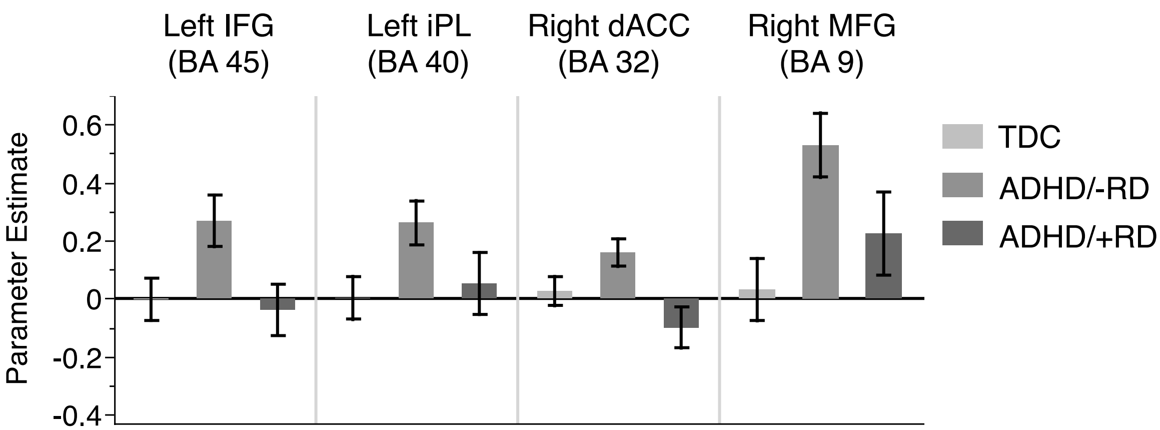



**Fig. 8** Parameter estimates extracted were plotted for four, representative clusters differing significantly between ADHD/-RD and TDC. Functional deviations from controls seen in ADHD/-RD were not observed in ADHD/+RD. Relative to controls, the directionality of right dACC (BA 24) activation differences were opposite in the ADHD subgroups. In light of a much stronger effect in ADHD/-RD, weak evidence of impairment in the right MFG (BA 9) is also seen in ADHD/+RD. Error bars represent SEM.

**Table 3. Conners' CPT-II performance**

| | Cognitive proxy | TDC | ADHD/-RD | ADHD/+RD | Group *p*-value | Tukey's HSD *post-hoc* |
|---|---|---|---|---|---|---|
| n | | 16 | 16 | 9 | | |
| Hit RT (msec) | Speed | 412 (70) | 395 (80) | 449 (101) | 0.33 | |
| Hit RT SE | Inattention | 9.3 (3.5) | 12.8 (7.2) | 16.5 (8.3) | 0.009 | a, $p$ = .0091 |
| Variability of Hit RT SE† | Inattention | 14.9 (9.8) | 28.0 (18.5) | 33.8 (20.2) | 0.004 | a, $p$ = .0093; b, $p$ = 0.017 |
| Sensitivity (d') | Target discrimination | .43 (.32) | .38 (.30) | .22 (.22) | 0.15 | |
| Hit RT ISI Change (sec) | Vigilance | .094 (.04) | .089 (.06) | .13 (.05) | 0.10 | |
| Hit RT Block Change | Vigilance | -0.0025 (.02) | 0.0075 (.04) | 0.033 (.04) | 0.059 | |

Note: RT = Reaction time; Standard deviations are bracketed; a = ADHD/+RD > TDC; b = ADHD/+RD > ADHD/-RD.
†Variability and Hit RT SE are similar, but distinct measures, with Variability reflecting the consistency of reactions between blocks as the study is executed.

## 2.4 Discussion

The focus of this first study was to assess behavioral and functional impairments related to sustained attention without confounding effects related to phonological processing in ADHD/+RD compared with ADHD/-RD and TDC. The sample of 46 boys was similar in age and FSIQ across all three diagnostic groups. Both ADHD groups evidenced elevated inattention and hyperactivity symptoms on the Conners' Parent/ Guardian Self-report relative to TDC and did not differ from one another (Table 1**.** Only scores from the standardized, WIAT-III reading assessment differentiated ADHD/ +RD from ADHD/-RD. Performance on the fMRI sustained attention task, n-CPT, did not differ between ADHD subgroups and TDC, which indicates that all three subject groups were equally compliant in carrying out the n-CPT in the MRI scanner. However, the patterns of functional activation differences between the ADHD subgroups and TDC were unique, as demonstrated in Figs. 6 and 7. Specifically and surprisingly, in response to sustained attention, ADHD/+RD showed no significant activation difference in the frontostriatal and frontoparietal attention areas compared to TDC. In contrast, ADHD/-RD showed increased prefrontal activation and decreased parietal activation relative to TDC. Several areas also showed differences when the two subgroups were compared head-to-head (Fig. 7). To my knowledge, this is the first, fMRI study explicitly contrasting functional activation differences of attention areas between ADHD/+RD and ADHD/-RD.

Behaviorally, the performance of the sustained attention n-CPT paradigm did not differ between the three groups (Fig. 5), including the variability of responses over time (Hit RT SE), which is typically reported as impaired in ADHD. The n-CPT was explicitly designed as a monotonous task, using numeric digits as tokens and lower target response ratio to decrease the emphasis on linguistic demands or response inhibition often assessed with similar paradigms (Hart et al., 2012). These adaptations ensured compliance between groups and attempted to eliminate any potential confounds related to basic reading processes, such as letter identification. Consequently, the adaptations may have also introduced different levels of engagement between ADHD/+RD and ADHD/-RD, which can have implications for activations related to sustained attention (Langner & Eickhoff, 2013).

As addressed above, the evidence supporting relatively greater attention deficits in ADHD/+RD compared to ADHD/-RD is compelling, which led to the hypothesis that

ADHD/+RD would show altered activation in frontostriatal and frontoparietal attention areas relative to both ADHD/-RD and TDC. Notably, ADHD/+RD did not evidence altered functional activation in attention areas compared with TDC. These preliminary results may reflect the relative engagement and proficiency of ADHD/+RD during the task, and further investigation would be helpful to clarify whether ADHD/+RD shows impairments in attention areas during a relatively more demanding, sustained attention task. In contrast, ADHD/-RD demonstrated increased functional activation in prefrontal areas [right MFG (BA 9), left IFG (BA 6 and 45), and left dACC (BA 24)], and decreased activation bilaterally in the parietal areas [medial sPL (BA 7)] compared with TDC (Fig. 6). Increased activation of these prefrontal and dACC areas may reflect effortful control of attention to redirect boredom in ADHD/-RD (Langner & Eickhoff, 2013), which also corresponds with the increased activation in the right caudate, left iPL (BA 40), and bilateral dACC (BA 32) in ADHD/-RD relative to ADHD/+RD (Fig. 7). Other studies have noted increases in activation of the dACC during significant effort to maintain engagement (Weissman et al., 2006) or in response to error monitoring tasks (Bush, 2011). Similarly, Xia *et al.* (2014) used graph theoretical techniques to assess small-world properties of neural attention systems in children with ADHD during a CPT. They noted an increased role of the left dACC as an essential hub in ADHD. Overall, the activation differences between ADHD/-RD and TDC suggest increased prefrontal effort in ADHD/-RD to sustain attention to a monotonous task, which corresponds with the typical symptomatology for the disorder.

Previous task-based fMRI studies with an attention-demanding component have shown functional hypoactivations of frontoparietal and frontostriatal attention areas in

ADHD (Banich et al., 2009; Burgess et al., 2010; Durston et al., 2003; Petersen & Posner, 2012; Posner & Petersen, 1990). However, many of these studies employ more complex versions of the go/no-go (e.g., Booth et al., 2005) or other sustained attention tasks, such as detection of stimuli at predictable and random intervals (Christakou et al., 2012). The lower demand of the n-CPT likely accounts for much of the lack of hypoactivation in ADHD compared with controls in the present study, specifically because of less robust activation patterns in control groups for task compared with baseline. This phenomenon has been reported in other fMRI studies using simplified tasks, including single letter go/no-go (Ma et al., 2012), leading to difficulty detecting hypoactivations in ADHD (e.g., Mostofsky et al., 2003).

Given the counterintuitive fMRI results, it was further investigated whether the ADHD/+RD sample demonstrated attention impairments under greater cognitive load. Interestingly, the Conners' CPT-II computerized assessment, which uses letters as tokens, did demonstrate relatively greater attention impairments in ADHD/+RD compared with ADHD/-RD. Consistent with previous studies, there were no significant differences distinguishing ADHD/+RD from ADHD/-RD with the CPT-II (Aaron, Joshi, & Phipps, 2004; Epstein et al., 2007; McGee, Clark, & Symons, 2000; Miranda et al., 2012); however, ADHD/+RD demonstrated greater impairments in multiple metrics related to sustained attention over time compared to TDC (Table 3). The differences in the ADHD/+RD group included significantly more variable responses throughout the study overall, as estimated by Hit RT SE, as well as higher variability of responses between the 18 blocks reported as Variability of Hit RT SE. There was also a trend toward longer RT in ADHD subgroups relative to TDC as the ISI changed throughout the study, indicating decreased vigilance. Together, the results suggest difficulty in sustaining attention over both short and long timeframes for those with ADHD, but with support of relatively greater impairments in ADHD/+RD (Cohen's *d* = .21 between ADHD subgroups). These observations are in line with numerous studies highlighting the utility of variability, rather than mean reaction time, for differentiating ADHD from controls when using Conners' CPT-II assessments (Epstein et al., 2011; Kofler et al., 2013). Furthermore, these observations are consistent with a recent study demonstrating a pattern of highly variable responses that were associated with ADHD/+RD (Miranda et al., 2012). Lastly, the Conners' CPT-II uses letters as the visual tokens, which may confer a slight disadvantage for those with ADHD/+RD and should be investigated further.

In conclusion, the findings from the Conners' CPT-II support a greater behavioral attention impairment in ADHD/+RD than ADHD/-RD compared with TDC. However, behavioral performance was comparable across all three groups during the less challenging n-CPT, allowing for assessment of basic activation differences in areas supporting sustained attention. The absence of activation differences in ADHD/+RD relative to TDC in response to the n-CPT suggests that attention networks responsible for sustaining attention during relatively low cognitive load are not significantly impaired in ADHD/+RD. This observation raises the question of whether altered activation would be evident under greater cognitive demand, such as use of linguistic stimuli or a more prolonged sustained attention task and is addressed in the second study (Chapter 3). Additionally, increased activations in ADHD/-RD compared with either TDC or ADHD/+RD suggested more effortful control in ADHD/-RD to sustain attention during the monotonous fMRI task.

Note: This study has been prepared for publication as “Functional activation patterns differentiate ADHD boys with and without a reading disability during sustained attention: a preliminary task-based fMRI study” by **Mohl B**, Goradia DD, Casey JE, Ofen N, Khatib D, Jones LL, Robin AL, Rosenberg DR, Diwadkar VA, Stanley JA.

# CHAPTER 3

## ATTENTION, BUT NOT READING, AREAS IMPLICATED IN ADHD/+RD RESPONDING TO A NOVEL RHYMING PARADIGM WITH ATTENTIONAL COMPONENTS

Current neuropsychological evidence supports the multiple deficit hypothesis of ADHD/+RD (McGrath et al., 2011; Willcutt et al., 2010), in which impairments related to the respective disorders co-occur in the same person (Sexton, Gelhorn, Bell, & Classi, 2012). Furthermore, the extent of cognitive impairments appear greater in ADHD/+RD than ADHD/-RD (de Jong et al., 2009; Katz, Brown, Roth, & Beers, 2011; Willcutt, Pennington, Olson, Chhabildas, & Hulslander, 2005). There is also evidence linking greater attention impairments with poorer phonological ability in ADHD/+RD (c.f., de Jong et al., 2009) and RD (Carroll, Maughan, Goodman, & Meltzer, 2005; Rogers, Hwang, Toplak, Weiss, & Tannock, 2011; Willcutt & Pennington, 2000) as well as with poorer literacy skills across stages of development (Sims & Lonigan, 2013). How the interplay of reading and attention translates to neural network alterations is unclear.

Dual subnetwork models of language and reading, such as the Dual Route Cascade (Coltheart, Rastle, Perry, Langdon, & Ziegler, 2001) or Connectionist Dual Process (Perry, Ziegler, & Zorzi, 2007; Ziegler et al., 2008), provide a framework for the development of fluent reading skills through two left-lateralized subnetworks that operate in conjunction with one another and may be controlled by executive functions (Binder, Medler, Desai, Conant, & Liebenthal, 2005; Hickok, 2009; Hickok & Poeppel, 2004; Schlaggar & Church, 2009; Ziegler et al., 2008). The reading subnetwork that will be referred to as the dorsal decoding subnetwork is chiefly comprised of the posterior superior temporal gyrus (pSTG; BA 22), inferior parietal lobe (iPL; BA 40), and inferior frontal gyrus (IFG; BA 44/45), and is the primary subnetwork for decoding (for review, Jobard, Crivello, & Tzourio-Mazoyer, 2003). Accordingly, impaired decoding ability has been associated most closely with decreased functional activation of the left pSTG and iPL using task-based fMRI (Hoeft, Meyler, et al., 2007a; Temple et al., 2001). It is currently unknown whether the phonological impairments in ADHD/+RD stem from similar neural dysfunctions. Therefore, acknowledging these gaps in understanding, the primary goal of this study was to investigate potential differences in the functional activation of the dorsal decoding subnetwork between ADHD/+RD and ADHD/-RD and TDC in response to a novel phonologically-based task.

A second objective of the current study is to identify to what extent ADHD/+RD and ADHD/-RD share altered functional activations in attention-related networks. Those with worse inattentive symptomatology or the inattentive subtype have a greater likelihood of being diagnosed with ADHD/+RD (Carroll et al., 2005; Levy, Young, Bennett, Martin, & Hay, 2013; Mayes & Calhoun, 2007; Willcutt et al., 2003). Accordingly in Ch. 2, ADHD/+RD showed greater variability in response time, which is a proxy for inattention, during a Continuous Performance Task (CPT) with letters as stimuli. However, in response to the fMRI task of sustained attention with digits as stimuli (i.e., a non-linguistic CPT task), we reported no activation differences along attention-related areas in ADHD/+RD compared to TDC. Therefore, a second objective of the current study is to identify to what extent ADHD/+RD and ADHD/-RD share attention network alterations during a novel, linguistic task that is attentionally demanding.

A novel paradigm, called the word rhyming CPT (wr-CPT), was implemented to assess phonological processing under prolonged attentional demands. The wr-CPT combines the phonological skills necessary to rhyme a target word and simple words with orthographically similar (e.g., “day - play”) and dissimilar ending rimes (e.g., “too - true”, Booth et al., 2002) with a sustained attention load similar to a conventional CPT (i.e., with a much longer block length than typical rhyming tasks; Langner & Eickhoff, 2013). Based on previous neuroimaging studies of children with RD showing phonological impairments (Hoeft, Meyler, et al., 2007a; Pugh et al., 2000; Temple et al., 2001), we postulated that those with ADHD/+RD would show extensive hypoactivation in the dorsal decoding subnetwork; that is, specifically in the left pSTG (BA 22) and left iPL (BA 40) compared with TDC or ADHD/-RD. We postulated that those with ADHD/+RD, but not ADHD/-RD, would show extensive hypoactivation in the left pSTG (BA 22) and left iPL (BA 40) compared with TDC. We also posited that ADHD/+RD would evidence some alterations in right hemispheric attention areas relative to TDC. This is an important step in assessing the neural correlates of poor phonological processing and attention in ADHD/+RD and would be concordant with the multiple deficit hypothesis.

**3.1 Sample Characteristics for the wr-CPT**

The sample for the wr-CPT is a subset of those reported in the first, n-CPT study. Ten boys with co-occurring ADHD and RD, fourteen boys with ADHD, but no RD, and fourteen TDC boys. Controls meeting criteria for reading disability were excluded from the current study. The ADHD/-RD group was composed of ten combined subtype and four inattentive subtype. Two combined subtype had co-morbid CD, and none had

ODD. One combined subtype had a secondary diagnoses of OCD. Twelve of the fourteen ADHD/-RD subjects were currently on a stable dose of psychostimulants (maintained for at the current dose for six months). Six of the ADHD/+RD group were combined subtype, four were predominately inattentive. Two combined subtype and one inattentive subtype had co-morbid CD. There were no other co-morbidities. Five of the ten ADHD/+RD subjects were receiving stable doses of psychostimulants. Two controls, one ADHD/-RD, and three ADHD/+RD subjects were left-handed; however, first-level fMRI data was assessed individually to confirm left-hemispheric language dominance.

### 3.2 Word Rhyming Continuous Performance Task (wr-CPT)

Since decreased sustained attention is thought to be one of the core dysfunctions in ADHD, the CPT has often been used to assess individuals' abilities to maintain focus over time. The common versions of the CPT use linguistic stimuli, typically letter identification, which could lead to difficulties in distinguishing between ADHD and learning disabilities, chiefly RD (Aaron, Joshi, Palmer, Smith, & Kirby, 2002; Miranda et al., 2012). In Ch. 2, the non-linguistic, numeric CPT was used to address this potentially confounding issue of linguistic stimuli; however, reading requires both attention and phonological ability. The wr-CPT was designed to simulate active reading, requiring prolonged attention and phonological skills, without the confounds of context, comprehension, or semantics. Kovelman *et al.* (2012) give a succinct rationale for choosing a rhyming task to evaluate reading skills, particularly when attempting to craft an equitable paradigm for disabled groups.

> "Rhyming tasks are commonly used for 3 reasons: rhyming judgments require phonological awareness of the constituent sound parts of words or letter names; rhyming is one of the earliest phonological awareness tasks that children master (Anthony *et al.* 2003); and rhyming is an effective predictor of later reading success for young children (Bradley and Bryant 1978; MacLean *et al.* 1987; Goswami and East 2000; de Jong and van der Leij 2002; Ziegler and Goswami 2005)." - Kovelman et al., 2012

Several elements were included to selectively investigate the interaction of sustained attention and phonological skills in a simulated, active reading condition. The novel wr-CPT consisted of two 90 sec. blocks of rhyming words and three, 30 sec. control blocks of passive fixation on pound symbols (i.e., "###"). Participants were instructed to press a button each time a token (duration = 1 sec; interstimulus interval = 1.5 sec) rhymed with the target word presented in the instructions. Rhyming tokens were not restricted to similar orthography (e.g., "flew" and "too"), and non-rhyming tokens did not require a response. All tokens were mono- or di-syllabic, familiar words (mean log HAL = 10.9; all stimuli log HAL > 7), three to five letters in length from the English Lexicon Project online database (Balota et al., 2007). To produce a relatively infrequent target rate, rhyming tokens were presented once for every four non-rhyming tokens, on average.

After receiving verbal instructions, all participants underwent 1min:30sec training outside of the scanner on a trial version of the task, using different a target word and tokens from those presented during the fMRI. Reaction times and responses during the fMRI scan were analyzed offline after the study. Sensitivity (d'), mean Hit Reaction Time (RT), and variance of Hit RT were calculated and reported in Table 3. Sensitivity reflects the accuracy-speed tradeoff of an individual (e.g., consistently responding to all stimuli results in a low d' score). Hit RT refers to the time between presentation onset and a correct response to a rhyming token.

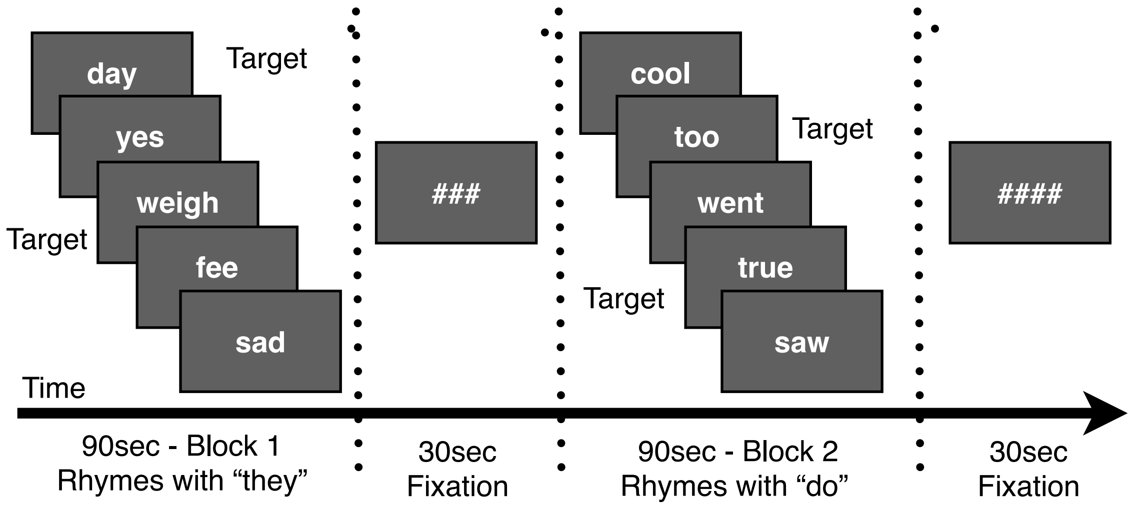



**Fig. 8** A diagram of the visual, word rhyming-CPT. Mono- and disyllabic, 3-5 letter stimuli were presented serially over 90 second attention blocks. Subjects determine whether each stimulus rhymes with a target word (e.g., "they" or "do"). First-level contrasts reflect activation in response to rhyming relative to fixation blocks.

<u>Imaging and processing protocol for the wr-CPT</u>

The total task duration for the wr-CPT is 6min:42s, though the first 90 sec. block of letter rhyming was excluded on the basis of the objectives for the present study. Gradient echo planar images were collected to assess functional activation. A Magnetization Prepared Rapid Gradient Echo sequence was used to obtain anatomical images for co-registration. Details are in Appendix D.

Directional, first-level contrasts compared activation during word rhyming blocks minus fixation blocks. To minimize confounding performance- and age-related effects in the interpretation of the fMRI results, d' and age were entered as covariates in the second-level functional activation group (diagnosis) analyses. Considering the neural response of the wr-CPT and the *a priori* hypotheses, the analyses investigating functional activation differences between groups excluded non-primary reading and attention areas (i.e., motor, occipital, ventral PFC, brainstem, and cerebellar areas) included the inferior and middle frontal gyri, dorsal anterior cingulate, basal ganglia, thalamus, parietal lobe, middle and superior temporal lobe, and fusiform gyrus.

Demographics and Behavioral Analysis

Age, FSIQ, and reading assessment scores were compared using an ANOVA with diagnosis as the main effect. Group differences on performance during the wr-CPT (d', Mean Hit RT, and Variance of Hit RT) were assessed by conducting ANCOVA tests with age as the covariate.

## 3.3 Results

### 3.3.a **Demographics and symptoms**

The three groups of boys, ADHD/+RD, ADHD/-RD, and TDC, did not differ in age ($F_{2,37}$ = .43; $p$ = .65) or FSIQ ($F_{2,37}$ = .32; $p$ = .73). Symptomatology did not differ between ADHD subgroups with regard to the Conners' Cognitive Problems/Inattention ($F_{1,23}$ = .49, $p$ = .49) or Hyperactivity ($F_{1,23}$ = .70, $p$ = .41) subscales. Concordant with the RD diagnosis, the ADHD/+RD group was significantly impaired on WIAT-III Word Reading, Pseudoword Decoding, and Spelling scores relative to either ADHD/-RD or TDC. Sentence Span did not differ between groups ($F_{2,37}$ = 1.1; $p$ = .34). Demographic and reading assessment results are available in Table 4.

**Table 4. Demographics for the wr-CPT**

| | TDC | ADHD/-RD | ADHD/+RD | *p* | Tukey's HSD |
|---|---|---|---|---|---|
| n | 14 | 14 | 10 | | |
| Age (years) | 11.7 (1.6) | 12.4 (2.0) | 12.2 (1.7) | 0.65 | |
| FSIQ | 112 (14) | 107 (16) | 110 (14) | 0.73 | |
| Conners' Cognitive Problems/Inattention | - | 57 (12) | 60 (10) | 0.49 | |
| Conners' Hyperactivity | - | 65 (18) | 71 (14) | 0.41 | |
| Word Reading (WIAT-III) | 103 (8) | 105 (10) | 90 (16) | 0.01 | a, $p$ = .044; b, $p$ = .014 |
| Pseudoword Decoding (WIAT-III) | 106 (8) | 109 (9) | 87 (20) | < .001 | a, $p$ = .002; b, $p < .001$ |
| Spelling (WIAT-III) | 106 (11) | 106 (12) | 85 (15) | < .001 | a, $p < .001$; b, $p < .001$ |
| Sentence Span - Completed items | 16.9 (1.9) | 18.0 (2.9) | 16.3 (3.1) | 0.34 | |

Standard deviations are bracketed. Sentence span requires verbatim recitation of spoken prompts, assessing both receptive language and verbal working memory capacity (see methods). a = ADHD/+RD < TDC; b = ADHD/+RD < ADHD/-RD.

3.3.b **wr-CPT behavioral performance**

All three groups demonstrated compliance to the best of their abilities in performing the wr-CPT. After covarying for age, there were no significant group differences in the variance of Hit RT ($F_{3,36}$ = .17, $p$ = .84), percent correct ($F_{3,36}$ = 3.08, $p$ = .059), or d' scores ($F_{3,36}$ = 2.60, $p$ = .089). However, mean Hit RT differed significantly between groups ($F_{3,36}$ = 3.38, $p$ = .046) with ADHD/+RD responding significantly slower than ADHD/-RD (Tukey's HSD, $p$ = .037), but not TDC (Tukey's HSD, $p$ = .25).

**Table 5. wr-CPT behavioral performance**

| | TDC | ADHD/-RD | ADHD/+RD | *p* | Tukey's HSD |
|---|---|---|---|---|---|
| Mean Hit RT (ms) | 683 (83) | 636 (90) | 743 (124) | 0.046 | a, *p* = .037 |
| Variance of Hit RT | 25784 | 24696 | 27250 | 0.84 | |
| Percent Correct | 82 (5) | 81 (5) | 69 (5) | 0.059 | |
| Sensitivity (d') | 2.7 (1.0) | 2.6 (0.9) | 2.0 (1.1) | 0.089 | |

Bracketed numbers are standard deviations. a = ADHD/+RD > ADHD/-RD.

**Table 6. Functional activation differences in response to word rhyming CPT**

| | Hemisphere | Region | Brodmann Area | $K_E$ | Peak *t*-score | MNI coordinates x | y | z |
|---|---|---|---|---|---|---|---|---|
| ADHD/+RD > TDC | | | | | | | | |
| | Right | iPL | 40 | 290 | 3.83 | 56 | -31 | 46 |
| ADHD/+RD < TDC | | | | | | | | |
| | Left | MTG | 21 | 225 | 3.01 | -50 | 3 | -32 |
| | | STG | 22 | 146 | 3.46 | -42 | -54 | 21 |
| | Right | iPL | 40 | 350 | 4.14 | 56 | -49 | 30 |
| ADHD/-RD > TDC | | | | | | | | |
| | Left | IFG | 9 | 185 | 3.68 | -46 | 6 | 28 |
| | Right | IFG | 44 | 647 | 3.94 | 51 | 18 | 19 |
| | | iPL | 40 | 168 | 3.32 | 39 | -34 | 37 |
| | | pSTG | 22 | 145 | 3.94 | 64 | -30 | 3 |
| | | sPL | 7 | 319 | 3.23 | 28 | -69 | 52 |
| ADHD/-RD < TDC | | | | | | | | |
| | Left | dPFC | 9 | 174 | 3.27 | -42 | 29 | 42 |
| | | STG | 21 | 217 | 3.21 | -38 | -10 | -8 |

aIns = anterior insula; IFG = inferior frontal gyrus; FG = fusiform gyrus; iPL = inferior parietal lobe; sPL = superior parietal lobe; MTG = middle temporal gyrus; dPFC = dorsal prefrontal cortex; STG = superior temporal gyrus

<u>3.3.c **fMRI activation differences in response to the wr-CPT**</u>

Following the classical, reading-related, dual route framework, comparisons of functional activation between groups were conducted within the two subnetworks, dorsal associated with decoding and ventral with recognition (Coltheart et al., 2001). Hypoactivation in ADHD/+RD compared with TDC was evident in both reading subnetworks (Table 6), including the left pSTG (BA 22) and left MTG (BA 21). Compared with TDC, ADHD/-RD demonstrated differences in reading-related areas, which included hyperactivation along the left, posterior dPFC (BA 9) and hypoactivation in the left STG (BA 21) and left dPFC (BA 9). Details are provided in Table 6.

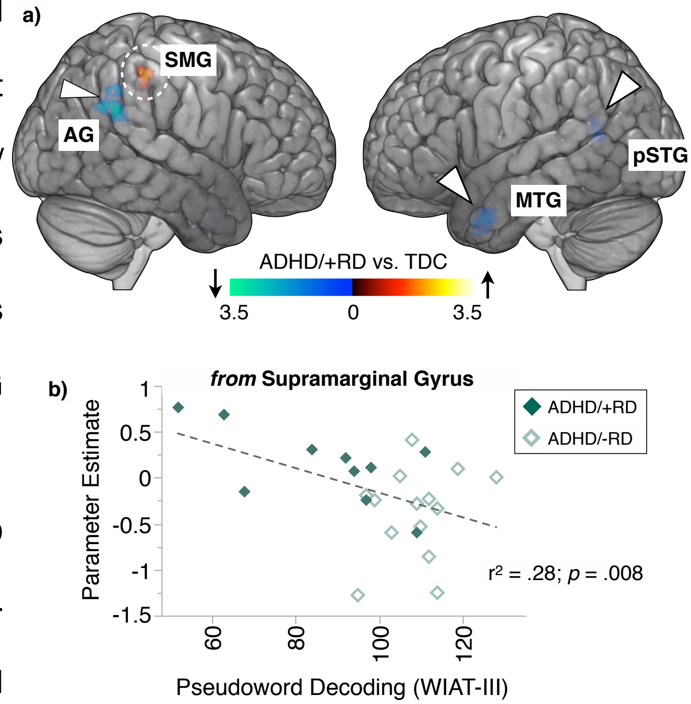



**Fig. 10** (**a**) In response to the wr-CPT, results showed decreased activation in the left pSTG (BA 22), left MTG (BA 21), right iPL (BA 40), as well as increased activation in the right, SMG (BA 40) of ADHD/+RD compared with TDC. (**b**) Extracted parameter estimates show a significant relationship between activation of the right SMG and phonological ability. AG = angular gyrus, MTG = middle temporal gyrus, pSTG = posterior superior temporal gyrus, SMG = supramarginal gyrus.

Group comparisons within right hemispheric regions associated with attention (Petersen & Posner, 2012; Posner & Petersen, 1990) also showed alterations, which were mainly increases in the ADHD subgroups. Specifically, hyperactivation of the right IFG (BA 44), right sPL (BA 7), and right pSTG (BA 22) were observed in ADHD/-RD compared with TDC (Fig. 12). Activation in the right supramarginal gyrus (BA 40) was also increased in both ADHD subgroups relative to TDC (Figs. 9a & 11a). Upon further inspection, the extracted parameter estimates for the right supramarginal gyrus (BA 40) show qualitatively higher activation in ADHD/+RD compared with ADHD/-RD or TDC (Fig. 12a). By contrast, the only hypoactivation in the right hemisphere for either ADHD group compared with TDC was in the right angular gyrus (BA 40), where ADHD/+RD showed significant deactivation relative to controls (Fig. 10a & 10b).

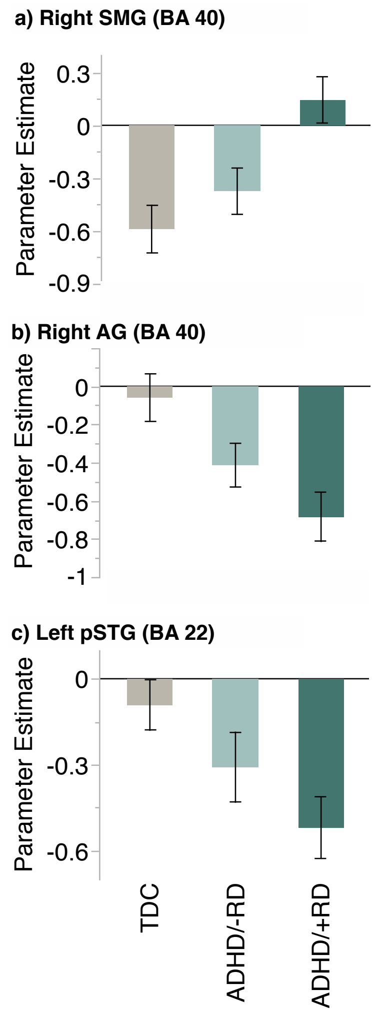



**Fig. 11** (**a**) Activation in the right supramarginal gyrus of higher appears to be relatively greater in ADHD/+RD compared with ADHD/-RD. ADHD/-RD evidenced intermediate activation within the right angular gyrus (**b**) and left pSTG (**c**) relative to TDC and ADHD/+RD. Error bars represent SEM. AG = angular gyrus, MTG = middle temporal gyrus, pSTG = posterior superior temporal gyrus, SMG = supramarginal gyrus.

Since differences in the right parietal lobe have also been reported in relation to reading tasks (McDermott, Petersen, Watson, & Ojemann, 2003; Pammer, Hansen, Holliday, & Cornelissen, 2006), we investigated the potential association between activation and standardized reading scores, specifically the WIAT-III Pseudoword Decoding subtest. Extracted parameter estimates from the right angular gyrus did not correlate with Pseudoword Decoding scores ($r^2$ = .006, $p$ = .73). However, correlating the right supramarginal gyrus parameter estimates with Pseudoword Decoding scores revealed a significant, inverse relationship ($r^2$ = .28, $p$ = .0078, Fig. 11b). The association may be important for elucidating the role of attention in phonological processing.

### 3.4 Discussion

In this study, we examined neural activation differences in decoding and attention areas using a novel word rhyming task (wr-CPT), which leverages phonological demands of rhyming and attentional demand of a typical CPT (Rosvold et al., 1956). Comparisons between three groups of boys, ADHD/+RD, ADHD/-RD, and TDC, revealed significantly poorer WIAT-III reading scores for ADHD/+RD, but no differences in ADHD symptoms between the patient groups (Table 4). Behavioral performance during the wr-CPT was also similar between groups except for a slower, average response in ADHD/+RD (Table 5). ADHD/+RD evidenced hypoactivations in left hemispheric areas associated with

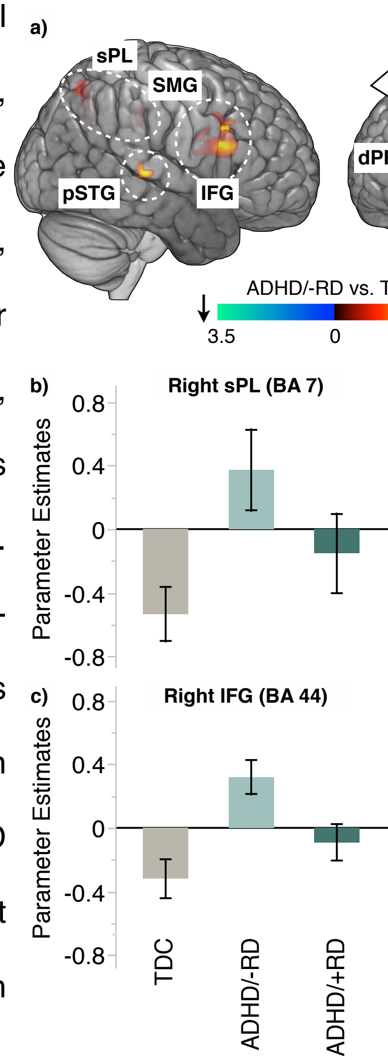



**Fig. 12** (**a**) In response to the wr-CPT, results showed hyperactivation in the left IFG (BA 9), right IFG (BA 44), right SMG (BA 40), right pSTG (BA 22), and right sPL (BA 7) along with hypoactivation in the left dPFC (BA 8), and left STG (BA 22) of ADHD/-RD compared with TDC. (**b-c**) Extracted parameter estimates from the right sPL (BA 7; **b**) and right IFG (BA 44; **c**) demonstrate the magnitude and directionality of activation differences across all three diagnostic groups. Interestingly, ADHD/+RD showed intermediate levels of activation in both attention areas. Error bars represent SEM. IFG = inferior frontal gyrus, dPFC = dorsal prefrontal cortex, iPL = inferior parietal lobe, sPL = superior parietal lobe, STG = superior temporal gyrus, pSTG = posterior superior temporal gyrus**,** SMG = supramarginal gyrus.

reading compared with TDC (Fig. 10a), though one may argue the extent is not striking considering the degree of phonologic impairment in ADHD/+RD. Both ADHD subgroups showed alterations in the right parietal lobe, but ADHD/-RD showed an additional, distinctive pattern of greater frontal and superior parietal activation versus TDC (Fig. 12). The data suggest ADHD/-RD exercised greater cognitive control or re-engagement (Weissman et al., 2006) that was not observed in ADHD/+RD. Thus, continued investigation is needed to further address these distinctive patterns in the attention network between subgroups and its impact on reading ability.

As noted, behavioral performance during the wr-CPT reflected the abilities of each group (Table 5). Similar variance of mean Hit RT further suggests comparable levels of attentional engagement throughout the task (cf., Kofler et al., 2013; Miranda et al., 2012). However, the ADHD/+RD group was slower (Mean Hit RT; $p$ = .046) and tended to be less accurate (Percent Correct; $p$ = .059). The poorer performance is in line with cognitive abilities, namely decoding (Table 4) and processing speed, that are often reported as diminished in ADHD/+RD relative to ADHD/-RD or TDC (Christopher et al., 2012; McGrath et al., 2011). In an attempt to account for the differences in performance, d' scores were included as a covariate of no interest in the random effects analysis of fMRI data.

The functional activation findings comparing ADHD/+RD with TDC (Fig. 10a) are consistent with decreased activation of posterior, reading network regions is commonly reported in neuroimaging studies examining reading disabilities without co-occurring ADHD (Hoeft, Ueno, et al., 2007b; B. A. Shaywitz et al., 2002; Temple et al., 2001) and also, regardless of cognitive ability estimated by IQ (Tanaka et al., 2011). This study demonstrated similar functional deficits in the dorsal decoding subnetwork of ADHD/+RD compared with TDC [i.e., in left pSTG (BA 22) and left anterior MTG (BA 21); Fig. 10a]. However, as noted above, the magnitude and extent of the differences in ADHD/+RD along the left pSTG in the current study were somewhat underwhelming given the relative degree of phonological impairment in the ADHD/+RD group compared with ADHD/-RD or TDC (Table 4), especially when compared to previous studies of RD alone compared with controls (Hoeft et al., 2006; Kovelman et al., 2012; Langer, Benjamin, Minas, & Gaab, 2013; S. E. Shaywitz & Shaywitz, 2008; Temple et al., 2001). Though extracted parameter estimates from significant peaks between ADHD/+RD and TDC indicate some level of hypoactivation in ADHD/-RD as well (Fig. 11), the ADHD/-RD group did not differ significantly from TDC in the dorsal decoding subnetwork (Fig. 12) functionally or behaviorally (Table 4). Overall, the findings provide some evidence of dysfunctions in reading-related areas in ADHD/+RD that are not evident in ADHD/-RD.

Despite similar inattentive symptomatology and attention-related performance on the wr-CPT, the two ADHD subgroups had distinct patterns of differences compared with TDC in the right hemispheric attention network areas. Differences in ADHD/+RD were limited to the right parietal lobe. By contrast, ADHD/-RD evidenced a greater extent of increased activation in frontoparietal attention-related areas, as well as the right temporal lobe, relative to TDC (Fig. 12). To a certain extent, the increased activation in frontal areas of ADHD/-RD is similar to our previous result of increased frontal activation in ADHD/-RD, but not ADHD/+RD, in response to a CPT with numeric tokens (Ch. 2). However, it remains unclear whether attention network dysfunctions that appear to be divergent between the ADHD subpopulations influence the extent of phonological processing impairments.

These differences in attention-related areas for both ADHD groups relative to controls are important in understanding the psychopathology of ADHD/+RD, since attention has been shown to mediate relationships between certain executive functions and reading outcomes (Rogers et al., 2011). The right angular gyrus showed hypoactivation in ADHD/+RD compared with TDC (Fig. 10a). ADHD/-RD showed a similar, but less robust, trend toward hypoactivation of the same area compared with TDC (Fig. 12b). Previously, an MEG study demonstrated an effect of attention on early word recognition processes through activation of the ventral iPL (Pammer et al., 2006). Another possible neural impairment contributing to the association between attention and phonological processing was observed in the current study. The right supramarginal gyrus showed increased activation in both ADHD/+RD and ADHD/-RD compared with controls (Fig. 11a). The magnitude of extracted parameter estimates and extent of hyperactivation in the right supramarginal gyrus (BA 40) was nearly twice as large in ADHD/+RD than ADHD/-RD relative to TDC (Fig. 11a, 12a, and Table 6). Additionally, the peak activation in the right supramarginal gyrus correlated with WIAT-III Pseudoword Decoding scores (Fig. 10b), suggesting it may also play a key role in modulating reading network areas. By extension, these findings may substantiate the association between inattention and phonological impairments from a neural activation perspective and warrants further investigation.

In conclusion, boys with ADHD/+RD demonstrated impaired phonological abilities compared to TDC and ADHD/-RD. However, corresponding neural evidence was not overwhelming for dysfunction in the dorsal decoding subnetwork, leading to the interpretation that other cognitive functions may contribute to poor phonology in ADHD/+RD. One of the chief constructs likely to influence phonological skill is attention (Levy et al., 2013; Mayes & Calhoun, 2007; Rogers et al., 2011; Willcutt & Pennington, 2000). Both ADHD subgroups evidenced dysfunctions in the right iPL, which have been linked with dysregulation of left hemispheric reading areas (Pammer et al., 2006) and may be involved in phonological processing (Booth et al., 2008; McDermott et al., 2003). Specifically, the shared hyperactivation in the right SMG and corresponding correlation between parameter estimates and WIAT-III Pseudoword Decoding scores suggested that attention may influence phonological processing through neural mechanisms. Additionally, the two ADHD subgroups showed starkly different profiles compared with TDC, wherein ADHD/-RD demonstrated a more generalized, frontoparietal effort to sustain attention during the wr-CPT. Collectively, our findings indicate that instead of the dorsal decoding subnetwork being grossly compromised in ADHD/+RD, other cognitive impairments, including the level of inattention, may contribute to the development of RD within ADHD. Continued investigation of the roles for attention and other executive functions, which may lead to sub-optimal reading strategies, is warranted.

Note: This study has been submitted to Brain and Cognition for publication as “Neural Dysfunction in ADHD with Reading Disability during a Word Rhyming Continuous Performance Task” by **Mohl B**, Casey JE, Ofen N, Khatib D, Jones LL, Robin AL, Rosenberg DR, Diwadkar VA, Stanley JA.

# CHAPTER 4

## REFRAMING READING DISABILITIES

### 4.1 Is a new classification needed?

The characterization of the ADHD/+RD sample showed predicted impairments for the Conners' CPT-II, computerized attention test, standardized WIAT-III reading subtests, and functional alterations in attention-related areas. However, beyond these initial observations, the separation of cognitive and neural profiles between ADHD subgroups were less consistent with neuropsychological predictions. The lack of distinguishing cognitive profiles raises the possibility that multiple combinations of cognitive impairments may contribute to the development of RD within ADHD. Furthermore, the heterogeneity of ADHD and cognitive impairments that are common within ADHD may provide an explanation for the high co-occurrence of reading disabilities. Conversely, it is conjectured that specific sets of cognitive strengths may lend themselves to developing preferred reading strategies, regardless of diagnosable RD. The following chapter outlines the key observations raising the question of different paths to ADHD/+RD and the rationale behind a novel classification based on classical, reading acquisition approaches.

Executive functions, including attention and working memory, may influence reading skills and strategies (Aaron, Joshi, Palmer, Smith, & Kirby, 2002; Rogers, Hwang, Toplak, Weiss, & Tannock, 2011; Semrud-Clikeman, 2012; van Lieshout, Luman, Buitelaar, Rommelse, & Oosterlaan, 2013). Inattentive symptomatology did not differ between ADHD subgroups (Table 1); yet, ADHD/+RD performed the worst with respect to attention during the Conners' CPT-II, which uses letters as stimuli

(Table 3). Additionally, performance was similar between groups during the non-linguistic n-CPT, but there were stark differences in activation of the right hemispheric attention networks between the two ADHD subgroups and TDC. For other executive functions, including processing speed and verbal working memory, the distributions of scores between the ADHD subgroups were indistinguishable (Suppl. Fig. 2). Previous studies have reported a mixture of which executive functions and how severe the impairment may be in ADHD/+RD relative to ADHD/-RD (Bental & Tirosh, 2007; Horowitz-Kraus, 2013; Miranda, Mercader, Fernández, & Colomer, 2013; Willcutt, Pennington, Olson, Chhabildas, & Hulslander, 2005). Collectively, the evidence suggests another type of classifier, based on neural differences, may provide insight into the emergence of RD within ADHD.

The findings related to reading also suggest that not all ADHD/+RD, or any group of readers, implement the same reading strategies to achieve single word reading during assessments. The significantly lower standardized WIAT-III reading subtest scores and behavioral data from the wr-CPT indicated phonological processing impairments in ADHD/+RD relative to either ADHD/-RD or TDC; however, the neural hypotheses for the impairments, borrowed from RD literature, were not strongly supported. Though there was some evidence of decreased activation of posterior, reading-related areas in ADHD/+RD, the data generally demonstrated a relatively intact, dorsal decoding subnetwork in ADHD/+RD compared with either TDC (Fig. 10a) or ADHD/-RD. The only other difference between ADHD/+RD and ADHD/-RD was in the left fusiform gyrus (Supp. Fig. 1). The lack of strong findings in the dorsal decoding subnetwork again suggests that the poor reading skills associated with ADHD/+RD may arise from multiple, cognitive impairment combinations. Therefore, the second half of the project was dedicated to investigating whether a factor other than formal RD diagnosis could delineate neural correlates of decreased reading skills and lead to more unified profiles of underlying differences contributing to the reading disabilities.

**4.2 Considering a new, strength-based metric: a Reading Tendency Index**

Beginning to characterize ADHD/+RD along a single dimension is advantageous and necessary for understanding fundamental differences relative to ADHD/-RD or controls; however, the approach also has an unfortunate potential for collapsing different neural patterns related to unique cognitive strategies into a generalization for the diagnosis. For example, initial group comparisons of activation patterns in response to phonologic and orthographic fMRI tasks (Appendix G) did not evidence differences in reading subnetworks between ADHD/+RD, ADHD/-RD, and TDC, as would be predicted by the WIAT-III scores and neuropsychological hypotheses. While lack of statistical power is a possible explanation for this negative finding, it is also plausible that different types of readers, who favor a particular reading strategy and have corresponding functional activation patterns, are equally distributed across DSM-IV-TR diagnoses.

A new metric may also help ameliorate the heterogeneity of cognitive impairments and, potentially, strategies inherent to groupings based on the current methods of diagnosing RD or ADHD (Fletcher, Francis, Rourke, Shaywitz, & Shaywitz, 1992; Katzir et al., 2006; McArthur et al., 2013; Spencer, Biederman, & Mick, 2007). The term equipotentiality describes the scenario where multiple pathways can produce a similar, diagnosable problem and has been posited for ADHD/+RD (Pennington, 2006).

Since fluent reading requires numerous skills, ranging from executive functions to word recognition (Benjamin & Gaab, 2011; Bental & Tirosh, 2007; Katzir et al., 2006), adequate development of and interplay between multiple, neural networks, including the two reading subnetworks, can have a considerable impact on reading outcomes. Current disability-based criteria are not poised to assess the use of different reading strategies nor separate the clusters of cognitive impairments that may promote ADHD/+RD. Some investigators have suggested the need for a dynamic, quantitative metric characterizing readers based on “observable linguistic behavior”, rather than arbitrary cutoffs designating a disability (Uppstad & Tønnessen, 2007). Thus, devising a metric that describes the relative capacity of both reading subnetworks will allow investigation of not only reading abilities, but the impact of various cognitive impairments on the execution of reading tasks and functional development of the reading network.

The following is an example of how this type of new metric could address and limit the effects of equipotentiality. Some genetic studies of RD have specifically introduced the possibility of anatomic differences in the dorsal decoding subnetwork (i.e., iPL ectopias in RD, Ramus, 2004) that may interfere with phonological processes and increase the propensity to rely on the ventral recognition subnetwork (Berninger, Raskind, Richards, Abbott, & Stock, 2008; Galaburda, Menard, & Rosen, 1994; Peschansky et al., 2010). In the case of ADHD, the cognitive impairments typically associated with the disorder may influence how the child approaches reading, since certain strategies (i.e., sight reading or decoding) may rely less on his or her specific impairments (e.g., poor visual working memory and processing speed). Either etiology leads to a greater likelihood of being diagnosed with RD; however, in the context of the proposed metric, the two situations would be differentiated on the basis of the individuals' relative strengths and remediation could proceed accordingly.

**4.3 Precedent for defining reading tendency groups based on subnetworks**

Several hypothesis-based classifications exist for dyslexia and are based on deficits specifically associated with one subnetwork or the other (e.g., McArthur et al., 2013; Stanovich, 1988). For example, neuroimaging studies often compare age-matched and younger, ability-matched controls with dyslexics to determine whether affects are delayed or aberrant development (Hoeft et al., 2007; Kovelman et al., 2012). Acquired dyslexia is often divided into surface dyslexia, the inability to recognize (especially irregular) words, and phonologic dyslexia, an impairment in converting graphemes to phonemes (Price et al., 2003; Sprenger-Charolles, Colé, Lacert, & Serniclaes, 2000). Similarly, Boder's model of developmental dyslexia classified poor readers as i) dyseidetic, or impaired in visual recognition, ii) dysphonetic, or phonologically impaired, and iii) dysphonoeidetic, both recognition and phonologically impaired (Boder, 1970). Lastly, Baron and Strawson (Baron & Strawson, 1976) proposed that even fluent readers could be divided into two groups, Phoenician (Decoders) or Chinese (Sight Readers), based on relative differences between reaction times to word or nonword stimuli.

This study proposes a novel Reading Tendency Index that is distinct from previous models in two dimensions. First, the new metric assesses relative proficiency and tendency, rather than disability (see Suppl. Fig. 4). This is a critical paradigm shift, since strength-based characterization may cluster similar cognitive approaches together and thereby reduce variability. Second, despite processing speed being implicated in RD (McGrath et al., 2011) and contributing to reaction time differences (Miranda et al., 2012), the Reading Tendency Index is one of the first metrics to account for processing speed differences directly in the assessment of reading abilities. By using a simplification of the Drift Diffusion Model (Ratcliff, 1978) to account for processing speed differences, the Reading Tendency Index has distinct advantages over delineations based purely on either reaction time or standardized scores. Both distinctions aim to circumvent equipotentiality and characterize groups based on similar cognitive approaches, ultimately leading to more distinct profiling and a better understanding of underlying neural differences.

**4.4 Predicted, cognitive profiles of each reading tendency**

Several logical, cognitive profiles can be predicted for clusters of readers based on educational and neuropsychological observations, but investigating the neural correlates provides a substantial step forward in understanding reading outcomes. From the beginning, it is important to note that the following predictions do not describe a diagnosis, but rather reinforcing relationships of cognitive patterns and neural correlates which are proposed to establish a reading tendency within an individual. As has been argued above due to equipotentiality, strict diagnostic criteria for ADHD or RD may not be sufficient to categorize the neural dysfunctions that produce poor attentive or reading abilities. In the new scheme, children with ADHD can fall into the same reading tendency categories as children without ADHD; this extends to RD. However, this new model presupposes that those with executive dysfunctions are at higher risk overall of developing an extreme reading tendency as a compensatory mechanism for the collection of impairments. Given the considerable heterogeneity of ADHD (Castellanos, Sonuga-Barke, Milham, & Tannock, 2006; Durston, van Belle, & de Zeeuw, 2011; Nigg, Willcutt, Doyle, & Sonuga-Barke, 2005; Sonuga-Barke, 2003; Spencer et al., 2007), predicting reading tendency based on clusters of cognitive strengths and weaknesses may provide a more powerful classification system to address the neural basis of the reading problems and investigate how the degree of inattention affects the reading subnetworks. The descriptions of Balanced, Decoders, and Sight Readers that follow highlight the cognitive and neural profile that would be predicted for each reading tendency.

Balanced Readers

Both reading subnetworks are essential for fluent reading, which is characterized by a broad vocabulary, relatively seamless reading, and good text comprehension (Samuels, 2002). Word recognition is efficient and accomplished through the ventral reading subnetwork (Sandak et al., 2004), but all readers also need to exercise decoding ability through activation of the dorsal subnetwork, particularly when encountering novel words (Jobard, Crivello, & Tzourio-Mazoyer, 2003; Wandell, 2011). Even highly proficient readers decode words automatically and implicitly (Booth, Mehdiratta, Burman, & Bitan, 2008; Brennan, Cao, Pedroarena-Leal, McNorgan, & Booth, 2012; Diaz & McCarthy, 2007), though the process requires less effort with better skills (Binder et al., 2003). Thus, Balanced Readers likely have the capability to decode and recognize words as well as sufficient executive functioning to switch between the two reading strategies fluidly. Based on a recent study demonstrating a minimum attention requirement for fluency in a normally developing population (Dittman, 2013), it is postulated that attention and cognitive flexibility are the key executive functions subserving development of balanced reading abilities. Overall, high scores on cognitive flexibility tasks, low inattentive symptomatology, and functional activation of both subnetworks during reading tasks are predicted to be hallmarks of Balanced Readers.

Sight Readers

Decoding is a demanding process, requiring attention (Deacon, Benere, & Castles, 2012; Dittman, 2013; Talcott, Witton, & Stein, 2013), letter and grapheme recognition (Wandell, 2011), verbal working memory (Christopher et al., 2012; de Jong et al., 2009; Rucklidge & Tannock, 2002), and phonological skills (Castles & Coltheart, 2004; Ramus et al., 2003). Studies have often provided evidence for the importance of attention and verbal working memory for fluent reading (Jacobson et al., 2011; Rapp & Dufor, 2011; Willcutt et al., 2005). Similarly, inconsistent attention may confound recoding processes, wherein phonemes are subvocally spliced together and compared to internal lexicons (Franceschini, Gori, Ruffino, Pedrolli, & Facoetti, 2012; Kyte & Johnson, 2006). Thus, children with ADHD whose predominant symptomatology implicates verbal working memory or high levels of inattention, may circumvent decoding processes in favor of sight reading methods. By classifying the children on the basis of a tendency to sight read, an interventionist may be able to tailor remediation differently than for a poor reader with decoding tendencies.

Decoders

Those with some capacity to decode words often improve their mental lexicon with consistent and increasing exposure to reading (Deacon et al., 2012; Sprenger-Charolles et al., 2000). However, since the reading approach is still not balanced, Decoders are likely to demonstrate delayed development of fluency (McNorgan, Alvarez, Bhullar, Gayda, & Booth, 2011; Talcott et al., 2013) and may remain somewhat lower on standardized assessments. Given the likelihood that Decoders have a delayed pattern, the cognitive impairments that lead to the tendency may not be all that severe. For example, a child with poor visual working memory or symbol processing may not build an adequate, mental lexicon for sight reading and instead, depends on decoding (Cutting, Koth, Mahone, & Denckla, 2003). Decreased processing speed and a poor mental lexicon may also result in deliberate, effortful reading and may have greater implications for difficulties in fluency or comprehension (Jacobson et al., 2011; Katzir et al., 2006; McNorgan et al., 2011).

**Summary of predicted reading tendencies**

Children with ADHD/+RD may gravitate toward either imbalanced reading tendency, since processing speed, working memory, and attention have all been implicated in the co-occurring disorders (Berninger et al., 2008; Christopher et al., 2012; Levy, Young, Bennett, Martin, & Hay, 2013; Mayes & Calhoun, 2007; McGrath et al., 2011; Rogers et al., 2011; Steele, Karmiloff-Smith, Cornish, & Scerif, 2012; Willcutt & Pennington, 2000). However, reclassifying the individuals in terms of relative abilities and neural correlates may narrow the profiles of poor readers and support earlier identification and more targeted educational support. For example, RD is often undiagnosed until later elementary (Levy & Hobbes, 1989; Sexton, Gelhorn, Bell, & Classi, 2012) and then remediated primarily with phonological approaches. The new scheme with Reading Tendencies does not negate the diagnosis, but rather could confirm that the child is a Sight Reader, who gave the initial appearance of developing fluency due to decent word recognition. However, inferences about the degree of reliance on sight reading that hid and hobbled the development of phonological abilities could also be drawn from the magnitude of the reading tendency. Testing the reliability and utility of the novel Reading Tendency Index to predict cognitive and neural profiles in the subsequent chapters is an important first step in considering how cognitive impairments, other than impaired phonology as assessed by a normative test, play into the development of fluency and may provide a wider range of therapeutic targets for poor readers with and without ADHD.

### 4.5 Choosing a computational model and estimating drift rates

Despite decreased processing speed in ADHD/+RD, few studies report group differences in mean reaction times, even between ADHD and TDC on attention tasks, like the CPT (Aaron et al., 2002; Aaron, Joshi, & Phipps, 2004; M. C. Miranda et al., 2012). Surprisingly, many studies simply covary with reaction time (RT; see exception, Zeguers et al., 2011), if processing speed is taken into account at all. In recent years, a few groups have taken a closer look at the distributions of the RT on an individual basis (for discussion, Matzke & Wagenmakers, 2009; Yap, Balota, Sibley, & Ratcliff, 2012), as the distribution of the RT may distinguish the two groups or may not be normal (see Suppl. Fig. 3). Particularly with ADHD, where the main problem is being “consistently inconsistent”, the outliers may indicate attention lapses (Esterman, Noonan, Rosenberg, & DeGutis, 2013; Weissman, Roberts, Visscher, & Woldorff, 2006). Two methods to quantify differences in RT distributions have emerged, ex-Gaussian and Drift Diffusion Modeling (Ratcliff, 1978), and are elaborated below.

Both models expect a non-normal distribution of reaction times, but differ with regard to the type and implications of derived estimates. Ex-Gaussian models describe the mean, standard deviation, and exponential component of the distribution. The full Drift Diffusion Model results in nine parameters to describe aspects of the subject's responses (Ratcliff, 1978; Ratcliff & McKoon, 2008). Two core strengths of the Drift Diffusion Model make it ideal for the current study. First, the model was produced to account for differences in processing speed. Second, neural models have been used to validate the claim that specific parameters within the model reflect underlying, hidden, cognitive abilities (Philiastides, Auksztulewicz, Heekeren, & Blankenburg, 2011). Since some investigators have interpreted estimates from the two models as reflecting cognitive processes similarly, Matzke and Wagenmakers (2009) investigated the ability of ex-Gaussian estimates to match with the cognitive-specific parameters from the Drift Diffusion Model. They found that the estimates do not correlate and suggest that ex-Gaussian values describe the distribution differences, but cannot be used to infer differences in cognitive abilities as the Drift Diffusion Model does.

The Drift Diffusion Model is predicated on RT from two-choice experimental designs (Ratcliff, 1978). The premise is that evidence for one of two choices is accumulated in a stochastic manner within neural circuits and that hidden cognitive skills can be inferred from the reaction time data. The metrics are derived from the variability and average response times and are related to underlying cognitive skills supporting the decision (Philiastides et al., 2011). One of the most useful outcome estimates is the drift rate, which reflects the speed of the decision and evidence accumulation for an individual (Ratcliff, Perea, Colangelo, & Buchanan, 2004). In the ensuing experiments (i.e., Ch. 5 & 6), drift rates for decoding and recognizing words are mathematically combined to estimate a child's reading tendency. For example, a larger drift rate on a decoding task reflects a longer process to be sure a stimulus is a pseudoword. The rate reflects a combination of cognitive processes related to the task of sounding out the word or realizing that the individual has never been exposed to the particular stimulus previously, without the confounds of motor speed and potential inattentive responses that lengthen an average RT. Likewise, a poor drift rate score on a word recognition task reflects an increased amount of time dedicated to make a decision that the stimulus is a word. The interpretation is that proficiency on a specific skill translates to quicker component processes that increase the rate of evidence accumulation and decrease the threshold for being certain of the choice.

Conventional drift diffusion modeling requires at least 10 errors to accurately model the drift rate (Wagenmakers, van der Maas, & Grasman, 2007). Since the phonologic and orthographic lexical decisions used in this study were created such that all participants would be highly successful, drift rates were estimated using an adaptation of the Drift Diffusion Model called EZ Diffusion Modeling (Wagenmakers, van der Maas, & Dolan, 2008; Wagenmakers et al., 2007) which produces comparable outcomes, but without the error constraint. The EZ Diffusion Model uses six parameters, instead of nine, effectively requiring fewer observations and simpler math. Computations can be done using algebra, instead of differential equations, since the required inputs are mean hit rate, mean RT, and standard deviation of RT.

The following two experiments demonstrate how drift rates estimating phonological and word recognition processes can be mathematically combined to form a novel Reading Tendency Index (Ch. 5). The data demonstrates that three Reading Tendencies (Decoders, Balanced, and Sight Readers) can be identified based on the difference between the inverse drift rates, the novel Reading Tendency Index. More importantly, the experiments show that the Reading Tendency Index effectively delineates subjects such that clusters of impairments and different functional activation patterns in subnetworks associated with reading correspond with decoding and recognizing words. By approximating individualized strengths and tendencies, the new metric has potential benefit for more targeted research questions and efficacious applications through instruction, intervention, or remediation.

# CHAPTER 5

## NOVEL INDEX QUANTIFIES TENDENCY TOWARD DECODING OR SIGHT READING

Subgroups of normal and dyslexic readers have previously been segregated based on prevailing decoding or sight reading impairments (e.g., Baron & Strawson, 1976; Sprenger-Charolles, Colé, Lacert, & Serniclaes, 2000; Wang, Marinus, Nickels, & Castles, 2014); however, neural correlates for these groups have not yet been elucidated. Recently, Yap *et al.* (2014) used Drift Diffusion Modeling to investigate the validity of Baron and Strawson's Phoenician (i.e., Decoders) and Chinese (i.e., Sight Readers) classification of fluent readers by evaluating reaction times of non-disabled adult readers responding to the English Lexicon Project (Yap, Sibley, Balota, Ratcliff, & Rueckl, 2014). While showing greater vocabulary knowledge was related to greater nonword drift rates, as predicted, they were not able to identify the specific subtypes of readers from clusters of Drift Diffusion Modeling parameters for individual skills. A similar idea was proposed by Stanovich (1988), who outlined specific predictions about the distributions of readers based on two dimensions of disabilities, phonological and orthographic. However, no metric was proposed to quantify individuals along the continuums in a concise manner nor to take processing speed into account.

This chapter re-examines the hypothesis that subgroups of readers can be identified using Drift Diffusion Modeling parameters, but from the perspective of predicting a "default reading tendency" through a simple mathematical manipulation of drift rates theoretically associated with each of the reading subnetworks proposed in dual route models (Coltheart, Rastle, Perry, Langdon, & Ziegler, 2001; Harm &

Seidenberg, 2004; McNorgan, Alvarez, Bhullar, Gayda, & Booth, 2011). The Index begins to describe a continuum of readers based on their propensity to use one or more strategies for single word reading. The goal is to address the equipotentiality of ADHD/+RD by identifying clusters of readers that use similar cognitive approaches for single word reading. It is proposed that this may be accomplished by directly comparing the decoding and word recognition drift rates to approximate the balance of the two reading strategies, which may reflect a more homogeneous set of cognitive abilities. Furthermore, the following discussion introduces the possibility of inattention and other executive dysfunctions related to ADHD affecting the likelihood or severity of an imbalanced reading tendency, while still providing an alternate characterization from the DSM-based diagnoses. Compared with the fluent, adult sample in the Yap et al. (2014) study, the broader symptomatology provided by the current ADHD sample increases the ability to detect differences related to reading strategies.

Cognitively speaking, three groups with defined profiles can be readily identified as Decoders, Balanced, or Sight Readers. Neurally, readers may be balanced in their approach and activation of the two reading subnetworks, or they may rely mainly on decoding or word recognition processes and the respective, functional subnetworks. In a fluent reader, one may speculate that neither subnetwork predominates and the child has adequate ability with respect to processing speed, attention, working memory, and importantly, cognitive flexibility to engage as needed on either subnetwork (Booth et al., 2004; Horowitz-Kraus, 2013). It is postulated that a predictable set of impairments produce an over-dependence on a particular reading strategy, regardless of the RD diagnosis (described in Ch. 4). Specifically, poor visual working memory and slower processing speed may lead to an underdeveloped mental lexicon in Decoders, while greater inattention and poor verbal working memory may dictate a dependance on word recognition in Sight Readers. Furthermore, since any number of these cognitive functions may be compromised in ADHD (Christopher et al., 2012; de Jong et al., 2009; Germanò, Gagliano, & Curatolo, 2010; Katz, Brown, Roth, & Beers, 2011; Martinussen, Hayden, Hogg-Johnson, & Tannock, 2005; McGrath et al., 2011; Rucklidge & Tannock, 2002), those with ADHD may be predisposed to rely on one reading subnetwork more than the other as a sequelae of the individual's combination of cognitive impairments. It is also hypothesized that the Reading Tendencies correspond with neural activation of specific reading subnetworks, discussed in greater depth in Chapter 6.

This study compares the cognitive profiles between classifications based on DSM-IV-TR diagnoses and the novel Reading Tendency Index. The comparison addresses whether the Index, based on realistic reading demands, can produce more homogeneous, cognitive profiles in domains that are not reading-specific, but may influence reading development. The overarching hypothesis is that classifying readers on the basis of the individual's tendency to rely on the dorsal decoding or ventral recognition subnetwork will reflect distinct patterns of cognitive and reading abilities. Sight reading is a quicker, less resource-intensive reading method mediated by the ventral recognition subnetwork (Mechelli et al., 2005; Olulade, Flowers, Napolielo, & Eden, 2012; Sandak et al., 2004; Vinckier et al., 2007). Chapter 1 described how executive functions are likely affected by the ability to sustain attention and outlined the association between greater inattention and poorer phonological processing throughout development (Dittman, 2013). It is hypothesized that higher levels of inattention and poorer verbal working memory (McGrath et al., 2011) give rise to a reliance on, and subsequent, preferential development of, the ventral recognition subnetwork. Additionally, given that more inattentive-related symptomatologies are likely to be diagnosed with RD (Carroll, Maughan, Goodman, & Meltzer, 2005; Levy, Young, Bennett, Martin, & Hay, 2013; Mayes & Calhoun, 2007; Willcutt et al., 2003) and phonology is a predictor of future reading gains, it is postulated that Sight Readers show the greatest number of children eligible for a formal RD and lowest reading scores. Conversely, those favoring decoding strategies and the dorsal subnetwork may not show severe inattentive symptomatology (Dittman, 2013; Miranda, Mercader, Fernández, & Colomer, 2013), but likely appear more deliberate due to poor visual working memory and slower processing speed. Dividing the reading tendency groups based on skill strengths and balances may reduce the variability associated with poor reading skill development, leading to more specific hypotheses about the etiology of and instruction for the different Reading Tendencies.

### 5.1 Essential methodology and sample for characterizing the Reading Tendency Index

42 boys between the ages of 9 and 16 years of age completed the orthographic and phonological lexical decision tasks as fMRI paradigms (See Appendix G for description). The drift rates for responding to pseudowords in the phonological lexical

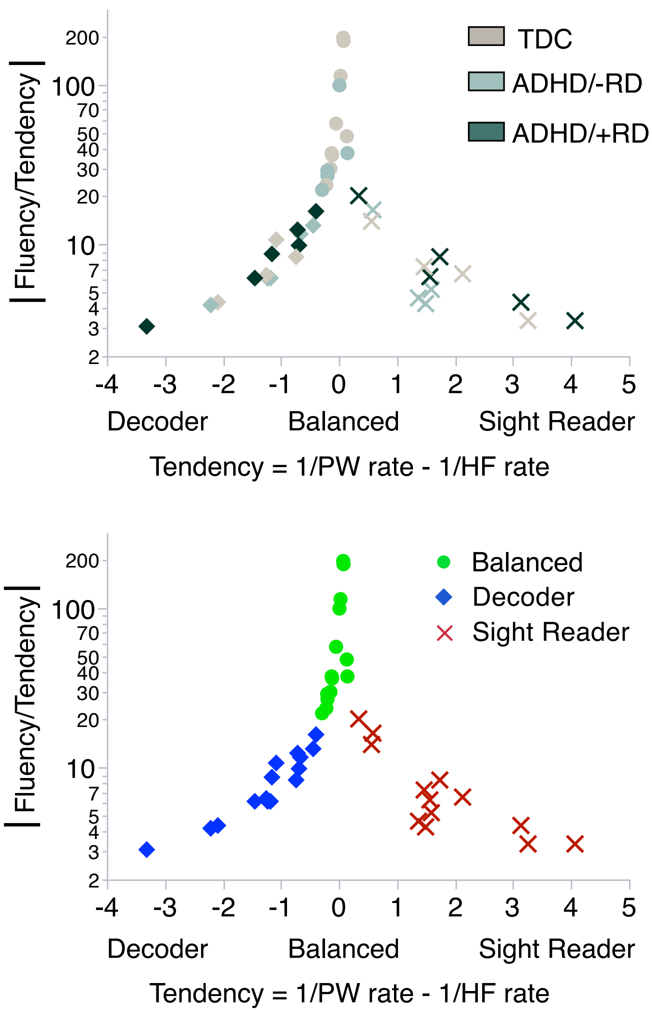



**Fig. 13** Individuals from the three reading tendency groups are represented by their Reading Tendency and Relative Fluency scores. The absolute value of Relative Fluency/Reading Tendency provides an approximation for the overall reading ability, as it penalizes subjects who have high drift rates in one, but not both, reading strategies. Since the sample is small, group size was a chief consideration in the delineations between reading type. Specific criteria for group membership are outlined in the methods section, but in general, scores greater than 0 indicate sight reading preferences and less than 0 suggest decoding tendencies.

decision and to high-frequency words in the orthographic lexical decision were calculated using the JavaScript-based EZ-Diffusion Model (http://www.ejwagenmakers.com/EZ.html). High frequency words are identified more quickly than pseudowords, because of higher familiarity and response certainty (Bergmann & Wimmer, 2008; Clements-Stephens et al., 2012; Table 14). Since indices are more intuitively understood when a balance perform is zero, a correction factor was adopted to maintain zero-centering for the overall index. To create the correction factor, the difference between the average word recognition drift rate and the sample average pseudoword drift rate for the entire sample was added to each subject's pseudoword drift rate. The relative differences between subjects was maintained, but the corrected pseudoword drift rates are used so the interpretation of a zero in the index is a well-balanced approach to reading.

To create the index score itself, the inverse word recognition drift rate was subtracted from the inverse of the corrected pseudoword drift rate to estimate the balance of the two skills. This value is plotted along the x-axis in Fig. 13. Under the suggestions by Stanovich (1988) and others, those with RD should have poor scores on both skills. Since drift rates could be so poor on both as to approach a “balanced” value, a second dimension, Relative Fluency, was also developed to provide a level of confidence that those deemed Balanced Readers were also fluent. The sum of the pseudoword and word recognition drift rates yielded an estimate called Relative Fluency. Together, the two scores can be plotted to show an individual’s reading preferences in view of his abilities.

Given the preliminary nature of the study and small sample size, subjects were grouped so that sample size was approximately equal for all three groups. Group membership was determined by the individual’s distance from zero on the Reading Tendency Index (x-axis, Fig. 13) and absolute value of Relative Fluency divided by Reading Tendency (Fluency:Tendency, Fig. 13). For the purposes of relatively equal groups, the divisions were as follows: Subjects with Reading Tendencies greater than 0 and Fluency:Tendency less than 21 were classified as Sight Readers (n = 12); less than 0 and Fluency:Tendency less than 21 were called Decoders (n = 16); near 0 and Fluency:Tendency greater than 21 were deemed Balanced (n = 14).

Diagnosis

As previously mentioned, the goal was to evaluate whether the Reading Tendency Index can produce more homogeneous groups, based on common approaches to single word reading and, theoretically, sets of cognitive skills that influence the preferred approach. To address the question, two grouping schemes were used for statistical comparisons: one was based on their Reading Tendencies as outlined above ; the other was based on their DSM-IV-TR diagnoses (see Appendix B). Two controls met criteria for a reading disability and were included in the reading tendency-based analyses, but not the diagnosis-based statistical comparisons.

For groups based on reading tendency, the Balanced Reader group was composed of nine controls, two ADHD-combined, three ADHD-predominately inattentive. The Decoders were four TDC, nine ADHD-combined subtype and three ADHD-inattentive subtype; co-morbidities for ADHD subjects included three subjects with conduct disorder, one with anxiety, and none with oppositional defiant disorder. The Sight Readers had five TDC, five ADHD-combined, and three ADHD-inattentive; two had co-morbid conduct disorder, but no other co-morbidities. The ADHD subjects on a stable dose of psychostimulants (maintained for at the current dose for six months) were distributed throughout the three groups with five on medication in the Balanced group, ten Decoders, and five Sight Readers. All subjects were free of psychostimulant medication for at least a 24-hour period prior to the MR examination, reading assessment, and Conners' CPT-II testing.

<u>Cognitive Assessments</u>

*Conners' CPT-II*

Since reading tendency-based groupings cross ADHD diagnoses, participants performed the Conners' CPT-II, detailed in the Appendix F, to characterize attention abilities. The key outcomes were Omissions, Hit RT, Hit RT Std Error, Variability of Hit RT, Detectability, Hit RT Block Change, and Hit RT ISI Change. Behavioral data was available for all subjects and is reported in Table 9.

*Cambridge Neuropsychological Test Automated Battery (CANTA*B)

Participants completed three assessments from the computerized CANTAB to estimate individuals' capabilities in key constructs subserving reading, visual working memory (WM; Delayed Match to Sample) and executive function/planning (Stockings of Cambridge), as well as the theoretical underpinning of the fluency within the novel Index, cognitive flexibility (Intra-/Extra-Dimensional Set Shifting). A fourth test, Match to Sample (MTS), was also completed to estimate the motor component of processing speed. Each assessment is described separately below. As noted in Table 11, CANTAB scores for five subjects (3 TDC, 2 ADHD/-RD, and 1 ADHD/+RD) were missing due to technical issues.

<u>Delayed Match to Sample</u> (DMS, 10 mins) assesses visual WM by presenting a patterned image and requiring subjects to choose the matching stimulus from among four options. The forced-choice is required after a 0, 4, 8, or 12 second delay from when the pattern stimulus is hidden, such that a participant must hold the spatial information in working memory for varying amounts of time. The mean RT that corresponds to each of the delays provides some insight about the subject's visual WM abilities.

Stockings of Cambridge (SOC, 10 mins) requires the participant to move virtual pieces from one location to another sequentially, similar to the classical Tower of Hanoi. For this study, executive functioning was estimated based on mean initial thinking time and mean moves taken to complete problems requiring five moves. These measures were chosen because five moves is the greatest number of moves, and thereby, maximum cognitive load, available for the assessment.

Intra-/Extradimensional Set Shifting (IED, 7 mins) is similar to the Wisconsin Card Sorting Test, wherein subjects must learn categorization rules that are subsequently changed within a dimension (e.g., color) or across dimensions (e.g., shape) after a set number of correctly identified trials. The number of trials varies by individual subject, depending on his ability to learn the classification rules. Cognitive flexibility is relative to the alacrity or difficulty in noticing and adapting to the rule switches. Thus, IED helps approximate cognitive flexibility through a series of outcome measures, including total trials to learn the rules, number of completed stages, and total errors.

Matching to Sample (MTS) is similar to the DMS in biasing visual attention and WM by requiring responses based on patterned images, but there are two major differences. First, MTS requires a visual search for the pattern among a number of similar images surrounding the center, target image. Second, the subjects maintain pressure on a button while completing their search and then release it to make a selection on the touch-screen. This response mechanism allows for measurement of RT and estimation of motor speed, since the time to observe, decide, and then initiate a motor response is separated from the action of mentally processing and choosing a response. The mean correct movement time is a key metric for this study, since that time would be included in processing speed calculations often reported to differ between groups.

Statistical Analysis

*Demographics*

To assess differences related to grouping criteria (DSM-IV-TR diagnosis or Reading Tendency group), two, separate ANOVAs with group as the main effect were completed for age, FSIQ, Conners' Inattentive subscale, and Conners' Hyperactivity subscale (Table 7). Normed and Ability-Achievement Discrepancy scores for the WIAT-III Word Reading, Pseudoword Decoding, and Spelling subtests, were compared by ANOVA for both classification schemes (Table 8). The Ability-Achievement Discrepancy scores were specifically compared to demonstrate that no reading tendency-based group was dominated by reading disabled persons.

*Behavioral analysis*

Group differences on Auditory Analysis, the Underlining Test, and Sentence Memory were compared using ANCOVA, with age as the covariate (Table 8). Drift and hit rates during the oLDT and pLDT (Table 8), performance during the CPT-II (Omissions, Mean Hit RT, SE Hit RT, Variability of Hit RT, Detectability, Hit RT Block Change, and Hit RT ISI Change; Table 9), and CANTAB outcomes (Table 11) were assessed by conducting ANCOVA tests with age and FSIQ as the covariates. Two repeated measures ANCOVAs (covariates were age and FSIQ) were also completed to test whether there was a significant impairment related to only one of the reading domains for Sight Readers and Decoders compared with Balanced Readers.

**5.2 Results**

5.2.a **Comparison of the sample population demographics depending on the diagnostic criteria**

The three groups reflecting different Reading Tendencies, Balanced, Decoders, and Sight Readers, did not differ with respect to age ($F_{2,42}$ = 1.04; $p$ = .36) or FSIQ ($F_{2,42}$ = 1.85; $p$ = .17). Participants with ADHD were equally distributed in all three groups ($\chi^2$ = 4.89, $p$ = .086), though no one with ADHD/+RD demonstrated a Balanced phenotype. Likewise, the ADHD subtypes ($\chi^2$ = 6.76, $p$ = .15) and those on stimulant medication ($\chi^2$ = 2.2, $p$ = .33) were not unevenly distributed between groups. While the Conners' Hyperactivity subscale did not differ between groups ($F_{2,42}$ = 2.2; $p$ = .12), Inattention did ($F_{2,42}$ = 5.8; $p$ = .006). Tukey's HSD *post-hoc* test revealed that Sight Readers had significantly more inattentive symptoms than Balanced Readers ($p$ = .004). Likewise, when only ADHD subjects were included in a *t*-test to assess whether Sight Readers showed more inattention symptoms than Decoders, Sight Readers had increased symptomatology ($p$ = .05). Comparisons are outlined in Table 7.

5.2.b **Standardized reading performance**

Group differences were evident on WIAT-III Word Reading ($F_{2,42}$ = 6.7; $p$ = .003) and Spelling ($F_{2,42}$ = 4.4; $p$ = .019), but not Pseudoword Decoding ($F_{2,42}$ = 3.2; $p$ = .051), as outlined in Table 7. The mean Achievement-Aptitude Discrepancy scores, which would have reflected a group dominated by reading disabilities, did not differ between the three groups (Word Reading, $p$ = .08; other $p$'s > .2). With regard to cognitive assessments (Table 8), there were no significant differences on the Auditory Analysis Test ($F_{2,42}$ = 2.7; $p$ = .077). Symbolic processing speed, measured by seven subtests of Underlining Test, also did not differ significantly ($F_{2,42}$ = .72; *p* = .49). However, the groups differed on Sentence Span, a test of verbal working memory, ($F_{2,42}$ = 6.3; *p* = .004) with Sight Readers performing more poorly than both Balanced Readers (*p* = .023) and Decoders (*p* = .005).

**Table 7. Demographics**

| | Balanced | Decoder | Sight Reader | RTI *p* | RTI Tukey's HSD | DSM-IV-TR grouping, *p* | DSM-IV-TR grouping, Tukey's HSD |
|---|---|---|---|---|---|---|---|
| n | 14 | 16 | 13 | | | | |
| ADHD without RD | 5 | 6 | 4 | | | | |
| ADHD with RD | 0 | 6 | 5 | | | | |
| RD without ADHD | 0 | 1 | 1 | | | | |
| Age (years) | 12.3 (2.1) | 11.5 (1.4) | 12.2 (1.8) | 0.36 | | 0.57 | |
| FSIQ | 114 (18) | 111 (15) | 103 (13) | 0.17 | | 0.73 | |
| Combined/ Inattentive Subtype | 2/3 | 9/3 | 5/3 | | | | |
| Conners' Cognitive Problems and Inattention | 46 (8) | 53 (12) | 61 (14) | 0.006 | SR > B, $p = .004$ | 0.001 | b, $p < .001$; c, $p < .001$; d, $p = .039$ |
| Conners' Hyperactivity | 52 (16) | 62 (16) | 63 (18) | 0.12 | | 0.001 | b, $p < .001$; c, $p < 0.001$; d, $p = .24$ |

Age, FSIQ and symptomatology were evaluated using ANOVA; DSM-IV-TR comparisons are shown to demonstrate the specificity of the Reading Tendency Index (RTI)-based system for reading skills. a = ADHD/+RD < ADHD/-RD, b = ADHD/+RD > control, c = ADHD/-RD > TDC, d = ADHD/+RD > ADHD/-RD

**Table 8. WIAT-III and Other Reading Characterization Assessments**

| | Balanced | Decoder | Sight Reader | RTI *p* | RTI Tukey's HSD | DSM-IV-TR grouping, *p* | DSM-IV-TR, Tukey's HSD |
|---|---|---|---|---|---|---|---|
| Word Reading (WIAT-III) | 106 (6) | 102 (13) | 91 (14) | 0.004 | B > SR, *p* = .004; D > SR, *p* = .034 | - | |
| AAD Word Reading | -2 (9) | -4 (9) | -11 (14) | 0.081 | | - | |
| Pseudoword Decoding (WIAT-III) | 107 (8) | 101 (15) | 92 (19) | 0.051 | | - | |
| AAD Pseudoword Decoding | 1 (8) | -4 (13) | -9 (18) | 0.22 | | - | |
| Spelling (WIAT-III) | 106 (13) | 100 (13) | 90 (15) | 0.019 | B > SR, *p* = .015 | - | |
| AAD Spelling | -2 (15) | -6 (13) | -11 (15) | 0.22 | | - | |
| Auditory Analysis (Elison and blending) | 34 (5) | 28 (8) | 27 (9) | 0.19 | | < 0.001 | a, b, *p* < .001 |
| Underlining Test (processing speed) | 111 (25) | 103 (27) | 101 (23) | 0.86 | | 0.64 | |
| Sentence memory (Verbal WM) | 18 (2) | 18 (3) | 15 (2) | 0.012 | D > SR, *p* = .005; B > SR, *p* = .023 | 0.29 | |

Auditory Analysis, Underlining Test, and Sentence Memory scores were evaluated with ANCOVA (age). Standard deviations are bracketed; D = Decoder, B = Balanced, SR = Sight Reader. Significance was not reported for the reading subtests, given that the WIAT-III subtests were the diagnostic criteria for determining ADHD/+RD.

**Table 9. Conners' CPT-II: Behavioral, Computerized Assessment of Attention**

| | Cognitive proxy | Balanced | Decoder | Sight Reader | RTI *p* | RTI Tukey's HSD | DSM-IV-TR grouping, *p* |
|---|---|---|---|---|---|---|---|
| Omissions | Inattention | 12 (13) | 17 (16) | 17 (19) | 0.94 | | 0.15 |
| Hit RT (msec) | Speed | 371 (70) | 464 (97) | 410 (58) | 0.048 | D > B, $p$ = .033 | 0.25 |
| Hit RT Std Error | Inattention | 8.5 (4) | 16.5 (8) | 13.5 (8) | 0.058 | D > B, $p$ = .036 | 0.005 |
| Variability of Hit RT† | Inattention | 15 (11) | 32 (20) | 30 (23) | 0.16 | | 0.002 |
| Detectability | Target discrimination | .41 (.32) | .29 (.24) | .34 (.27) | 0.88 | | 0.080 |
| Hit RT Block Change | Vigilance | 0.0031 (.03) | 0.025 (.04) | 0.0008 (.04) | 0.30 | | 0.054 |
| Hit RT ISI Change | Vigilance | 0.075 (.04) | 0.13 (.05) | 0.11 (.05) | 0.075 | | 0.090 |

Note: RT = Reaction time; Standard deviations are bracketed; D = Decoder, B = Balanced
†Variability and Hit RT SE are similar, but distinct measures, with Variability reflecting the consistency of reactions between blocks as the study is executed.

5.2.c **Conners' CPT-II Computerized Assessment**

The three groups differed with respect to Hit RT ($F_{3,38}$ = 3.3; $p$ = .048) and Hit RT SE ($F_{3,38}$ = 3.1; $p$ = .058). Decoders, but not Sight Readers, were slower ($p$ = .033) and less consistent ($p$ = .036) than Balanced Readers. However, the RT measures were also highly correlated with mean correct response movement time from the Match to Sample subtest ($r^2$ = .26; $p$ = .0012), indicating that the differences may be due to processing speed, and less so inattention (see Discussion). The other outcome metrics, including number of omissions, variability of Hit RT, Detectability, Hit RT Block Change, and Hit RT ISI Change, did not meet criteria for significance. All outcomes are detailed in Table 9.

5.2.d **Cambridge Neuropsychological Test Automated Battery (CANTAB)**

Significant group differences were apparent on two of the three subtests of the CANTAB, shown in Table 10. Cognitive flexibility, measured by Intra-/Extra-dimensional Set Shifting (IED), showed differences in Total Trials - adjusted ($F_{3,37}$ = 6.9; $p$ = .003), Total Errors ($F_{3,37}$ = 6.9; $p$ = .003), and Stages Completed ($F_{3,37}$ = 6.9; $p$ = .003). Sight Readers showed less flexibility than Balanced Readers in each measure as assessed by Tukey's HSD analysis. Sight Readers attempted significantly more IED trials ($p$ = .002), committed more errors ($p$ = .011), and completed fewer stages than Balanced Readers ($p$ = .012). Tukey's HSD did not reach significance between Balanced Readers and Decoders or between the imbalanced tendencies. No significant differences reflecting visual working memory were observed on Delayed Match to Sample RT for the average of all delays, nor for specific intervals of four or twelve second delays. Planning and executive function, assessed with Stockings of

Cambridge, revealed differences in Mean Initial Thinking Time (5 moves; $F_{3,38} = 4.1$; $p = .024$), Problems Solved in the Minimum Moves ($F_{3,37} = 5.4$; $p = .009$), but not Mean Moves (5 moves; $F_{3,37} = .61$; $p = .55$). Subsequent Tukey's HSD *post-hoc* analysis showed that Sight Readers took significantly less time for the initial move ($p = .032$), but completed fewer problems in the minimum number of moves ($p = .008$) as compared with Balanced Readers.

**Table 10. CANTAB: Computerized Assessment of Cognitive Skills**

| Task | Cognitive Process | Measure | Balanced | Decoder | Sight Reader | RTI $p$ | RTI Tukey's HSD | DSM-IV-TR, $p$ | DSM-IV-TR grouping, Tukey's |
|---|---|---|---|---|---|---|---|---|---|
| *Intra-/Extra-Dimensional Set Shift* | | | | | | | | | |
| | Cognitive Flexibility | n | 13 | 13 | 12 | | | | |
| | | Total trials - adjusted | 79 (12) | 108 (40) | 131 (44) | 0.010 | SR > B, $p$ = .007 | 0.51 | |
| | | Total Errors | 4.9 (6.1) | 13.1 (11.6) | 15.8 (11.6) | 0.024 | B > SR, $p$ = .019; D > SR, $p$ = .20 | 0.52 | |
| | | Stages Completed | 9.0 (0) | B (1.1) | 8.0 (.95) | 0.022 | B > SR, p = .025; B > D, p = .086 | 0.79 | |
| *Delayed Match to Sample* | | | | | | | | | |
| | Visual WM | | | | | | | | |
| | | Mean Hit RT - all delays | 3570 (889) | 4451 (1746) | 3841 (945) | 0.30 | | 0.017 | +RD > -RD, p = .012 |
| | | Hit RT - 4s delay | 3887 (1471) | 3789 (969) | 3934 (906) | 0.88 | | 0.11 | |
| | | Hit RT - 12s delay | 3994 (1060) | 5432 (2807) | 4439 (1026) | 0.24 | | 0.011 | +RD > -RD, p = .009; +RD > TDC, p = .088 |
| *Stockings of Cambridge* | | | | | | | | | |
| | Planning/Executive function | | | | | | | | |
| | | Mean initial thinking time (5 moves; msec) | 4687 (3746) | 1848 (1811) | 1568 (2983) | 0.012 | B > SR, $p$ = .021; B > D, $p$ = .030 | 0.011 | TDC > +RD, p = .017; TDC > -RD, p = .037 |
| | | Problems solved in minimum moves | 8.7 (1.7) | 6.9 (1.7) | 6.4 (1.9) | 0.025 | B > SR, $p$ = .022; B > D, $p$ = .15 | 0.19 | |
| | | Mean moves (5 moves) | 7.5 (1.3) | 7.2 (1.0) | 7.7 (1.4) | 0.41 | | 0.19 | |

ANCOVA (age and FSIQ); dx-based differences remain even after covarying for mean correct movement time during Match-to-Sample. a = ADHD/+RD > ADHD/-RD; b = ADHD/+RD > TDC, c = TDC > ADHD/+RD, d = TDC > ADHD/-RD

5.2.e **High-Frequency word and pseudoword drift rates**

When the word recognition and pseudoword drift rates were compared between ADHD and RD diagnostically-based groups with ANCOVA (age and FSIQ), there were no group differences (word recognition, $p = .23$; pseudoword, $p = .13$; Table 11). Using the novel Reading Tendency Index-based divisions, both word recognition drift rates ($F_{2,42} = 6.3$; $p = .003$) and pseudoword drift rates ($F_{2,42} = 6.3$; $p = .007$) were significantly different, as expected. Tukey's HSD *post-hoc* tests evidenced Sight Readers had decreased pseudoword drift rates compared with Balanced Readers ($p = .002$) and Decoders ($p = .019$). Decoders showed poorer word recognition drift rates than Balanced Readers ($p = .006$) and Sight Readers ($p = .007$). Table 10 further outlines drift rate and performance differences.

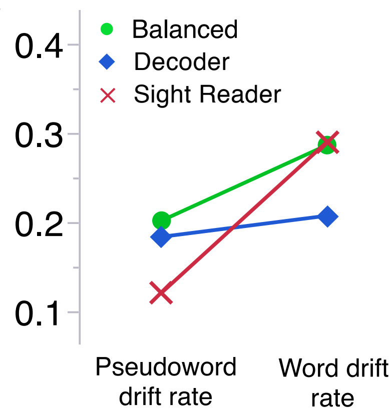



**Fig. 14** Repeated measures ANCOVA (age, FSIQ) showed interactions between the three groups defined by the novel Reading Tendency Index.

Comparing Sight and Balanced Readers, the overall between subjects model was not significantly different ($F_{3, 23} = 2.0$; $p = .17$). Within subject comparisons showed a significant Group*Drift Rate interaction ($F_{3, 23} = 37.9$; $p < .001$). The between subject comparison for the Decoders and Balanced Readers did not reach significance ($F_{3, 25} = 3.5$; $p = .074$); however, the within subject comparison showed a significant Group*Drift Rate interaction ($F_{3, 25} = 32.1$; $p < .001$). The interactions are depicted together in Fig. 14, showing the drift rates of the respective strength for each imbalanced group did not differ from Balanced Readers.

**Table 11. Reading performance during lexical decision tasks**

| | Balanced | Decoder | Sight Reader | RTI *p* | RTI Tukey's HSD | DSM-IV-TR grouping, *p* | DSM-IV-TR grouping, Tukey's HSD |
|---|---|---|---|---|---|---|---|
| Word Recognition Drift Rate | .29 (.08) | .19 (.06) | .29 (.08) | 0.003 | B > D, $p = .006$; SR > D, $p = .007$ | 0.23 | |
| High-Frequency word hit rate | .95 (.04) | .88 (.08) | .94 (.03) | 0.017 | B > D, $p = .022$ | 0.32 | |
| Pseudoword drift rate | .21 (.07) | .18 (.05) | .12 (.07) | 0.007 | B > SR, $p = .002$; D > SR, $p = .019$ | 0.13 | |
| Pseudoword hit rate | .93 (.05) | .90 (.10) | .80 (.13) | 0.002 | B > SR, $p = .007$; D > SR, $p = .004$ | 0.046 | a, $p = .040$ |

Drift rates were compared with ANCOVA, where age and FSIQ were covaried. Standard deviations are bracketed; D = Decoder, B = Balanced, SR = Sight Reader. All comparisons $p < .01$ between diagnostic groups. a = ADHD/+RD < ADHD/-RD, b = ADHD/+RD > control,

## 5.3 Discussion

The current study demonstrates the utility of a novel, quantitative method to describe reading tendencies in a population of boys expressing varied symptomatology related to ADHD or RD. Grouping based on reading tendency, rather than co-occurring RD diagnosis, revealed distinct psychological characterizations that may have significant implications for future investigations involving reading disabilities and remediation that better targets ones tendency towards reading. In general, the Balanced Readers demonstrated, as expected, the highest scores on all neuropsychological and reading assessments, including cognitive flexibility (CANTAB IED set shifting) and attention (symptomatology and Conners' CPT-II outcomes). The pattern of impairments in Decoders reflected generally poorer reading abilities along with slower and greater variability in reaction times during the Conners' CPT-II relative to Balanced Readers (Tables 7 and 9). Sight Readers showed the greatest reading and cognitive impairments, including poor verbal working memory and inattentive symptomatology, in comparison with the other two subgroups. To my knowledge, this is the first attempt to characterize readers based on their reading tendencies, as opposed to reading disabilities, within the framework of dual reading subnetworks. The Index estimates the relative strengths of neural, reading subnetworks and an overall reading tendency. Stronger tendencies reflect imbalanced use or development of a specific subnetwork, which may be precipitated by the presence of attentional or reading impairments. Previous studies using RD-based diagnostic criteria (e.g., Stanovich, 1988) have suggested sets of cognitive impairments, leading to an RD diagnosis; however, there has been limited success identifying RD subgroups with these hypothesized profiles, when using disability-based classifications. Overall, the Reading Tendency Index introduced here resulted in identifying groups of readers based on cognitive performance that demonstrated the hypothesized, cognitive profiles in a compelling manner, suggesting that the Index may also predict correlates within neurobiological network models with greater specificity (Ch. 6).

The participants completed a phonologic lexical decision and orthographic lexical decision during an fMRI scan and, prior to re-grouping by using the Reading Tendency Index, were evaluated for cognitive differences according to DSM diagnostic criteria for ADHD/-RD, ADHD/+RD, and TDC. This series of analyses was necessary to show consistency in the cognitive impairments between the ADHD/+RD subgroup and other reports, as well as evaluate the relative homogeneity of impairments within the subgroups. Congruent with the diagnoses, attention was poorer in both ADHD/-RD and ADHD/+RD subgroups compared with TDC, as indicated by the Conners' CPT-II variability over time (Table 9) and inattentive symptomatology. ADHD/+RD showed significantly impaired visual working memory (DMS, Table 10), and poorer executive functioning/planning (SOC, Table 10) relative to ADHD/-RD and TDC. However, the distributions of cognitive performance scores in the ADHD subgroups were overlapping, and the RD diagnostic-based subgroups did not differ significantly with respect to three other key areas that are necessary for developing fluency: verbal working memory ($p$ = .29, Table 8), processing speed ($p$ = .64, Table 8), and cognitive flexibility (IED *p's* > .5, Table 10; (Christopher et al., 2012; Horowitz-Kraus, 2013; Sela, Izzetoglu, Izzetoglu, & Onaral, 2012). These findings demonstrate the type of heterogeneity that has made disentangling the core impairments leading to ADHD/+RD somewhat difficult and inconsistent between neuropsychological studies (Bental & Tirosh, 2007; Castellanos, Sonuga-Barke, Milham, & Tannock, 2006; Katzir et al., 2006; Nigg, Willcutt, Doyle, & Sonuga-Barke, 2005; Sonuga-Barke, 2003; Willcutt, Pennington, Olson, Chhabildas, & Hulslander, 2005).

To provide additional insight into the reading abilities across diagnoses and co-occurring RD conditions, the drift rates for phonological and orthographic abilities were estimated. The working hypothesis is that the relative strength and balance between the reading subnetworks, which is being termed reading tendency, can be numerically represented by the difference between the inverses of a decoding and a word recognition drift rate. By using the Reading Tendency Index and estimating overall fluency (the sum of the drift rates), subjects were re-classified as Balanced, Decoders, or Sight Readers. The surprising finding was that the two imbalanced tendency groups contained an equal mix of TDC, TDC/+RD, ADHD/-RD, and ADHD/+RD (Table 11), indicating tendencies exist regardless of formal RD status, but also underscoring the necessity of having a metric capable of predicting reading abilities without the arbitrary cut-offs endemic to the current RD diagnostic criteria.

The cognitive profiles for each of the reading tendency groups generated from the Reading Tendency Index are generally consistent with a number of logical predictions. First, dual subnetwork models predict that the ventral recognition subnetwork is quicker and used for word recognition processes (Brennan, Cao, Pedroarena-Leal, McNorgan, & Booth, 2012; and review, Price & Devlin, 2011). Conversely, a pseudoword cannot be recognized, since it is a collection of pronounceable syllables that is not real word, and therefore by definition, has no previous mental representation. Thus, the dorsal decoding subnetwork is postulated to carry out this more effortful processing of pseudowords (Bergmann & Wimmer, 2008; Binder et al., 2003). A repeated measures - ANCOVA, collapsed across reading tendency groups, showed modest support for greater drift rates for high-frequency words compared with those for pseudowords ($p$ = .057, covariates: age and FSIQ), consistent with previous studies (Ratcliff, Perea, Colangelo, & Buchanan, 2004; Zeguers et al., 2011). A second logical prediction was that Balanced Readers ought to be able to perform equally as well as either Decoders or Sight Readers on the subgroup's respective strength or tendency. Fig. 14 reflects the competency of Balanced Readers in both decoding and word recognition relative to the imbalanced tendency groups (*post-hoc* for Group*Drift Rate, both *p's* < .001). Thirdly and importantly, whereas the comparisons between DSM diagnostic-based groups show no differences on intra-/ extra-dimensional set shifting, the Reading Tendency Index-based groups show significant disparity between groups with respect to the cognitive flexibility scores (Table 10). Sight Readers were the least flexible, followed by Decoders, and then, Balanced Readers, providing support for Balanced Readers likely being the most capable of switching strategies efficiently, depending on word knowledge and exposure (Booth et al., 2004; Horowitz-Kraus, 2013). The finding also produces an important prediction that the strength of effective connectivity of reading subnetworks is greater in Balanced Readers, which can be tested directly using fMRI in conjunction with the Reading Tendency Index in the future.

A major advantage of basing the Reading Tendency Index on drift rates rather than standard RT's is that processing speed, which is frequently noted as impaired in ADHD/+RD, has considerably less influence on the outcome (Katz et al., 2011; Shanahan et al., 2006; Tamm et al., 2014). Two analyses involving the motor component of processing speed (Jacobson et al., 2011), mean correct movement time on the CANTAB Match-to-Sample, substantiate this claim. Movement time was highly correlated with mean Hit RT on the Conners' CPT-II; however, movement time did not correlate with either type of drift rate or the composite Reading Tendency Index. As an additional consideration, IQ scores did not differ between the three reading tendency groups; however, lower IQ's appeared to predict Sight Reader membership slightly ($p = .17$). This is not entirely unexpected as Ratcliff *et al.* (2010) have demonstrated that better drift rates may correspond with higher IQ and quicker assimilation rates. Additionally, higher IQ or greater processing speed may mitigate minor impairments in working memory, symbol processing or attention, leading to an ability to develop both subnetworks and corresponding skills in a balanced manner (Sela et al., 2012). Overall, the data suggest that while cognitive impairments may influence the neural development of a tendency, processing speed impairments do not directly affect the estimation of the Reading Tendency Index.

In conclusion, the Reading Tendency Index is an innovative tool to estimate the balance between decoding and word recognition abilities after accounting for processing speed. By comparing the degree of preference for one skill over the other, the novel Reading Tendency Index is able to predict distinct cognitive profiles for groups of readers. The predictions of the model, including cognitive flexibility and overall reading scores, suggests the new approach may be a powerful method to study RD and to begin individualizing reading remediation to an even greater extent than is currently available and feasible. More work is needed to verify and extend the utility of the Reading Tendency Index; however, this is a significant first step towards understanding and quantifying how fluent and non-fluent readers approach reading tasks and may influence the development of neural, reading networks.

# CHAPTER 6

## PREDICTING SUBNETWORK DYSFUNCTION WITH THE READING TENDENCY INDEX

The novel Reading Tendency Index capitalizes on Drift Diffusion Modeling to estimate an individual's single word reading ability and indicate whether the individual favors a particular reading strategy, namely decoding or sight reading as elaborated in Chapter 5. Each of three subgroups defined by the Reading Tendency Index may be loosely defined by a characteristic set of cognitive strengths and weaknesses, which are postulated to have a reciprocal relationship in forming and reinforcing the Reading Tendency. The theoretical framework for the Index also leads to predictions about neural correlates for each reading process and, subsequently, tendency. This chapter places the Reading Tendency Index within the context of reading subnetworks and discusses neural implications for extreme, imbalanced tendencies.

Cognitive flexibility, attention, processing speed, and verbal working memory (WM) have all been implicated to differing degrees in ADHD/+RD (McGrath et al., 2011; Rucklidge & Tannock, 2002; Shanahan et al., 2006; Willcutt et al., 2010) and were key characteristics of the different subgroups that were defined by the Reading Tendency Index (Ch. 5). In particular, Sight Readers demonstrated higher levels of ADHD symptomatology along with poorer verbal WM, planning, and flexibility compared with Decoders or Balanced Readers (Table 7 & 8). Sight Readers also qualitatively demonstrated the worst WIAT-III reading subtest scores and discrepancies (Table 8), suggesting that a large number of Sight Readers may also be sub-threshold or meet criteria for RD. Given previous RD neuroimaging results (for meta-analyses, Maisog, Einbinder, Flowers, Turkeltaub, & Eden, 2008; Richlan, Kronbichler, & Wimmer, 2009; 2011) and the fact that phonological skills are typically the impairment prompting an RD diagnosis (Lyon, Shaywitz, & Shaywitz, 2003), it is hypothesized that Sight Readers show decreased dorsal reading subnetwork activation relative to Decoders. The dorsal decoding subnetwork includes the posterior superior temporal gyrus (pSTG; BA 22), inferior parietal lobe (IPL; BA 39/40), and inferior frontal gyrus (IFG; BA 44). In lieu of a highly functional, dorsal decoding subnetwork and corresponding cognitive skills, it is postulated that Sight Readers develop a compensatory, and increased, activation of the ventral recognition subnetwork relative to Decoders during reading tasks.

The term Decoder refers to someone who *relies* on the ability to sound out words, rather than transitioning to word recognition as more fluent readers do. While the prognosis is more favorable for these types of readers to make gains to full fluency (Deacon, Benere, & Castles, 2012; McNorgan, Alvarez, Bhullar, Gayda, & Booth, 2011; Sprenger-Charolles, Colé, Lacert, & Serniclaes, 2000; Talcott, Witton, & Stein, 2013), the imbalanced approach may still potentiate decreased reading abilities, as shown in Table 13. The cause for a Decoding tendency is postulated to reflect poor visual working memory, limited word exposure, or slow processing speed alone or in combination with neural dysfunctions within the ventral recognition subnetwork. The ventral recognition subnetwork includes the left middle temporal gyrus (MTG; BA 21) and occipitotemporal junction and has been associated with word recognition and semantics in response to functional neuroimaging tasks (for review, Paulesu, Danelli, & Berlingeri, 2014; Wandell, 2011). The working hypothesis is that, in response to basic word reading tasks, Decoders preferentially activate the dorsal decoding subnetwork and show relatively decreased activation within the ventral recognition subnetwork compared with Sight Readers during reading tasks.

To begin addressing these neural, reading subnetwork predictions, boys with and without ADHD or RD performed an orthographic and phonologic lexical decision task during fMRI scans. The original study was designed to assess differences based on DSM-IV-TR diagnostic criteria and provide evidence for possible neural correlates of ADHD/+RD. While the new classification deviates from DSM-IV-TR grouping, the exaggerated representation of cognitive and reading impairments due to a large sub-sample of ADHD+/-RD provides a unique and beneficial platform to examine differences stemming from imbalanced Reading Tendencies. There are also three, key assumptions for the lexical decision (LDT) experiments based on prior, empirical evidence (Fiebach, Friederici, Müller, & Cramon, 2002; Harm & Seidenberg, 2004; Jobard, Crivello, & Tzourio-Mazoyer, 2003; Papanicolaou et al., 2003; S. E. Shaywitz et al., 1998): familiar word reading is primarily mediated by the ventral recognition subnetwork; novel word reading by the dorsal decoding subnetwork; both subnetworks ought to be activated to some degree by Balanced Readers (Suppl. Fig. 5; Booth et al., 2004), leading to the greatest neural differences being between those with extreme Reading Tendencies.

Acknowledging these assumptions and the current gaps in knowledge, the current study evaluated three specific predictions about the functional activation of the subgroups during the functional paradigms which stress familiar word reading (oLDT) or pseudoword reading (pLDT). First, if Balanced and Sight Readers are both relatively proficient in recognizing familiar words, then word recognition drift rates and ventral recognition subnetwork activation patterns from the oLDT should both be comparable between the two groups. Second, if the Reading Tendency Index successfully predicts those with Sight Reading proclivities, then Balanced and Sight Readers should also show greater word recognition drift rates and activation of ventral recognition subnetwork areas relative to Decoders. Lastly, those identified as Decoders should evidence similar pseudoword drift rates compared with Balanced Readers and greater activation of the dorsal decoding subnetwork relative to Sight Readers under decoding conditions. Collectively, these predictions reflect a considerable amount of neural differences between the imbalanced Reading Tendencies.

**6.1 Sample characteristics for the orthographic and phonological lexical decision tasks**

41 boys between the ages of 9 and 16 years of age were divided into three reading ability groups based on their estimated Reading Tendency Index score (see Ch. 5.1 for full description). Briefly, Relative Fluency was estimated by adding the inverses of the drift rates; the Reading Tendency was calculated by subtracting the inverse drift rates. Taking the absolute value of the ratio between the Fluency and Tendency provides a relative metric of how proficient and balanced an individual reader is. For the purpose of equal group membership, Relative Fluency and then Reading Tendency were evaluated, resulting in 14 Balanced, 15 Decoding, and 12 Sight Readers (Fig. 13). All participants completed the orthographic and phonologic lexical decision task as outlined in Appendix G.

Statistical Analysis

*Demographics*

Age, FSIQ, Conners' Inattentive subscale, and Conners' Hyperactivity subscale scores were compared using an ANOVA with reading tendency group as the main effect (Table 12). Normed and Ability-Achievement Discrepancy scores for the WIAT-III Word Reading, Pseudoword Decoding, and Spelling subtests, were compared for both classification schemes by ANOVA (Table 13).

*Behavioral analysis*

Group differences on Auditory Analysis, the Underlining Test, and Sentence Memory were compared using ANCOVA, with age as the covariate (Table 13). Drift and hit rates during the oLDT and pLDT were assessed by conducting ANCOVA tests with age and FSIQ as the covariates (Table 14).

**6.2 Results**

6.2.a **Demographics**

The sample for this fMRI study is a subset of those characterized in Ch. 5, since two participants were excluded for excessive motion during the scans. The 14 Balanced Readers were 9 TDC, 5 ADHD/-RD, and no ADHD/+RD boys; 3 TDC, 6 ADHD/-RD and 6 ADHD/+RD made up the 15 Decoders; 2 TDC, 1 TDC/+RD, 4 ADHD/-RD, and 5 ADHD/+RD were the 12 Sight Readers. Further descriptions, including ADHD subtype, is available in Table 12. The groups did not differ on age ($F_{2,40}$ = 1.0; $p$ = .37) or FSIQ ($F_{2,40}$ = 1.2; $p$ = .31). Partially due to the distribution of subjects with ADHD, the Conners' Inattentive symptoms differed ($F_{2,40}$ = 4.88; $p$ = .013) with Sight Reader showing higher symptomatology than Balanced (Tukey's HSD, *p* = .011), but not Decoders. Neither the Conners' Hyperactivity subscale ($F_{2,40}$ = 2.35; *p* = .11) nor the Conners' Restlessness-Impulsivity composite ($F_{2,40}$ = 2.83; *p* = .07) reached statistical significance.

**Table 12. Demographics for the lexical decision tasks, based on the Index**

| | Balanced | Decoder | Sight Reader | *p* | Tukey's HSD |
|---|---|---|---|---|---|
| n | 14 | 15 | 12 | | |
| Age (years) | 12.3 (2.1) | 11.5 (1.4) | 12.2 (1.8) | 0.37 | |
| FSIQ | 114 (18) | 110 (15) | 105 (12) | 0.31 | |
| ADHD alone | 5 | 6 | 4 | | |
| ADHD with Reading Disability | 0 | 6 | 5 | | |
| Conners' Cognitive Problems and Inattention | 46 (8) | 54 (12) | 59 (12) | 0.013 | SR > B, *p* = .011 |
| Conners' Hyperactivity | 52 (16) | 64 (15) | 63 (19) | 0.11 | |

ANCOVA for drift rates included age and FSIQ. Standard deviations are bracketed; D = Decoder, B = Balanced, SR = Sight Reader.

6.2.b **Reading assessments**

With respect to reading skills, WIAT-III Word Reading ($F_{2,40}$ = 5.44; *p* = .008) and Spelling ($F_{2,40}$ = 3.79; *p* = .032) differed between groups. Tukey's HSD *post-hoc* showed that Sight Readers were significantly impaired relative to Balanced (*p* = .008) and Decoders (*p* = .046) in Word Reading, but only Balanced Readers (*p* = .025) on the Spelling subtest. There were no significant group differences on Pseudoword Decoding ($F_{2,40}$ = 2.40; *p* = .10). In line with the Reading Tendency Index grouping, pseudoword drift rates were different ($F_{4,40}$ = 4.9; *p* = .013) with Sight Readers being significantly worse that Balanced Readers (Tukey's HSD, *p* = .013), but not statistically different from Decoders (Tukey's HSD, $p$ = .061). The cognitive skills supporting reading showed differences only in verbal working memory (Sentence Span, $F_{4,35}$ = 4.9; $p$ = .014) and cognitive flexibility (CANTAB IED total trials; $F_{4,35}$ = 4.98; $p$ = .013), but not Elison ($F_{4,35}$ = 1.5; $p$ = .23) or symbol processing ($F_{4,35}$ = .21; $p$ = .81). More details are available in Table 13.

**Table 13. WIAT-III and Other Reading Characterization Assessments**

| | Balanced | Decoder | Sight Reader | p-value | Tukey's HSD |
|---|---|---|---|---|---|
| Word Reading (WIAT-III) | 106 (6) | 103 (13) | 92 (14) | 0.008 | B > SR, $p$ = .008; D > SR, $p$ = .046 |
| AAD Word Reading | -2 (9) | -3 (9) | -11 (15) | 0.10 | |
| Pseudoword Decoding (WIAT-III) | 107 (8) | 101 (16) | 94 (19) | 0.11 | |
| AAD Pseudoword Decoding | 1 (8) | -4 (13) | -9 (18) | 0.29 | |
| Spelling (WIAT-III) | 106 (13) | 101 (13) | 91 (15) | 0.032 | B > SR, $p$ = .025 |
| AAD Spelling | -2 (15) | -5 (12) | -11 (16) | 0.25 | |
| Sentence memory (Verbal WM) | 18 (2) | 18 (3) | 15 (2) | 0.007 | D > SR, $p$ = .008; B > SR, $p$ = .040 |
| Auditory Analysis (Elison) | 34 (5) | 28 (8) | 27 (9) | 0.11 | |
| Underlining Test (processing speed) | 111 (25) | 104 (27) | 102 (24) | 0.61 | |

Standard deviations are bracketed; D = Decoder, B = Balanced, SR = Sight Reader.

**Table 14. Behavioral Performance during the lexical decision tasks**

| | Balanced | Decoder | Sight Reader | *p* | Tukey's HSD |
|---|---|---|---|---|---|
| **Consonant strings** | | | | | |
| Median RT (msec) | 587 (75) | 598 (65) | 562 (85) | 0.62 | |
| Hit rate | .94 (.05) | .90 (.09) | .94 (.08) | 0.22 | |
| Drift rate | .29 (.1) | .21 (.08) | .30 (.1) | 0.088 | |
| Boundary Separation | .11 (.02) | .12 (.01) | .11 (.01) | 0.32 | |
| Non-decision time | .43 (.07) | .40 (.06) | .42 (.07) | 0.32 | |
| **High-Frequency words** | | | | | |
| Median RT | 584 (67) | 620 (78) | 580 (81) | 0.55 | |
| Hit rate | .95 (.04) | .88 (.08) | .94 (.04) | 0.037 | B > D, *p* = .064; SR > D, *p* = .075 |
| Drift rate | .29 (.08) | .19 (.06) | .30 (.08) | 0.003 | B > D, *p* = .007; SR > D , *p* = .014 |
| Boundary Separation | .11 (.01) | .11 (.01) | .10 (.01) | 0.15 | |
| Non-decision time | .43 (.07) | .39 (.05) | .42 (.08) | 0.11 | |
| **Pseudowords** | | | | | |
| Median RT | 952 (131) | 960 (169) | 1029 (190) | 0.40 | |
| Hit rate | .93 (.05) | .90 (.09) | .78 (.13) | 0.002 | B > SR, *p* = .003; D > SR, *p* = .007 |
| Drift rate | .21 (.07) | .18 (.05) | .12 (.07) | 0.007 | B > SR, *p* = .007; D > SR, *p* = .032 |
| Boundary Separation | .14 (.02) | .14 (.03) | .13 (.01) | 0.16 | |
| Non-decision time | .66 (.09) | .66 (.13) | .76 (.18) | 0.10 | |

Assessed with ANCOVA using age and FSIQ as covariates. Standard deviations are bracketed; D = Decoder, B = Balanced, SR = Sight Reader.

### 6.2.c **Functional Activations**

*Orthographic Lexical Decision (oLDT)*

Functional hyperactivation was observed in the left dACC (BA 24), left iPL (BA 40), left MFG (BA 9/46), right frontal eye field (BA 8) and right IFG (BA 45) in Decoders relative to Balanced Readers, while the left MTG (BA 22), right dACC (BA 24), right MTG (BA 21), and right sPL (BA 7) showed decreased activation (Fig. 16). Decoders also showed hypoactivation in the left iPL (BA 40), left sPL (BA 7), left STG (BA 38), bilateral precuneus (BA 7/19), right dACC (BA 24), and right iPL (BA 39) compared with Sight Readers (Fig. 17). Sight Readers demonstrated decreased activation of the left precuneus (BA 7) and right iPL (BA 40), along with hyperactivation of the left dACC (BA 32), left IFG (BA 45), left MFG (BA 9), right frontal eye field (BA 8), and right iPL (BA 39) relative to Balanced Readers (Fig. 15). Details can be found in Table 15.

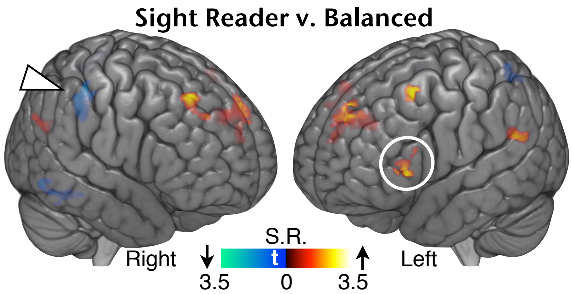



**Fig. 15** Activation in the dorsal subnetwork of Sight Readers differed from Balanced Readers during the orthographic lexical decision task. Hyperactivation of the left inferior parietal lobe (BA 40), left inferior frontal gyrus (BA 44), and medial prefrontal cortex are apparent in the Sight Readers.

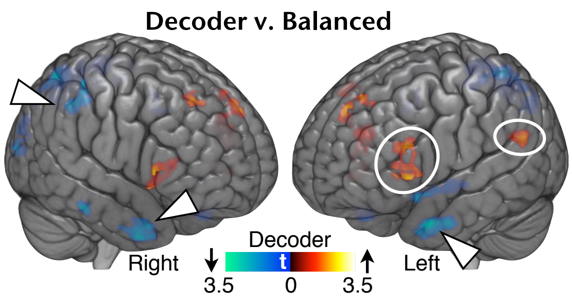



**Fig. 16** Decoders evidence activation differences in both the dorsal and ventral subnetworks relative to TDC. Both the left inferior parietal lobe (BA 40) and inferior frontal gyrus (BA 44) show increased activation in Decoders. Furthermore, bilateral decreased activation in the middle temporal gyrus was observed in Decoders versus TDC.

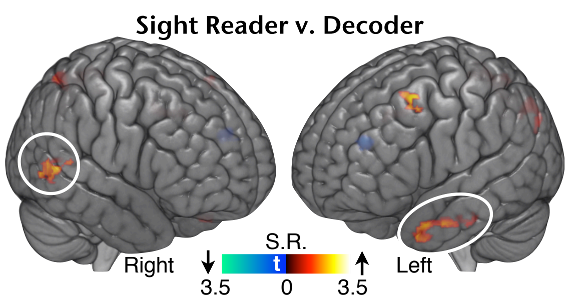



**Fig. 17** Activations for the directional contrast word rhyming epochs > fixation epochs are illustrated for ADHD/+RD compared to TDC. Relative to TDC, ADHD/+RD showed decreased activation in the left pSTG (BA 22), left MTG (BA 21), and right iPL (BA 40). Increased activation of a dorsal region in the right, dorsal iPL (BA 40) was also observed in ADHD/+RD compared with controls. (**b**) Extracted parameter estimates revealed that the activation of the right, dorsal iPL was also significantly higher in ADHD/+RD than ADHD/-RD (Tukey's HSD, *p* = .036). Error bars represent SEM. iPL = inferior parietal lobe, MTG = middle temporal gyrus STG = superior temporal gyrus

**Table 15. Functional activation differences in response to oLDT**

| | Hemisphere | Region | Brodmann Area | Cluster Extent | Peak t-score | MNI coordinates x | y | z |
|---|---|---|---|---|---|---|---|---|
| Decoder > Balanced | | | | | | | | |
| | Left | dACC | 24 | 233 | 3.18 | -8 | 34 | 1 |
| | | iPL | 40 | 249 | 3.56 | -60 | -51 | 24 |
| | | MFG | 46 | 497 | 3.53 | -40 | 32 | 7 |
| | | MFG | 9 | 566 | 5.23 | -15 | 38 | 25 |
| | | MFG | 9 | 313 | 3.48 | -8 | 48 | 40 |
| | Right | FEF | 8 | 157 | 2.85 | 27 | 35 | 48 |
| | | IFG | 45 | 417 | 3.09 | 56 | 22 | 6 |
| Decoder < Balanced | | | | | | | | |
| | Left | MTG | 22 | 645 | 4.21 | -42 | 5 | -29 |
| | Right | dACC | 24 | 171 | 3.08 | 4 | -4 | 37 |
| | | MTG | 21 | 475 | 3.73 | 39 | 6 | -32 |
| | | sPL | 7 | 3566 | 4.37 | 26 | -66 | 56 |
| Decoder < Sight Reader | | | | | | | | |
| | Left | iPL | 40 | 156 | 2.78 | -57 | -36 | 46 |
| | | Precuneus | 19 | 453 | 3.28 | -32 | -73 | 39 |
| | | sPL | 7 | 1863 | 3.62 | -3 | -70 | 40 |
| | | STG | 38 | 312 | 3.25 | -39 | 9 | -32 |
| | Right | dACC | 24 | 410 | 3.85 | 2 | -4 | 39 |
| | | iPL | 39 | 196 | 3.59 | 48 | -55 | 7 |
| | | Precuneus | 7 | 205 | 2.72 | 22 | -60 | 52 |
| Sight Reader < Balanced | | | | | | | | |
| | Left | Precuneus | 7 | 356 | 3.21 | -22 | -61 | 55 |
| | Right | iPL | 40 | 322 | 3.69 | 46 | -37 | 36 |
| Sight Reader > Balanced | | | | | | | | |
| | Left | dACC | 32 | 168 | 2.99 | -4 | 42 | -3 |
| | | IFG | 45 | 519 | 3.85 | -46 | 29 | 7 |
| | | iPL | 40 | 266 | 4.22 | -57 | -48 | 22 |
| | | MFG | 9 | 1621 | 4.45 | -4 | 41 | 31 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Right | FEF | 8 | 358 | 4.05 | 27 | 33 | 46 |
| | iPL | 39 | 247 | 2.65 | 48 | -60 | 24 |

aIns = anterior insula, dACC = dorsal anterior cingulate cortex; IFG = inferior frontal gyrus; FEF = frontal eye field; FG = fusiform gyrus; iPL = inferior parietal lobe; sPL = superior parietal lobe; MFG = middle frontal gyrus; MTG = middle temporal gyrus; STG = superior temporal gyrus

*Phonological Lexical Decision (pLDT)*

Sight Readers showed hypoactivation relative to Decoders in the bilateral aIns (BA 13), left iPL (BA 40), left precuneus (BA 7), right dACC (BA 32), and right MFG (BA 9); increased activation was observed in the right MTG (BA 39) and is depicted in Fig. 20. Compared with Balanced Readers (Fig. 18), Sight Readers showed greater activation in the left MFG (BA 9) and right FG (BA 37). Decoders and Balanced Readers differed (Fig. 19) with Decoders demonstrating hyperactivation of the left FG (BA 19), left iPL (BA 40), right dACC (BA 32), and right SFG (BA 6).

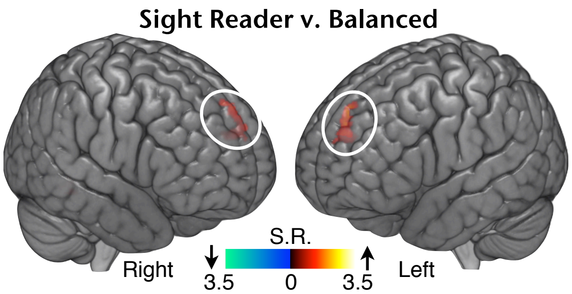



**Fig. 18** The pseudoword > letter contrast revealed few differences between Sight and Balanced Readers.  Hyperactivation by Sight Readers was evident in the MFG (BA 9) and FG (BA 37).

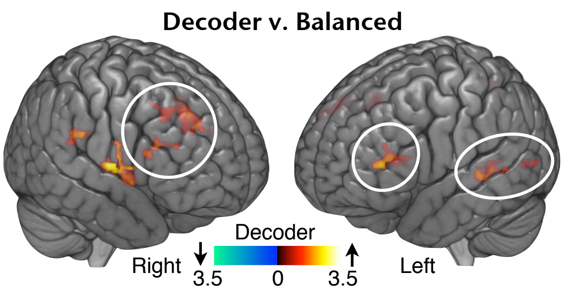



**Fig. 19** Differences were apparent in attention and reading networks when comparing pseudowords to letters between Decoders and Balanced Readers. Of particular importance is the hyperactivation of the left pSTG (BA 22) and right PFC (BA 9/46).

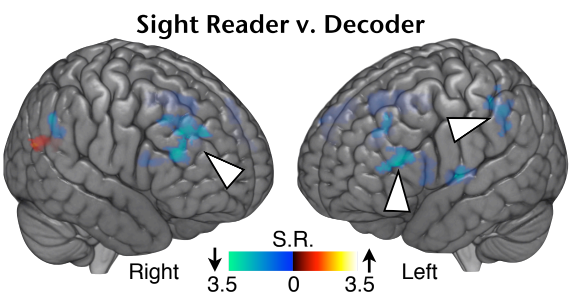



**Fig. 20** When comparing activations in response to pseudowords > letters, Sight Readers demonstrated several hypoactivations, including the left dorsal decoding subnetwork and right PFC. Hypoactivation of the decoding subnetwork provides support for dividing groups based on Reading Tendency Index scores, since the difference follows specific predictions from dual subnetwork reading theories.

**Table 16. Functional activation differences for pseudowords > letters**

| | Hemisphere | Region | Brodmann Area | Cluster Extent | Peak t-score | MNI coordinates x | y | z |
|---|---|---|---|---|---|---|---|---|
| Sight Reader < Decoder | | | | | | | | |
| | Left | aIns | 13 | 550 | 4.00 | -40 | -9 | 0 |
| | | iPL | 40 | 199 | 2.89 | -64 | -33 | 31 |
| | | Precuneus | 7 | 170 | 2.76 | -16 | -73 | 45 |
| | Right | aIns | 13 | 196 | 3.52 | 39 | 14 | 13 |
| | | dACC | 32 | 1123 | 3.96 | 3 | 11 | 46 |
| | | MFG | 9 | 689 | 3.51 | 40 | 39 | 36 |
| Sight Reader > Decoder | | | | | | | | |
| | Right | MTG | 39 | 369 | 3.43 | 48 | -60 | 22 |
| Sight Reader > Balanced | | | | | | | | |
| | Left | MFG | 9 | 380 | 3.37 | -6 | 45 | 22 |
| | Right | FG | 37 | 123 | 3.23 | 33 | -48 | -15 |
| Decoder > Balanced | | | | | | | | |
| | Left | FG | 19 | 181 | 3.2 | -21 | -67 | -14 |
| | | iPL | 40 | 182 | 3.11 | -52 | -30 | 18 |
| | Right | dACC | 32 | 236 | 3.32 | 3 | 18 | 45 |
| | | SFG | 6 | 318 | 4.08 | 1 | 10 | 63 |

aIns = anterior insula, dACC = dorsal anterior cingulate cortex; IFG = inferior frontal gyrus; FG = fusiform gyrus; iPL = inferior parietal lobe; sPL = superior parietal lobe; MFG = middle frontal gyrus; MTG = middle temporal gyrus; SFG = superior frontal gyrus

## 6.3 Discussion

The aim of this study was to extend our understanding of the novel Reading Tendency Index with regard to specific neural correlates associated with each reading tendency, as predicted by the Index. The central tenets of dual subnetwork reading models specify neural subnetworks primarily responsible for decoding and word recognition processes (Coltheart, Rastle, Perry, Langdon, & Ziegler, 2001; Fiebach et al., 2002; Harm & Seidenberg, 2004; Jobard et al., 2003). Two main findings begin to establish the validity of the Reading Tendency Index from a neural perspective within the context of dual subnetwork models. Increased activation in the ventral subnetwork of Sight Readers relative to Decoders during high-frequency word recognition (Fig. 17), and increased activation in the dorsal subnetwork of Decoders relative to Sight Readers during the phonological condition (Fig. 20) follow theoretical, dual reading subnetwork predictions. Though other classification schemes (Baron & Strawson, 1976; Sprenger-Charolles et al., 2000; Stanovich, 1988; Yap, Sibley, Balota, Ratcliff, & Rueckl, 2014) have previously attempted to sort readers on the basis of their relative phonologic and orthographic deficits, this is the first study to combine measures of reading proficiencies in order to predict neural function. Overall, the behavioral and functional data provided support for predictable, neural underpinnings segregating readers based on their Reading Tendency Index scores. Further, the findings exhibit the potential utility of the novel Reading Tendency Index for advancing theoretical understanding of reading disabilities, as well as reading pedagogy and intervention. For example, a person with a high likelihood of Sight Reading tendencies as estimates by the Index may benefit from more traditional, phonologic remediation; whereas, a Decoder would increase fluency quicker through visual working memory exercises and word exposure to increase his or her lexicon.

The response to reading highly familiar words in the orthographic lexical decision task (oLDT) provided evidence for two specific predictions about the functional activation of reading subnetworks. The Decoders showed hypoactivation when compared with either Balanced (Fig. 19) or Sight Readers (Fig. 20) along part of the ventral recognition subnetwork, the MTG (BA 22). The word recognition drift rate was also significantly better for both Sight and Balanced Readers compared with Decoders (Table 14), indicating relative mastery of word recognition even in Sight Readers. The findings are consistent with other studies showing that familiar word reading is primarily mediated by the ventral recognition subnetwork (Mechelli et al., 2005; Olulade, Flowers, Napolielo, & Eden, 2012; Vinckier et al., 2007) and is less demanding of neural resources (Edwards, Pexman, Goodyear, & Chambers, 2005), because it is quicker than decoding (Bergmann & Wimmer, 2008; Ratcliff, Gomez, & McKoon, 2004). Together, the data also provides support for the reading tendency divisions from a neural perspective.

There were two important, negative findings from the oLDT, as well. First, Sight Readers did not differ from Balanced Readers regarding activation of the ventral recognition subnetwork (Fig. 15), as predicted. Second, the three reading tendency subgroups did not evidence significantly different mean RT or Drift Diffusion estimates for consonant strings. Rather, Decoders showed specific impairments on high-frequency word recognition scores relative to the other two subgroups (Table 14). The later finding is important because it suggests visual, symbol processing is not a core issue affecting the Reading Tendency Index estimation, as has been posited as a possible contributor to RD (Chouake, Levy, Javitt, & Lavidor, 2012; Livingstone, Rosen, Drislane, & Galaburda, 1991; Pammer, Hansen, Holliday, & Cornelissen, 2006; Vidyasagar & Pammer, 2010). Without the confound, the focus of future work can be maintained on the neural correlates of reading skills as predicted by the Index.

In response to the phonologic lexical decision, Sight Readers showed significantly decreased activation of dorsal decoding subnetwork areas relative to Decoders (Fig. 20). By contrast, Balanced Readers did not differ from Decoders in the dorsal subnetwork, likely due to similarities in implicit, subvocal decoding (Brennan, Cao, Pedroarena-Leal, McNorgan, & Booth, 2012; Diaz & McCarthy, 2007). This is unsurprising given that the stimuli were completely novel to all the participants. Thus, the decoding process would be required for each and every stimulus. Those with adequate decoding abilities, whether Balanced Readers or not, therefore ought to have similar activation in response to pseudowords. In contrast, the presence of substantial activation differences between Decoders and Sight Readers (Figs. 16 & 19) suggests that the Index delineates properly between reading types and suggests the future work to understand other neural correlates differentiating the two tendencies is merited.

It is important to note the potential advantages of the Reading Tendency Index score and classification. The Reading Tendency Index classified six ADHD/+RD as Decoders. If the variance truly reflected a traditional “disability”, splitting those who qualify for RD between the groups should have resulted in fewer functional activation differences. This statement is especially true in the pseudoword condition, since phonological processing is noted as a core impairment in ADHD/+RD. Further, Sight Readers scored significantly worse than both comparison groups on the WIAT-III Word Reading subtest and are the most likely to fit within the strict definition of RD. Yet, despite being worse readers overall on standardized tests, Sight Readers demonstrated significant word recognition ability and activation of the ventral recognition subnetwork in response to a cognitive test (oLDT) with more ecological validity than standardized assessments. This suggests that the Index may have a significant advantage over traditional RD diagnostic methods in identifying the neural etiology, and consequently the prognosis, of poorer readers. Using the Index classifications likely has considerable implications for tailoring the appropriate instruction and remediation to the individual students that is essential for maximal growth and recovery of potential (Eden & Vaidya, 2008).

With regard to attention network alterations, both imbalanced subgroups showed hypoactivation in the right supramarginal gyrus compared with Balanced Readers during the orthographic condition. It is unclear whether this effect is due to an overrepresentation of ADHD in both groups or serves as a neural correlate linking attention and reading performance in a broader sense (Levy, Young, Bennett, Martin, & Hay, 2013; Mayes & Calhoun, 2007; Rogers, Hwang, Toplak, Weiss, & Tannock, 2011; Steele, Karmiloff-Smith, Cornish, & Scerif, 2012; Willcutt & Pennington, 2000). As shown in Chaper 3, both ADHD/+RD and ADHD/-RD showed hyperactivation of the dorsal iPL/supramarginal gyrus and hypoactivation of more ventral aspects of the iPL relative to controls during a rhyming task with a prolonged attention component. Other studies have also demonstrated that altered activation of the right iPL is associated with dysregulation of left hemispheric reading areas (Pammer et al., 2006) and may be involved in phonological processing (McDermott, Petersen, Watson, & Ojemann, 2003). Additionally, the differences within the right hemisphere in the iPL and IFG during the phonologic condition (Fig. 10a) are consistent with other studies demonstrating involvement of both areas in RD (Bolger, Hornickel, Cone, Burman, &

Booth, 2008; Frost et al., 2009) and suggest an attentional component. More research is need to determine whether the effects in the right hemispheric, attention networks are related to ADHD or a more general mechanism predisposing those with poor attention to develop imbalanced Reading Tendencies.

Overall, the functional results provide important evidence that individuals may favor a particular reading subnetwork, which may also coincide with the presence of specific cognitive impairments. Moreover, the relative functionality of and balance between the two reading subnetworks can be quantified using the novel Reading Tendency Index based on drift rates, as proposed in Chapter 5. The functional activation data showed that Balanced and Sight Readers did not differ with respect to the activation of the ventral recognition subnetwork in response to familiar words. Conversely, Decoders evidenced hypoactivation of the ventral recognition subnetwork relative to either group. During the phonological lexical decision, Sight Readers demonstrated significantly less activation of dorsal decoding subnetwork areas relative to Decoders, providing further evidence for neural correlates distinguishing the two tendencies. Together, these experiments provide preliminary evidence for the validity and predictive power of the novel Reading Tendency Index within a dual subnetwork framework and suggests continued investigation is merited.

# CHAPTER 7

## CONCLUSION

One goal of this project was to elucidate whether distinct, neural mechanisms contribute to ADHD/+RD as compared with ADHD/-RD. Activational differences within attention and reading networks were assessed with a non-linguisic, numeric CPT (n-CPT) and novel, word rhyming CPT (wr-CPT). Not only was this study the first functional assessment of attention and reading network activation in ADHD/+RD, but the experimental results also prompted a novel classification, called the Reading Tendency Index, to be devised. The second goal of this project was to introduce and furnish preliminary evidence for the Reading Tendency Index through assessing cognitive and neural profiles for groups defined using the Index. The results from both goals are a substantial and original contribution, with the later providing a potentially powerful quantitative tool for future study and educational improvement.

Inattention and phonologic impairments related to DSM-IV-TR criteria were the initial focus for the experimental paradigms and comparisons. The functional alterations in attention-related areas between ADHD/+RD and ADHD/-RD relative to TDC suggested that those with ADHD/-RD may have to re-engage attention mechanisms more frequently than ADHD/+RD, due to boredom (Ch. 2 & 3). This finding suggests that RD should be a specific screening criterion for ADHD studies identifying functional alterations in attention networks, given that affected areas were rather distinct between the ADHD subgroups. The relative paucity of alterations in reading subnetworks and shared differences in attention-related areas during the wr-CPT for the ADHD subgroups relative to TDC (Ch. 3) led to a key finding that a novel continuum index provides classification of Reading Tendencies that captures cognitive (Ch. 5) and neural profiles (Ch. 6) better than classical ADHD and RD diagnostic criteria.

The collective results suggested a paradigm shift for assessing reading skills in ADHD/+RD investigations from deficit- or disability-based categorization to data-driven estimation of reading tendencies. The new conceptualization has multiple benefits, including a quantitative, dimensional approach to reading assessment and individualized prognosis from early schooling. Additionally, tendency-based research would focus on intact processing pathways, rather than potential functional alterations that may be more or less detectable depending on the comparison group. This is important since there may be many causes for RD within ADHD and working to re-characterize readers on the basis of reading strategies provides a different approach more in line with identifying endophenotypes as well as developing better targeted interventions.

Another advantage for the novel Reading Tendency Index over previous methods of classifying those with reading disabilities (e.g., Sprenger-Charolles, Colé, Lacert, & Serniclaes, 2000) is that the cognitive profiles associated with the imbalanced tendencies have implications for higher order reading tasks, as well. For example, comprehension may be more difficult for Sight Readers, because of their poor verbal working memory (Berninger, Raskind, Richards, Abbott, & Stock, 2008) and a limited mental lexicon. Likewise, without adequate word recognition, the fluidity of a sentence or thought may be difficult to discern for Decoders (Cain & Bignell, 2014). Lastly, the Reading Tendency Index is based on measuring cognitive abilities with specific, predicted neural correlates; however, once the neural framework is established, the cognitive assessments can be carried out independent of neuroimaging. This is attractive for broader extension and application of future research using the tendency-based method, since the method promises to provide specificity without high cost.

The Reading Tendency Index was based on theoretical implications of dual subnetwork language hypotheses (Jobard, Crivello, & Tzourio-Mazoyer, 2003; Pugh et al., 2001) and estimates of reading skills from Drift Diffusion Modeling (Ratcliff, 1978; Ratcliff, Gomez, & McKoon, 2004; Wagenmakers, van der Maas, & Grasman, 2007). The major advantage of using drift rates to estimate phonological and orthographic abilities is that drift rates are independent of processing speed differences when calculated by either Drift Diffusion Modeling or the simpler EZ-diffusion Modeling. As previously addressed, ADHD/+RD has often been associated with decreased processing speed (Christopher et al., 2012; McGrath et al., 2011; Sela et al., 2012), which affects reaction times and has been somewhat of an unspoken confound in many studies. By limiting or removing the effects of different processing speeds, this project is able to consider the core abilities or skills related to basic reading processes. Furthermore, the core abilities are directly relatable to cortical, reading subnetworks, allowing for specific hypotheses about neural differences related to the cognitive profiles.

The drift rates can be easily manipulated mathematically to yield a relative tendency toward sight reading or decoding and re-classify subjects accordingly. Several, predictable profiles emerged as the cognitive data was examined using the new classifications of Balanced, Decoding, or Sight Readers. Decoders were slower, had more variable responses to speeded tasks, and showed less cognitive flexibility than Balanced Readers. Sight Readers had more inattentive symptoms, regardless of whether the TDC were removed from the analysis, and scored the poorest on verbal WM and cognitive flexibility. It should be noted that both of the imbalanced tendency groups had a higher percentage of ADHD than the Balanced Reader group, providing a potential confound of generally greater, and potentially heterogeneous, cognitive impairments in the imbalanced groups. However, the resulting cognitive profiles were significantly different between the imbalanced subgroups, suggesting instead that the Reading Tendency Index may delineate the groups succinctly even according to cognitive impairments generally associated with ADHD. The profiles were also consistent with many observed and theoretical characterizations leading to RD (Bental & Tirosh, 2007; Rucklidge & Tannock, 2002; Sprenger-Charolles et al., 2000; Stanovich, 1988; Willcutt et al., 2010); however, to the best of my knowledge, this study is the first to define the clusters using a quantitative metric related to individual performance and in view of potential neural correlates. With greater characterization, the novel index may show an advantage over disability-based investigation, since the implications of even mild imbalances may be useful for remediation, as opposed to relying on an arbitrary cutoff of disability (Fletcher, Denton, & Francis, 2005 and see discussion in Fletcher, Francis, Rourke, Shaywitz, & Shaywitz, 1992). The evidence presented here makes a strong case for further assessment of the Reading Tendency Index as it shows promise of predictive power for individual patterns and may greatly enhance future research in intervention or remediation strategies.

Functional data from the phonological and orthographic lexical decision tasks provided evidence for the proposed neural correlates of the three Reading Tendencies. As shown in Chapter 6, Decoders were less likely to activate the ventral recognition subnetwork to the same extent as either Balanced or Sight Readers during word recognition. Fig. 20 demonstrates the functional activation differences between Sight Readers and Decoders in response to the phonological lexical decision task. The widespread hypoactivation of the dorsal decoding subnetwork in Sight Readers relative to Decoders is compelling and concurs with the orthographic lexical decision task results. Together, the functional tasks demonstrate the potential utility of the Reading Tendency Index in predicting the relative strength of and balance between the two, left hemispheric reading subnetworks.

Developing a novel index has implications for educational intervention, as well. Following the hypothesis that deficits in phonology or exception word reading may stem from specific etiologies (e.g., Norton et al., 2014; Stanovich, 1988), a recent study showed those with poor phonological skills tended to have an alternate, developmental trajectory, while those with poor exception word reading were simply delayed in their reading development (McNorgan, Alvarez, Bhullar, Gayda, & Booth, 2011; Sprenger-Charolles et al., 2000; Talcott, Witton, & Stein, 2013). Another study showed that greater exposure to word reading (i.e., with increasing education) predicted orthographic processing abilities, but vice versa (Deacon, Benere, & Castles, 2012), suggesting that sight reading alone is not sufficient to make substantial reading gains (McNorgan, Alvarez, Bhullar, Gayda, & Booth, 2011). Together, the observations suggest that those relying on sight reading methods may make some reading gains with continuous exposure, but are essentially at the highest risk for RD. Thus, being able to identify these types of readers versus delayed Decoders would help direct both the educator's efforts and resource allocation, including the individual student's time allotment for specific skill remediation. A computerized, short assessment leading to an automatically generated Reading Tendency score may be useful for practitioners and decrease the cost of remediation efforts in terms of both time and resources.

Overall, introducing the Reading Tendency Index and Drift Diffusion Modeling-based metrics is a significant step forward for understanding reading ability in ADHD. Validation and refinement of the stimuli and paradigms would be beneficial, but the concept and current implementation of the Reading Tendency Index already has implications for educational policy changes, such as screening measures at multiple stages of a child's academic career to track and correct progress. Further work on the Reading Tendency Index within the framework of dual subnetwork models is also needed address questions regarding effective network connectivity and potentially even genetics-based, anatomical theories of developmental dyslexia. By shifting from a disability-based diagnosis to a reading tendency framework, the variability associated with equipotentiality and the heterogeneity of both ADHD and RD may be reduced and may help bring about greater gains in understanding the neural circuitry related to the co-occurring disorders.

# APPENDIX

## A. ADHD Diagnosis

Clinical determination of ADHD status was based on a semi-structured interview given by our clinical neuropsychologists using the Kiddie Schedule of Affective Disorders - Present and Lifetime (K-SADS-PL, Kaufman et al., 1997). The Disruptive Behavior Disorders Scale (DBD) and Iowa Conners Hyperactivity/Impulsivity Scale questionnaires were also given to the subject's parent/guardian and teacher to augment the K-SADS-PL diagnostic interview. The Wechsler Abbreviated Scale of Intelligence (WASI; PsychCorp, Pearson Education; San Antonio, TX) was administered to estimate the FSIQ. To be included, those with ADHD receiving medication were required to be on a stable dosage for at least six months prior to the study assessments. All subjects were free of psychostimulant medication for at least a 24-hour period prior to the MR examination, reading assessment, and Conners' CPT-II testing.

## B. Reading Disability Diagnosis

The Word Reading, Pseudoword Decoding, and Spelling subtests of the Wechsler Individual Achievement Test - III battery (WIAT-III; PsychCorp, Pearson Education; San Antonio, TX) were administered to characterize reading abilities. Control or ADHD subjects with a significant discrepancy ($p$ = .01) between the predicted and achieved scores per the WIAT-III Aptitude Achievement Discrepancy tables in at least two of the three subtests were diagnosed as having an RD.

## C. Demographic and Behavioral Analysis

Age, FSIQ, and reading assessment scores were generally compared using an ANOVA with diagnosis or reading tendency group as the main effect. Group differences on performance during the n-CPT and wr-CPT were assessed by ANCOVA, with age as the covariate, for d', Mean Hit RT, and Variance of Hit RT. Similar analyses were completed for the oLDT and pLDT, but FSIQ was also included with age as a covariate in the ANCOVA. Each chapter details the comparisons of behavioral and computerized assessment outcomes specific to the study. When appropriate, Tukey's HSD *post-hoc* analyses were performed for main effects reaching $p = .05$. All statistics were modeled using JMP 11 (SAS; Cary, NC).

**D. Imaging Protocol**

The structural and functional imaging data were collected on a 3 Tesla Siemens MAGNETOM Verio system (Siemens, Erlangen, Germany) using a 12-channel receive-only volume head coil. Anatomical $T_1$-weighted images using the Magnetization Prepared Rapid Gradient Echo (MPRAGE) sequence were collected with the following parameters: TR = 2.2 sec, TE = 3 msec, TI = 799 msec, flip-angle = $13^0$, FOV = 256x256 $mm^2$, 256 axial slices, slice thickness = 1 mm, matrix = 176x256, and scan-time = 6min:27s. Blood oxygen level-dependent (BOLD) fMRI images were collected using the gradient echo planar imaging sequence with the following parameters: ascending, interleaved sequence, TR = 2.6 sec, TE = 29 msec, FOV = 256x256 $mm^2$, matrix = 128x128, 36 axial slices, and pixel dimension = 2x2x3$mm^3$. This sequence provides near full-brain coverage.

**E. Image processing and Analyses**

$T_1$-weighted images were filtered using the spatial adaptive non-local means Gaussian scheme (Manjón, Coupé, Martí-Bonmatí, Collins, & Robles, 2010), averaged, corrected for field inhomogeneities, and segmented with tissue probability maps. The processed, $T_1$-weighted images became the anatomical basis for co-registration of the fMRI data during post-processing. All functional scans met the movement inclusion criteria of greater than 75% of the volumes registering less than 0.3 degrees rotational or 3.0mm translational displacement between volumes and were processed using Statistical Parametric Mapping (SPM8, Wellcome Department of Imaging and Neuroscience). The first four volumes were discarded to allow for magnetization effects to subside. Functional MRI images were unwarped to correct for motion-based susceptibility (Andersson, Hutton, Ashburner, Turner, & Friston, 2001), realigned to a mean image of the series, and co-registered to the subjects' $T_1$-weighted images. Forward deformations from the $T_1$-weighted, structural segmentation were applied to the co-registered fMRI images to normalize the fMRI data to the Montreal Neurological Institute European template brain. A 6mm full width at half maximum isotropic Gaussian kernel (1.5mm$^3$) was applied to smooth the normalized data. fMRI data was detrended using a high-pass filter (1/256s, n-CPT; 1/300s wr-CPT; 1/128s, oLDT and pLDT) to remove signal due to scanner drift, and an autoregressive model, AR(1), was used to account for serial correlations. Reference waveforms were generated by convolving boxcar functions with the canonical hemodynamic response function for the blocks of interest.

Subject motion during the fMRI scans is especially problematic (Hutton et al., 2002; Oakes et al., 2005) and was common in our pediatric ADHD sample. While the unwarping step was added to mitigate some of the effects of minor motion (Andersson et al., 2001), additional evaluation of all volumes was completed using the artifact detection toolkit (ART, http://www.nitrc.org/projects/artifact_detect/). Outlier volumes were identified automatically by the toolkit, which uses realignment parameters and global signal standard deviation to generate a matrix for covariates of no interest. By including the covariate matrix, outlier volumes are effectively excluded from the estimation of the activation related to the task and the degrees of freedom are limited for subjects with more noisy data without disrupting the high-pass filtering across the experiment. Normalized, unwarped fMRI volumes were marked as outliers for motion exceeding 2.0 mm of translation or 0.2 degrees of rotation or signal change greater than 3.0 standard deviations.

To constrain the interpretation of the fMRI results to differences in neural function and not performance, d' was entered along with age as covariates of no interest in the second-level functional group (diagnosis or reading tendency) analyses. Since the focus of these studies was activation in reading subnetworks and attention areas, motor, occipital, ventral PFC, brainstem, and cerebellar regions were not examined in the current analysis. Clusters within the regions of interest masks generated with Wake Forest PickAtlas (Maldjian, Laurienti, Kraft, & Burdette, 2003) were reported after multiple comparison correction to cluster-level significance of $\alpha < .05$ based on $10^4$ iterations of a Monte Carlo simulation within 3dClustSim (AFNI; Ward, 2000). Given the limited sample size, a value of $p < .02$ at the peak-level was chosen to generate the maps necessary for cluster-level correction. To supplement the characterization of functional activation differences, extracted parameter estimates from within 5 mm of significant peaks based on the two-group directional contrasts were plotted to depict relative differences.

**F. Cognitive assessments**

Conners' CPT-II Behavioral Testing

The Conners' CPT-II is a computerized attention task lasting 14 minutes as outlined by Conners *et al.* (2003). The stimuli are letters and are presented individually in the middle of the screen for approximately 250 milliseconds. During the task, participants press the space bar for each stimulus trial, only withholding the response for an "X". Each of the 18, randomized blocks contains 20 trials presented at 1, 2, or 4 second inter-stimulus intervals (ISI), which are consistent within the block. Ten percent of the 360 stimuli were non-targets ("X"). The outcome metrics of interest included Hit Reaction Time (RT; speed), Hit RT Standard Error (SE; inattention), Variability of Hit RT SE (inattention), Detectability, Hit RT ISI Change (vigilance), and Hit RT Block Change (vigilance).

Neurocognitive Assessment

To further characterize the cognitive abilities related to decoding, verbal working memory, and processing speed, three pencil and paper tests were completed by each subject under the administration of a clinical neuropsychologist.

*Auditory Analysis*

Elison and blending skills were assessed using the Auditory Analysis test (Rosner & Simon, 1971). For each word in a list of 30 items from one to four syllables, the assessor spoke the word and then instructed the participant to repeat the word disregarding a specific phoneme or morpheme (e.g., Say “cowboy” without “boy”). Discontinuation criteria was four consecutive errors.

*Sentence Memory*

To assess verbal working memory, participants listened to and then repeated grammatically correct sentences, which progressed in number of words and phrase complexity. Correct sentences were repeated verbatim on the first attempt with allowance for logical article or small preposition substitutions (e.g., “a” instead of “the”). The assessment was discontinued after three consecutive sentences containing errors.

*Underlining task*

The pencil-and-paper task is chiefly associated with processing speed, but also requires visual working memory and visual discrimination (Rourke & Orr, 1977). A four symbol sequence was provided as a target sequence to be identified among rows of four symbol distractor sequences printed down the entirety of a page. Participants identified and underlined as many of the targets on a page as possible within one minute. Scores for each subtest were corrected for false alarms and misses. The composite of seven subtests spanning symbol and letter sequences, one pseudoword, and one word subtest is reported.

**G. fMRI paradigms**

<u>Continuous Performance Tasks (CPT)</u>

The numeric CPT and wr-CPT are described in Ch. 2 and 3, respectively. Briefly, the two variations were used to assess sustained attention with (wr-CPT) and without (n-CPT) the potential confound of language. 90-second blocks are longer than typically employed in reading paradigms, providing the additional insight into the effects of prolonged attention during a rhyming task.

Phonologic Lexical Decision Task (pLDT)

Pseudowords and low frequency words were selected for the pLDT to approxiamate decoding abilities and, by proxy, dorsal decoding subnetwork functionality. By using unfamiliar stimuli, the task biases phonological processing and allows for estimation of decoding abilities (Bergmann & Wimmer, 2008; Binder et al., 2003; Hickok:2009dt; Blackmon et al., 2010; Hickok & Poeppel, 2007). Pseudowords are legal, pronounceable combinations of graphemes, but not pseudohomophones (e.g., “bair”). Since none of the subjects have explicit, prior exposure to the stimuli, the participant must decode each pseudoword. Low frequency words appear in print occasionally, and thus, also are more likely to evoke decoding processes than highly familiar words. The demanding nature of the task required consistent interaction with the paradigm in order to perform better than chance.

The pLDT was adapted for and performed as an fMRI block-design task. Each task block is 18 sec long, followed by a 13.75 sec fixation on multiple pound symbols (i.e., “####”), resulting in a 5 min 42 sec task. Subjects identify three to five letter, monosyllabic stimuli pseudowords and low frequency words (mean log HAL = 8.4, range = 6.6 - 9.6; duration 1.6 sec; interstimulus interval = 2.25 sec) during twelve decoding blocks. Six blocks were predominately (> 60%) pseudowords and six were mostly low frequency words. Mean bigram frequency did not differ between blocks.

Orthographic LDT (oLDT)

The oLDT uses consonant strings and high frequency words to estimate sight reading abilities and quantitate a proxy for ventral recognition subnetwork function. Consonant strings provide data about pure symbol processing, since they have no phonological equivalent. This is an important test condition to make sure there are no perceptual differences between diagnostically- or ability-based groups that feedforward into higher level processing. Using highly familiar words at a stimulus duration half that of the pLDT requires word recognition, rather than overt decoding.

112 monosyllabic, high-frequency words (mean log HAL = 11.8, range = 10.0 - 15.0; duration 0.8 sec; interstimulus interval = 1.2 sec) were selected from the English Lexicon Project (Balota et al., 2007) and matched with consonant strings. Thirteen blocks of monosyllabic, high frequency words (mean log HAL = 11.8, range = 10.0 - 15.0; duration 0.8 sec; interstimulus interval = 1.2 sec) and consonant strings alternating between 80% words (7 blocks) and 80% strings (6 blocks) were interspersed with nine fixation blocks, each lasting 13.75s. Fixation blocks consist of four or five pound characters presented for 13.75 seconds and required no responses. The total running time for the paradigm was 6 minutes 35 seconds. Stimuli and responses for both paradigms were controlled by Presentation® software (15.0, www.neurobs.com). All stimuli were presented in white, Arial font size 112, on a gray background in the center of a screen viewed through a mirror above the head coil. Responses were recorded with an MRI-compatible, two-button response box in the right hand and managed with the software.

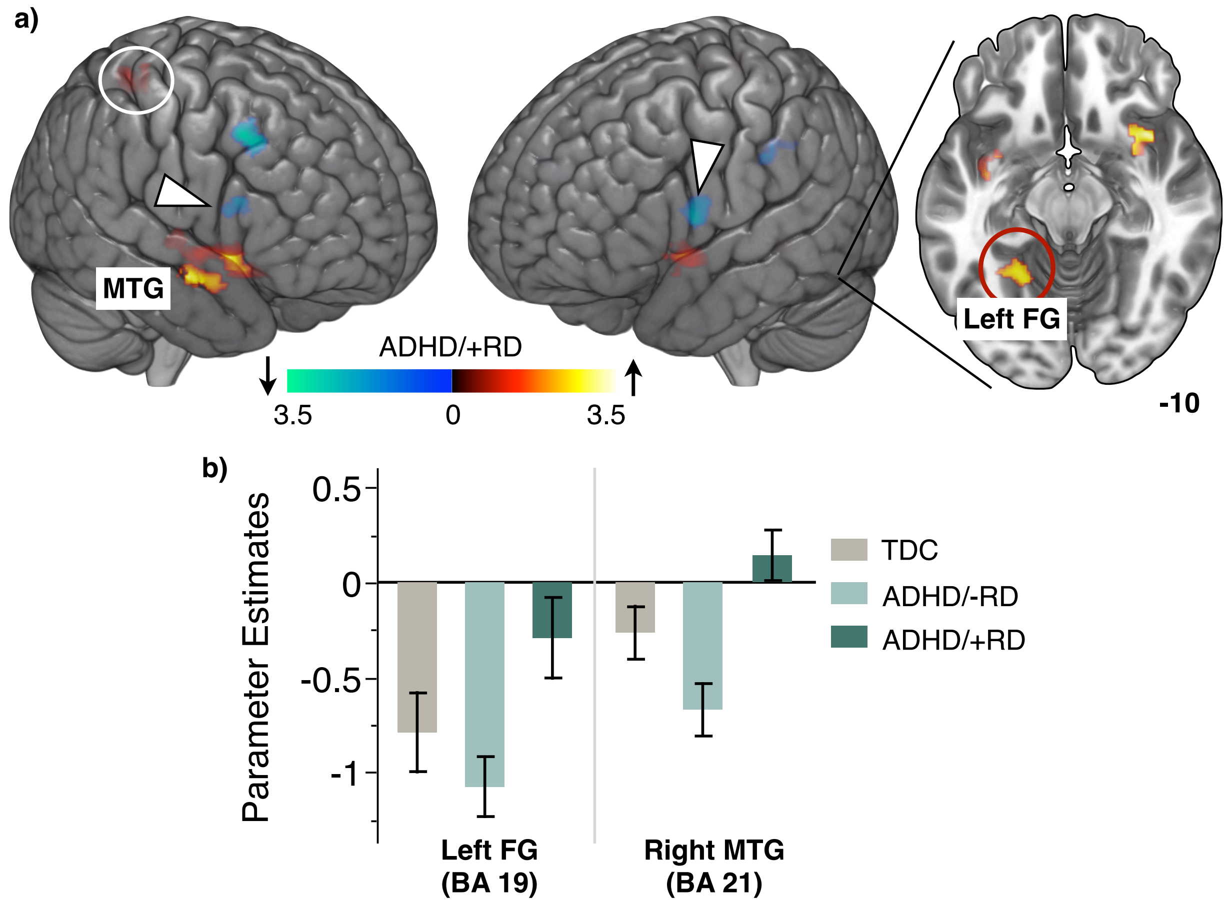
**H. Statistical tests of distributions for Drift Diffusion Modeling**

To test the probability of the skew being symmetric for either lexical decision task, the skew and standard error of skewness were estimated and converted to a z-score (Suppl. Fig. 3). The skew was calculated within JMP 11 (SAS; Cary, NC). Since the number of observations is large, the approximation for standard error of skewness, $\sqrt{(6/n)}$, was appropriate. The z-score was determined through dividing the skew by the standard error of the skewness (SES below). The actual calculations for the z-scores for oLDT (24.7) and pLDT (15.7) follow and demonstrate a high probability that the reaction times are not symmetrically distributed.

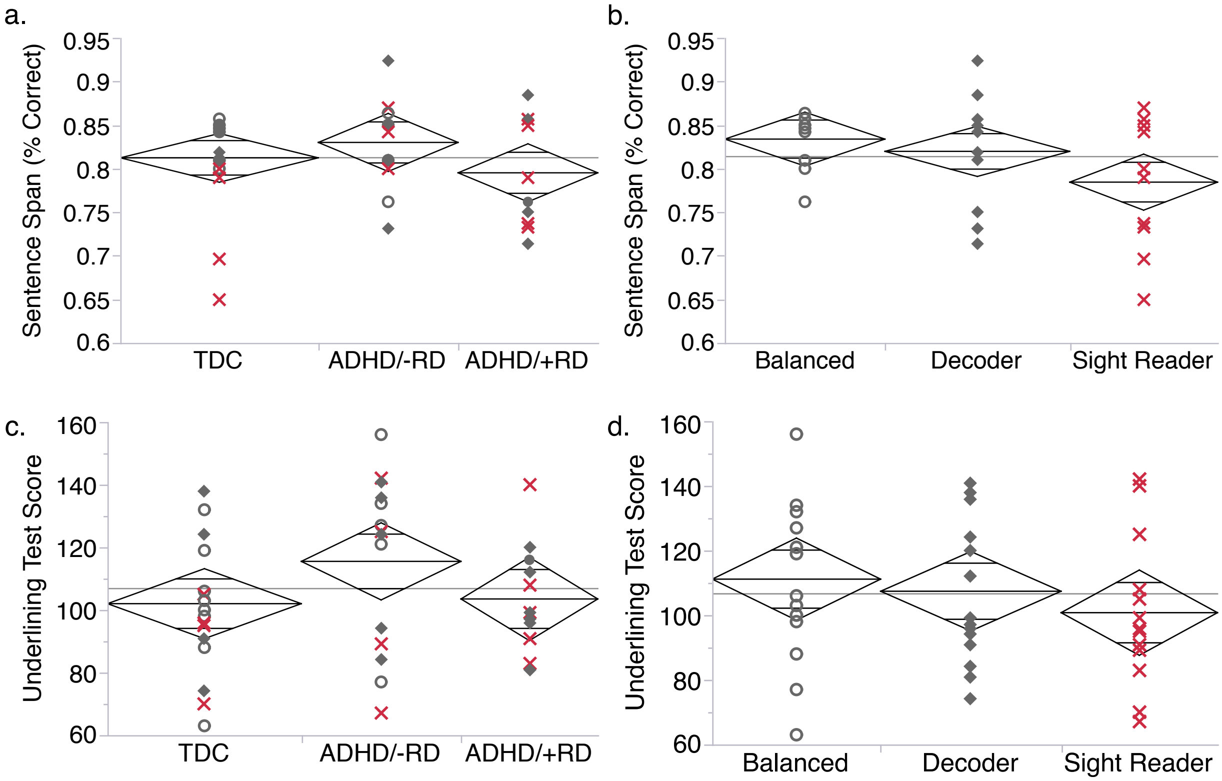
| **oLDT** | **pLDT** |
|---|---|
| n = 3802 | n = 2136 |
| skew = .980 | skew = .833 |
| SES = .0397 | SES = .0529 |

$$\frac{.980}{.0397} = \mathbf{24.7} \qquad \frac{.833}{.0529} = \mathbf{15.7}$$

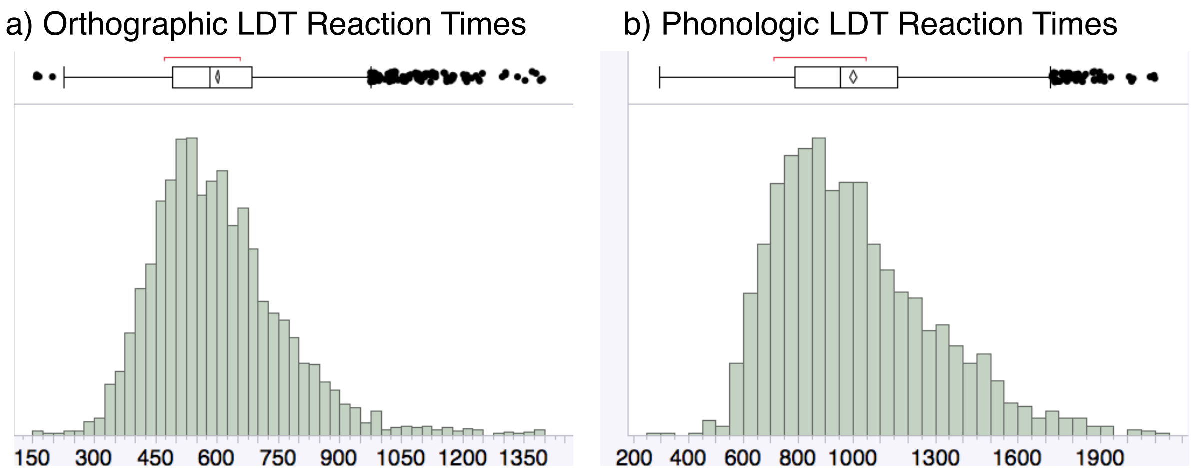
**I. Supplemental figures**



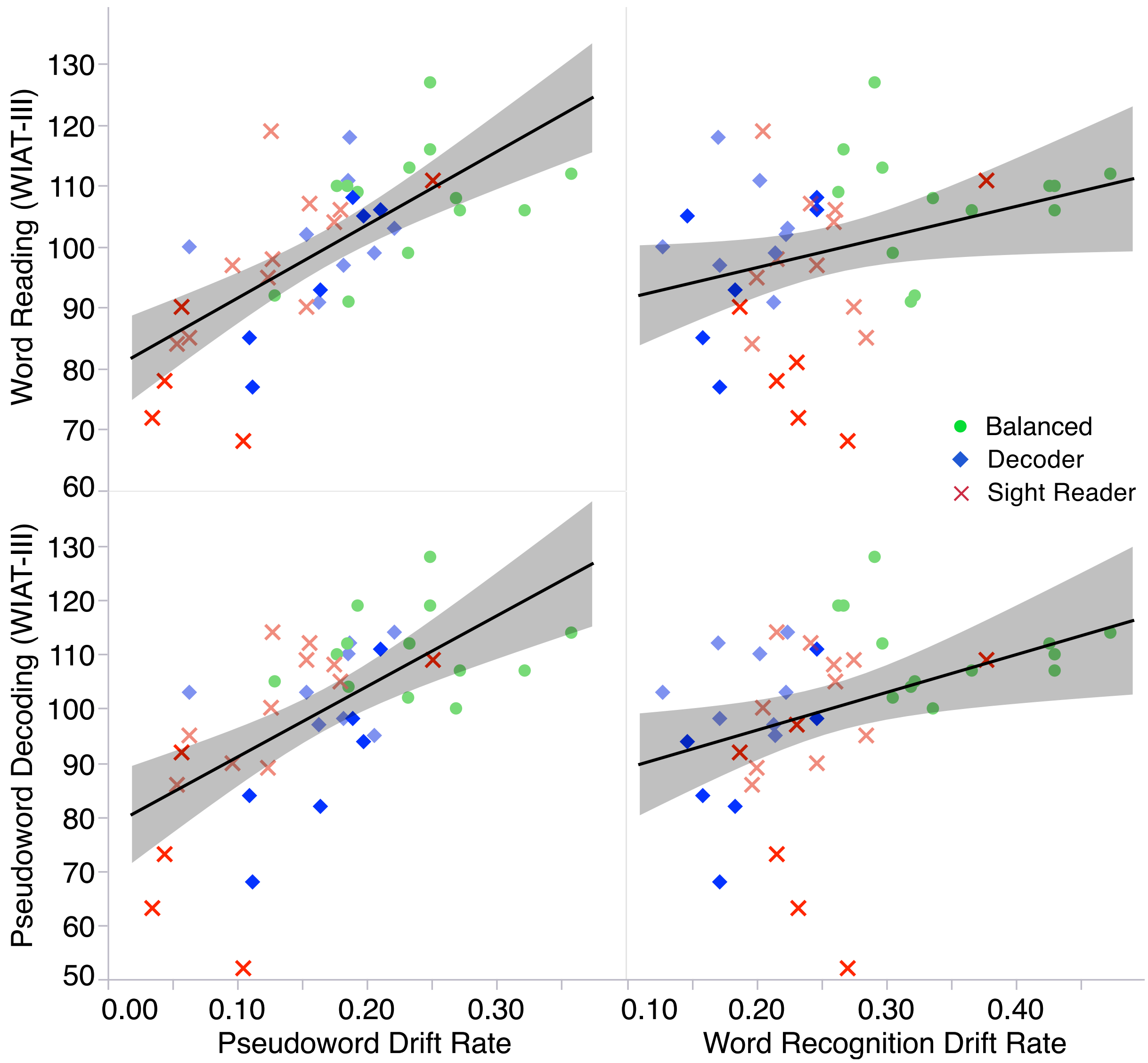

**Suppl. Fig. 1** When compared head to head during the word rhyming task, ADHD subgroups evidence activation differences in multiple cortical areas. **a)** ADHD/+RD showed greater activation in left FG (BA 19), left aIns (BA 13), right sPL (BA 7), right MSTG and STG (BA 21/38). Conversely, ADHD/+RD demonstrated decreased activation in bilateral IFG (BA 44/45), right MFG (BA 8), and left iPL (BA 40) relative to ADHD/-RD. **b)** Parameter estimates from the peak differences in the left FG and right MTG were extracted and plotted to show relative differences between all three groups. Error bars represent SEM. FG = fusiform gyrus, iPL = inferior parietal lobe, sPL = superior parietal lobe, MFG = middle frontal gyrus, STG = superior temporal gyrus



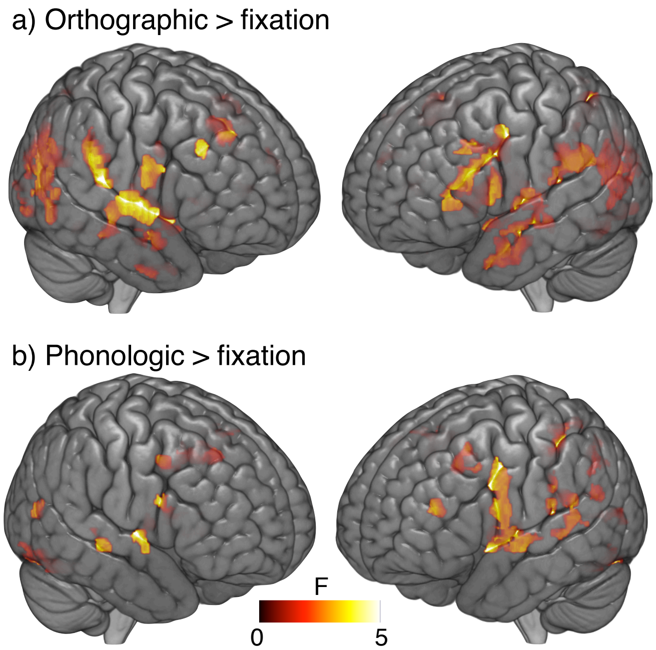

**Suppl. Fig. 2** ADHD/+RD does not differ from ADHD/-RD with respect to performance on a Sentence Span task, requiring verbal working memory (**a**), or an Underlining test, reflecting processing speed (**c**). While not reaching statistical significance, the grouping based on the novel Reading Tendency Index (**b, d**) demonstrates some qualitative advantages over DSM-IV-TR diagnostic groups.




**Suppl. Fig. 3** The distributions of the reaction times for both lexical decision tasks are right skewed with numerous outliers. While these distributions are problematic for statistical tests assuming normality, the Drift Diffusion Model and EZ Diffusion Model assume this type of distribution. Further explanation of the skewness statistical tests are available in Appendix H. (**a**) The positive skew (.98) is statistically significant (z = 24.7) for the oLDT RT. (**b**) The positive skew (.83) is also statistically significant (z = 15.7) for the pLDT.




**Suppl. Fig. 4** The pseudoword and word recognition drift rates show some consistency with standardized reading scores from the WIAT-III. Boys with ADHD/+RD are highlighted. Note the pseudoword drift rate predicts Word Reading (top left), as others have also reported.




**Suppl. Fig. 5** Activation patterns for task greater than fixation in Balanced Readers during the orthographic (**a**) and phonologic (**b**) lexical decision tasks. Both reading subnetworks were significantly activated in the tasks. Peak $p$ = .02, $K_E$ > 125 voxels.

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# ABSTRACT

## NEURAL ALTERATIONS INFLUENCING SKILLED READING IN ADHD: A TASK-BASED FMRI STUDY

**by**

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Attention-Deficit/Hyperactivity Disorder (ADHD) is a heterogeneous, neurodevelopmental disorder which co-occurs often with Reading Disability (RD). ADHD with and without RD consistently have higher inattentive ratings compared with typically developing controls, with co-occurring ADHD and RD (ADHD/+RD) also demonstrating impaired phonological processing. Accordingly, inattention has been associated with greater phonological impairment, though neither the neural correlates of the co-occurring disorders nor the association are well understood from a functional neuroimaging perspective. The goal was to assess to what extent ADHD/+RD differ from ADHD without RD (ADHD/-RD) and typically developing controls (TDC) in functional activation of attention- and reading-related areas during various tasks. The general hypothesis was that ADHD/+RD would show more extensive alterations in attention-related areas and unique alterations in reading-related areas compared with the other two groups.

The results indicated differences between ADHD/+RD and ADHD/-RD in attention processing; ADHD/-RD showed greater activation of frontoparietal areas for digit and word rhyming continuous performance fMRI tasks. Additionally, though some dysfunction was observed in decoding-related areas in ADHD/+RD relative to TDC, the results showed greater evidence of other cognitive impairments influencing decoding abilities across the ADHD/+RD and ADHD/-RD. Once the groups were re-characterized to reflect relative reading abilities in decoding and word recognition, specific cognitive and functional activation profiles surfaced for three groups: Balanced, Decoders, and Sight Readers.

Two findings contribute to a better understanding of ADHD and RD. First, the functional activation differences between the ADHD subgroups suggest that RD needs to be characterized specifically in ADHD neuroimaging studies and that non-linguistic stimuli should be used to mitigate RD-related confounds in ADHD studies. Second, the role of cognitive impairments, including the level of inattention, on phonology requires clarification from a neuroimaging perspective. Lastly, the novel Reading Tendency Index provides an estimation of an individual's preferred strategy for single word reading without the influence of variable processing speeds. The Index corresponds with predictable neural activations and has implications for instructional and remediation practices.

## AUTOBIOGRAPHICAL STATEMENT

Neuroscience has long captured my fascination prompting questions such as, how does a collection of calcium, phosphorous, sodium, potassium, and water communicate an idea that is understood by another collection of the same materials? However, I have also always had a passion for helping others understand concepts, which developed into a desire use education to infect students' brains with an insatiable curiosity. My overarching career goal is to investigate ways of improving pedagogy and interventions from an educational neuroscience perspective. Areas of specific interest include students with exceptionalities and science education, itself.

My training in science education through Colorado State University and Peak to Peak Charter School (Lafayette, CO) granted insight into the best practices in education from some of the top educators in the country. These experiences were essential to my aspirations of improving pedagogy through neuroscience research, which I began to pursue through the Translational Neuroscience Program at Wayne State University. As a graduate student, supervised by Dr. Jeffrey Stanley, I was encouraged to develop a cross-disciplinary research project between neuroscience and education. This work has received multiple awards from both general and specialized audiences at the university and has been presented at numerous national and international meetings. I am grateful for the opportunity to begin a discussion about reframing our conceptualization of reading abilities and hope that the students benefit from more individualized instruction in the relatively near future.