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Not All Reading Disabilities Are Dyslexia: Distinct Neurobiology of Specific Comprehension Deficits

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Abstract

Although an extensive literature exists on the neurobiological correlates of dyslexia (DYS), to date, no studies have examined the neurobiological profile of those who exhibit poor reading comprehension despite intact word-level abilities (specific reading comprehension deficits [S-RCD]). Here we investigated the word-level abilities of S-RCD as compared to typically developing readers (TD) and those with DYS by examining the blood oxygenation-level dependent response to words varying on frequency. Understanding whether S-RCD process words in the same manner as TD, or show alternate pathways to achieve normal word-reading abilities, may provide insights into the origin of this disorder. Results showed that as compared to TD, DYS showed abnormal covariance during word processing with right-hemisphere homologs of the left-hemisphere reading network in conjunction with left occipitotemporal underactivation. In contrast, S-RCD showed an intact neurobiological response to word stimuli in occipitotemporal regions (associated with fast and efficient word processing); however, inferior frontal gyrus (IFG) abnormalities were observed. Specifically, TD showed a higher-percent signal change within right IFG for low-versus-high frequency words as compared to both S-RCD and DYS. Using psychophysiological interaction analyses, a coupling-by-reading group interaction was found in right IFG for DYS, as indicated by a widespread greater covariance between right IFG and right occipitotemporal cortex/visual word-form areas, as well as bilateral medial frontal gyrus, as compared to TD. For S-RCD, the context-dependent functional interaction anomaly was most prominently seen in left IFG, which covaried to a greater extent with hippocampal, parahippocampal, and prefrontal areas than for TD for low- as compared to high-frequency words. Given the greater lexical access demands of low frequency as compared to high-frequency words, these results may suggest specific weaknesses in accessing lexical-semantic representations during word recognition. These novel findings provide foundational insights into the nature of S-RCD, and set the stage for future investigations of this common, but understudied, reading disorder.

Key words: dyslexia; fMRI; reading comprehension; reading disorder; specific comprehension deficits

Introduction

Dyslexia (DYS) is the most common type of learning disability, with prevalence estimates between 5 and 17.5 percent of the population. It is characterized by difficulty with accurately and fluently recognizing and decoding words, or with phonological-to-orthographic conversions (Fletcher et al., 1998; Lyon, 1995). These weaknesses result in difficulty with a comprehending written material (Adams, 1990; Shankweiler, 1999; Torgesen, 2000). The neural basis of DYS has been found to be associated with structural and functional abnormalities in left posterior perisylvian regions; in particular, functional neuroimaging studies have revealed that DYS is associated with underactivation in left occipitotemporal and

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temporoparietal regions, and overactivation in homologous right hemisphere regions as compared to typically developing readers (TD) (Paulesu et al., 2001; Pugh et al., 2000a; Richards et al., 1999; Rumsey et al., 1997; Shaywitz et al., 1998, 2002; Simos et al., 2000).

Although DYS is the most common type of reading disability (RD), other types of reading disorders have been reported. It has been reported that anywhere from 3 to 10 percent of school-age children show adequate word-level abilities (word recognition and decoding), but nevertheless struggle with comprehension of written text (Specific Reading Comprehension Deficits [S-RCD]) (Aaron et al., 1999; Cain and Oakhill, 2006, 2011; Catts et al., 2003; Leach et al., 2003; Nation, 2001). S-RCD has been a neglected subtype of RD in terms of understanding its neurobiological origin, despite the fact that the number of children and adolescents who struggle with S-RCD is nontrivial. Presence of S-RCD becomes especially critical as readers move from learning to read (decode) and shift to learning from reading, which occurs around fourth grade. At this point, readers have to be able to learn from informational text, and it at this time when S-RCD can especially emerge as debilitating.

The cognitive profile of S-RCD is characterized by weaknesses in a variety of areas, including semantics, syntax, inference making, self-monitoring, and executive function (Cain, 2006; Cain and Oakhill, 2011; Cain and Towse, 2008; Cutting et al., 2009; Locascio et al, 2010; Pimperton and Nation, 2010). In terms of semantic deficits, Nation and Snowling (1998, 1999) have shown that individuals with S-RCD are less sensitive to semantic information as evidenced by impaired performance on semantic priming tasks, but comparable performance to TD on a rhyme judgment task. These findings suggest that while S-RCD is associated with adequate phonological and orthographic representations, one component of their cognitive profile is weak semantic representations. Such a profile is in contrast to DYS, which is a group that often attempts to compensate for weaknesses in orthographic–phonological representations (O-P) by over-relying on the semantic context and showing poor word-reading accuracy and fluency (Stanovich, 1980).

The occurrence of being weak at some aspects of word recognition, but not others, might be most readily interpretable through the lens of the lexical quality hypothesis (LQH) (Perfetti et al., 2007), which posits that rich phonological, orthographic, and semantic representations of words must all be present for the occurrence of efficient word processing. The behavioral literature clearly suggests that S-RCD have intact O-P representations, but the degree to which they have adequate lexical-semantic representations of words is not certain. In contrast, it is well established that DYS do not have intact O-P representations.

To date, there have been no neurobiological investigations of S-RCD, so it is not known if any specific anatomical and/or functional abnormalities are associated with this type of RD. It is important to know if there are particular neural abnormalities associated with S-RCD, especially at the word-level, given the large literature on the neurobiological profile of word-level processing in DYS. Even though S-RCD show equivalent performance behaviorally on word-level measures as compared to TD when the O-P system is stressed, this does not necessarily appear to be the case when the semantic system is stressed (Nation and Snowling, 1998, 1999). Thus, within an LQH framework, when viewing words, one might expect to see normal processing for S-RCD in the brain regions primarily found to be responsible for the O-P aspect of word reading, most predominately the putative visual word-form area (VWFA) within the left occipitotemporal region, but not necessarily in other regions. Such information may contribute central insights toward understanding more about the mechanisms for disassociations between decoding and meaning-based processing, as well as underlying etiologies of and best treatments for S-RCD.

Here we investigated the word-level abilities of adolescents with S-RCD as compared to TD and DYS by examining the blood oxygenation level-dependent (BOLD) response to words and context-dependent connectivity between reading-related regions. To comprehensively test the S-RCD word recognition system, our lexical decision design placed varying levels of stress on lexical access. Specifically, in addition to pseudowords, which are absent of meaning, we manipulated stimuli in terms of lexical access demands by using high- and low-frequency words. High- and low-frequency words both have lexical-semantic representations, but the latter is thought to have a less-enriched representation, which would therefore suggest greater processing demands. In general, we hypothesized that we would see the well-established finding of abnormal word processing associated with DYS, with underactivation in the left occipitotemporal and temporoparietal regions due to their weaknesses in O-P processing. In terms of our central focus of understanding more about the neurobiological profile of S-RCD, we hypothesized that we would see evidence for a typically developing O-P system in S-RCD, as reflected by normal processing on all word-like stimuli (both real words and pseudowords) in classic word recognition regions (left occipitotemporal/VWFA and supramarginal gyrus [SMG]). However, given the notion that low-frequency words place greater demands on lexical access due to impoverished lexical quality, we hypothesized that we would see areas of abnormality with low frequency words in S-RCD if their deficits affect the lexical-semantic quality (thus greater frequency differences in this group even if O-P processing is relatively intact), which would be consistent with behavioral findings reporting weaknesses in accessing semantic representations. Together, this pattern of findings would suggest an intact O-P system, but specific weaknesses in accessing semantic representations; such findings would be consistent with the LQH theory of poorer-quality semantic representations available during word recognition for S-RCD.

Methods and Materials

Participants

Fifty-one adolescents (mean age = 12.06 ± 1.26; range 10–14) met the eligibility criteria and participated in the study. Participants were recruited in the community via flyers, Websites, and school announcements [see (Locascio et al., 2010) for complete recruitment procedures; participants were a subset of individuals from this study]. All participants met the following inclusion criteria: (1) native English speakers; (2) normal hearing and vision; (3) no history of major psychiatric illness; (4) no history of traumatic brain injury/epilepsy; and (5) no contraindication to the MRI environment. In accordance with the Johns Hopkins Medical Institutional Review

Board, before joining the study, parents gave written consent, while a separate written assent was obtained from each child.

Eligible participants completed a comprehensive battery of standardized tests. As reported in Table 1, various standardized intellectual and academic achievement measures were selected for inclusion in this study (Delis et al., 2001; Dunn and Dunn, 1997; Kaplan et al., 1999; Karlsen and Gardner, 1995; MacGinitie et al., 2000; Newcomer, 2001; Newcomer and Hammill, 1997; Torgesen et al., 1999; Wechsler, 2003; Wiederholt and Bryant, 2000; Woodcock, 1998). Experimental tests of word and pseudoword-reading efficiency were also administered [a lexical decision measure (Olson et al., 1989) and a measure of naming words and pseudowords (Sabatini, 1998)]. All participants earned a standard score of at least 80 on Full Scale IQ, the Verbal Comprehension Index, and/or the Perceptual Reasoning Index of the Wechsler Intelligence Scales Children-III (Wechsler, 2003).

The criterion for DYS was a standard score at or below the 25th percentile rank on the Basic Reading Composite (BR) on the Woodcock Reading Mastery Test-Revised/Normative Update (WRMT-R/NU), which consists of real word reading (Word Identification) and pseudoword reading (word attack). The criterion for S-RCD was performance at or above the 37th percentile on BR, and at or below the 25th percentile on two of four reading comprehension measures; multiple measures of reading comprehension were used, given the well-known inconsistencies with using one measure [e.g., (Cutting and Scarborough, 2006)]. Similar to other S-RCD studies (Cain and Towse, 2008; Nation et al., 2010), the discrepancy between word-level abilities and reading comprehension was notable (mean of 14 standard score points), a pattern not evident for TD or DYS (see Table 1). The criterion for TD was a standard score at or above the 37th percentile on BR, and as well as on at least three out of the four of the reading comprehension measures. From the pool of eligible participants, 20 met criteria for DYS; 12 met criteria for S-RCD; and 19 were identified as TD. Two adolescents in each of the S-RCD and TD groups met our research diagnostic criteria for attention deficit hyperactivity disorder (ADHD) (see Locascio et al., 2010, for specific criteria, inclusion, and rationale for comorbid diagnoses, and greater details regarding medication), while six in the DYS group met the research criteria for ADHD; this difference was not statistically significant either in distribution or by the continuous measure of ADHD symptoms (provided in Table 1). Of the 10 individuals that were classified by the research criteria as ADHD, 5 had formal ADHD diagnoses, and three additional parents indicated that they did not have a formal diagnosis for their

Table 1. Behavioral Profiles for the Different Reader Groups (Means ± Standard Errors)

	TD	*S-RCD*	*DYS*
	Demographic and general intelligence measures		
Age	12.2 ± 0.3	11.6 ± 0.4	12.3 ± 0.3
Gender	9 M, 10 F	7 M, 5 F	15 M, 5 F
VCI-StS	119.0 ± 2.3[a]	97.3 ± 2.9	96.6 ± 2.2
PRI-StS	110.0 ± 2.7[a]	94.3 ± 3.4	98.1 ± 2.6
Conner's DSM-IV total scale-T	53.0 ± 2.8	53.8 ± 3.5	58.0 ± 2.7
	Word-level, language, and executive function measures		
LWID-StS	105.0 ± 1.6[b]	100.8 ± 2.0[b]	83.1 ± 1.6
WA-StS	105.1 ± 1.3[b]	104.3 ± 1.7[b]	85.4 ± 1.3
BR-StS	105.47 ± 1.6[b]	102.42 ± 1.97[b]	82.84 ± 1.56
TOWRE SWE-StS	106.0 ± 2.3[b]	97.1 ± 3.0[b]	84.4 ± 2.3
TOWRE PDE-StS	105.0 ± 2.3[b]	99.9 ± 2.9[b]	78.4 ± 2.3
PPVT-StS	118.5 ± 2.7[a]	100.9 ± 3.4	101.4 ± 2.7
TOLD-grammatical understanding-StS	112.5 ± 3.3[a]	96.7 ± 4.2	87.11 ± 3.33
Spatial span backward-StS	101.9 ± 3.3	94.1 ± 4.2	96.3 ± 3.1
Tower-StS	101.4 ± 2.4	95.9 ± 3.0	103.0 ± 2.2
Move accuracy ratio-StS	94.7 ± 3.4	85.5 ± 4.4	101.0 ± 3.3[d]
Rule violations per item ratio-StS	101.9 ± 0.8[e]	99.5 ± 1.0	99.0 ± 0.74
	Experimental measures		
LD (Olson)-RS	68.8 ± 2.0[b]	69.1 ± 2.3[b]	57.5 ± 2.1
SARA-RW naming-RS	71.3 ± 4.03[b]	71.3 ± 4.7[b]	55.3 ± 4.2
SARA-PW naming-RS	54.2 ± 3.2[b]	48.2 ± 3.7[b]	18.0 ± 3.3
	Standardized comprehension measures		
SDRT-StS	112.5 ± 2.92[a]	87.25 ± 3.68	87.58 ± 2.92
GM-StS	115.95 ± 3.17[a]	87.58 ± 3.98	84.63 ± 3.17
DAB-ScS	105.00 ± 3.14[a]	82.92 ± 3.95	83.95 ± 3.14
GORT Comp-StS	114.21 ± 2.81[a]	95.41 ± 3.54	92.63 ± 2.81
Average BR-reading comprehension difference	−6.45 ± 1.90	14.13 ± 2.39[c]	−3.8 ± 1.85

[a]TD > DYS and S-RCD, $p < 0.05$; [b]TD and S-RCD > DYS, $p < 0.05$; [c]S-RCD > TD and DYS, $p < 0.05$, [d]DYS > S-RCD, [e]TD > DYS.

StS, standard score or standard score equivalent; RS, raw score; T, T-score; VCI, verbal comprehension index; PRI, perceptual reasoning index; FSIQ, full-scale intelligence quotient; LWID, letter word identification (from WRMT-R/NU); WA, word attack (from WRMT-R/NU); BR, basic reading cluster (from WRMT-R/NU); TOWRE, test of word-reading efficiency; SWE, sight word efficiency; PWE, pseudoword efficiency; PPVT, pea body picture vocabulary test; LD (Olson), lexical decision; RW, real words; PW, pseudowords; GM, gates macginitie; DAB, diagnostic achievement battery; GORT, gray oral reading test; SDRT, Stanford diagnostic reading tests; TOLD, test of language development; DYS, dyslexia; S-RCD, specific reading comprehension deficits; TD, typically developing readers; WRMT-R/NU, woodcock reading mastery test—revised/normative update.

child, but concerns about ADHD had been raised. Children who were taking stimulant medications were asked to stop taking them the day before and during testing. Behavioral profiles can be found in Table 1. For all statistical comparisons of the behavioral tests, multivariate analysis of variance (MANOVA) were used, and all *post hoc* analyses were Sidak-corrected for multiple comparisons.

In addition to the standardized testing, parents completed a reading questionnaire. Four central questions were selected for inclusion in this study: (1) Have you ever been concerned about your child's reading ability? (2) Did your child have trouble learning how to sound-out words? (3) Has your child ever received tutoring specifically for reading? and (4) Does your child read on his/her own? Chi-square tests (Fisher's Exact Test) revealed significant differences for the first three questions for TD versus DYS (all ps < 0.003), but not for the last question ($p > 0.11$), suggesting that although parents of those with DYS reported that they had all the characteristics of struggling with reading, they still tend to read on their own. In contrast, for TD versus S-RCD, no statistically significant differences were observed for the first three questions ($p > 0.47$); however, there were statistically significant differences between groups for the last question ($p < 0.01$), suggesting that despite the absence of perceived reading difficulty in this group, S-RCD are less apt to read on their own than TD.

FMRI task

In the lexical decision task, participants viewed individual stimuli on the center of a screen and indicated by a button press whether the item was a real word (right index finger) or a pseudoword (left index finger). Words varied on the level of familiarity, with three categories of interest: pseudowords, high-frequency words, and low-frequency words. Word frequency was established via the Educator's Word Frequency Guide (Zeno et al., 1995), with high-frequency words having a standard frequency index (SFI) ≥ 60, and low-frequency words having an SFI of ≤ 49.9. Low- and high-frequency words were matched on length, abstract/concreteness, and regularity/irregularity. Mean concreteness rating was 441 (± 148) and 427 (± 158), respectively, for high- and low-frequency words, which was not statistically significant ($p = 0.57$). Regularity was determined by following the grapheme–phoneme conversion rules published in Rastle and Coltheart (1999) with an even division of regular and exception words across the high- and low-frequency categories (40 regular and 40 irregular in each category). Pseudowords were created by changing the first letter of similarly matched real monosyllabic words not used in the study. All word and pseudoword stimuli were matched on length. Before the MRI session, participants completed a mock scanning session in an MRI simulator.

This was an event-related design, with four separate runs, each consisting of 50 stimulus items. During each run, 80% of the items were real words, and 20% were pseudowords. Items were presented in a completely randomized order, with each stimulus appearing on the screen for 1500 ms, with a jittered interstimulus interval ranging in duration from 1000 ms to 3000 ms in which participants viewed a blank screen (fixation); three 10-sec rests were also included to provide a baseline. Participants viewed the paradigm via an LCD projector on a rear projection screen at the head of the scanner via a 45°-angled mirror affixed to the MRI head coil. E-Prime (Psychology Software Tools, Pittsburgh, PA) was used to present the task and record the timing of both stimulus presentations and participant responses.

MRI data acquisition

A 3.0 Tesla Philips Gyroscan NT (Philips Medical Systems, Andover, MA), equipped with a SENSE parallel imaging head coil (MRI Devices, Inc., Waukesha, WI), was used for scanning at the F.M. Kirby Research Center for Functional Braining Imaging at the Kennedy Krieger Institute in Baltimore, MD. For the fMRI task, BOLD signals were acquired using single-shot, gradient-recalled echo-planar images as follows: Axial acquisition geometry, FOV = 240 mm, 80×80 acquisition matrix, SENSE factor 2.5, TR = 2200 ms, TE = 30 ms, flip angle = 90°, 40 slices, 3-mm slice thickness, slice gap = 1 mm, aligned parallel to the line from the anterior to posterior commissures.

Image processing and data analysis

Statistical parametric mapping (SPM) using SPM8 software (www.fil.ion.ucl.ac.uk/spm) was used for postacquisition image processing and MatLab R2009b (Mathworks, Inc., Natick, MA) was used for all analyses. Images obtained from the scanner were converted to an NIfTI format, time-corrected, realigned, spatially normalized to the Montreal Neurological Institute (MNI)-labeled space, resampled into 2-mm^3 voxels, and smoothed using an 8-mm^3 Gaussian kernel. After smoothing, the data were then entered into Art-Repair (Mazaika et al., 2007) to detect and repair bad volumes; there were no group differences between those that were either deweighed [$F(2, 48) = 0.20$, $p = 0.82$] or repaired [$F(2, 48) = 0.03$, $p = 0.97$]. Task-associated brain activation was assessed using an event-related design, and SPMs were created corresponding with the time course for each condition of interest: high-frequency words, low-frequency words, and pseudowords. All responses, correct and incorrect together, were modeled. Voxel-wise contrast maps for each subject were carried to a second-level analysis to examine the within- and between-group effects.

As a first pass, SPMs for all stimuli collapsed were entered into separate one-sample t-tests for each group, and ANOVAs were used for group comparisons (restricted to significant regions associated with the main effect). SPMs were corrected for multiple comparisons ($p < 0.05$) using a cluster-based threshold procedure (uncorrected $p < 0.001$, extent = 34) based on Monte Carlo simulations run using AlphaSim (NIMH, Bethesda, MD; http://afni.nimh.nih.gov/pub/dist/doc/manual/AlphaSim.pdf). For the analyses in which an inclusive mask of the main effects was used, the masks were thresholded at uncorrected $p < 0.001$, extent = 34, and subsequent *post hoc* analyses for specific group comparisons were thresholded at $p < 0.005$, extent = 34. All local maxima of significant clusters were assigned neuroanatomic labels using Talairach Client. Note that we restricted analyses to supratentorial regions.

Region-of-interest analyses. To examine more fine-grained distinctions in neural activity associated with the lexical decision task, region-of-interest (ROI) analyses were utilized. Four key reading-related regions taken from previous literature were investigated: inferior frontal gyrus (IFG;

BA 44), angular gyrus (AG), SMG, and several specific areas within the occipitotemporal cortex (OT). The IFG and SMG were defined by 6-mm spheres centered on MNI coordinates (IFG: $x = \pm 57$, $y = 12$, $z = 16$; SMG: $x = \pm 42$, $y = -44$, $z = 40$). For the OT, we used a series of five posterior-to-anterior 6-mm sphere ROIs based on previous literature (Brem et al., 2006; van der Mark et al., 2009): $x = \pm 42$, y = range from −30 to −80, z = range from −14 to −20. The AG was defined via predefined masks within PickAtlas (Maldjian et al., 2003). The percent signal change was extracted using Marsbar (Brett et al., 2002) from each cluster and were analyzed using IBM SPSS Statistics for Windows, Version 20.0 (SPSS) with separate mixed analysis of covariance (ANCOVA) for condition (2: high- and low-frequency words) and hemisphere (2: right, left) as within-subject factors, and group (3: TD, S-RCD, and DYS) as a between-subject factor. Given the small number of pseudoword stimuli and small ratio of pseudoword to word stimuli, separate exploratory analyses were conducted with the pseudowords in SPSS using mixed-ANCOVAs with hemisphere (right, left) as a within-subject factor and group (TD, S-RCD, and DYS) as a between-subject factor.

Psychophysiological interaction analyses. Psychophysiological interaction (PPI) analyses are used to examine whether the correlation in activity between brain areas is different during differential psychological contexts (Friston et al., 1997) using a design matrix that consists of three regressors: the psychological variable, the physiological variable, and the interaction term of the psychological and physiological variables. In the current experiment, for each participant, these three terms were entered into a general linear model (GLM) as regressors. A contrast image was generated for the interaction term to examine the whole-brain activation influenced by the seed ROI. At the second level, one-sample *t*-tests, and group comparisons were conducted. SPMs were corrected for multiple comparisons using the previously described cluster-based threshold (uncorrected $p < 0.001$, extent = 34). It was decided that, *a priori*, given our specific focus on S-RCD, the seed regions for PPI analyses for all groups (TD, DYS, and S-RCD) would be selected from the ROIs that showed an anomalous BOLD signal (percent signal change) for S-RCD as compared to TD.

Results

For all analyses, within-subject factors were corrected for nonsphericity using Greenhouse–Geisser probabilities, and *post hoc* analyses were Sidak-corrected for multiple comparisons; simple-effect contrasts were used for determining the origin of any significant main effect of diagnosis. Note that nonsignificant main effects and interactions are not reported.

FMRI behavioral task performance

Given the ratio of words to pseudowords (80–20), a nonparametric measure of sensitivity was calculated (A′). Values for A′ range from 0 to 1, with 1 indicating perfect sensitivity. Across all participants*, the average A′ value for high-frequency words was 0.95 (±0.06), with A′ values of 0.97 (±0.02), 0.92 (±0.08), and 0.95 (±0.03) for the TD, DYS, and S-RCD groups, respectively. However, the average A′ value for low-frequency words was 0.81 (±0.10), with A′ values of 0.90 (±0.05), 0.76 (±0.09), and 0.78 (±0.11) for the TD, DYS, and S-RCD groups, respectively. Differences among groups for A′ values showed that DYS had lower A′ values for high-frequency words as compared to TD ($p < 0.03$), and both the DYS and S-RCD had lower A′ values for low-frequency words as compared to TD ($p < 0.003$). While there were no group differences among the reaction times, analyses showed that there were differences in the reaction time across the different word types, with high-frequency words showing the fastest reaction time (851.14 ± 16.36), followed by low-frequency words (984.37 ± 12.74), and finally pseudowords (1000.53 ± 14.22, all ps < 0.05).

FMRI whole-brain results

Across all groups, significant activity for all stimuli collapsed was seen in regions traditionally associated with the processing of visual words, including bilateral extrastriate (BA 18/19) as well as fusiform gyri (left only for TD). As expected, activity in motor preparation and response areas was seen across groups (i.e., supplementary motor area, cingulate gyrus, and postcentral gyrus). Moreover, across groups, there was activity in the frontal cortex: TD and DYS had activity in bilateral IFG (BA 47) and insula, and S-RCD showed activity only in left IFG (BA 44/45) and insula. Additional activation was seen for TD in the left superior temporal gyrus (BA 20/38) and the bilateral inferior parietal lobe (BA 40); in the left inferior parietal lobe (BA 40) for S-RCD; and for DYS right putamen and caudate, as well as the left inferior parietal lobe (BA 40) (see one-sample *t*-tests in Figure 1).

In group comparisons, significance between group differences was observed (Table 2). Notably, both TD and S-RCD showed greater activity in left OT regions than DYS. In contrast, few differences were observed between TD and S-RCD, with the exception of TD showing greater activity bilaterally in visual areas (BA 17 and 18). While the TD > DYS results were expected, the S-RCD > DYS results were similar to TD > DYS. These findings, along with few differences observed between S-RCD and TD, suggested that at least at the whole-brain level, the S-RCD response to word stimuli was normal (see Fig. 1 and Table 2).

FMRI ROI results: high- and low-frequency words

For the first OT ROI, there was a significant difference for Type, $F(1, 48) = 10.35$, $p = 0.002$ ($\eta_p^2 = 0.18$), with an increase in the percent signal change for low-frequency words as compared to high-frequency words. For the second OT ROI, there was a significant difference among groups, $F(2, 48) = 3.62$, $p = 0.034$ ($\eta_p^2 = 0.13$), with TD and S-RCD both showing greater activity than DYS ($p < 0.04$), which were not significantly different from each other ($p = 0.99$). There was also a significant main effect of Type, $F(1, 48) = 5.88$, $p = 0.019$ ($\eta_p^2 = 0.11$), with low-frequency words showing a greater percent signal change than high-frequency words, as well as a significant main effect of Side, $F(1, 48) = 5.06$, $p = 0.029$ ($\eta_p^2 = 0.10$), with an increased signal change in left versus right. For the third OT ROI, there was a marginally significant difference among groups, $F(2, 48) = 2.56$, $p = 0.09$ ($\eta_p^2 = 0.10$); the results of simple-effect contrasts were also marginally significant with both TD and S-RCD showing a

*Three participants (one S-RCD and two TDs) had missing data due to hardware problems.

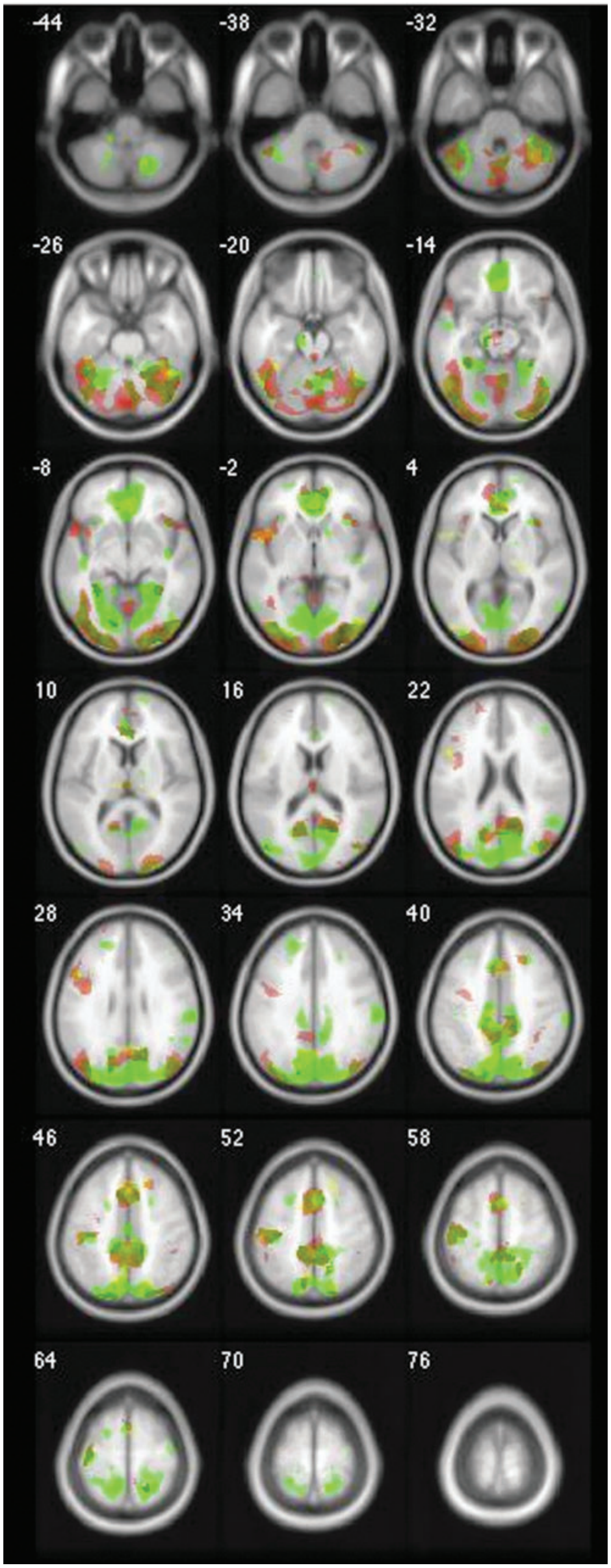

FIG. 1. Whole-brain results. Activity for TD is in red; activity for the S-RCD group is in yellow; and activity for the DYS group is in green. Images are presented in neurological convention (L = L), $p < 0.001$, k = 34. DYS, dyslexia; S-RCD, specific reading comprehension deficits; TD, typically developing readers.

higher percent signal change than DYS ($p < 0.07$); the TD and S-RCD comparison yielded a $p = 0.75$. Additionally, there was a significant main effect of Side, $F(1, 48) = 12.37$, $p = 0.001$ ($\eta_p^2 = 0.21$), with a greater percent signal change for left versus right. For the fourth OT ROI, there was a significant difference among groups, $F(2, 48) = 3.41$, $p = 0.041$ ($\eta_p^2 = 0.13$), with TDs and S-RCDs showing greater activity than DYS ($p < 0.04$), but the TD and S-RCD comparison was not significant ($p = 0.93$). There were also significant main effects for Side, $F(1, 48) = 23.53$, $p < 0.001$ ($\eta_p^2 = 0.33$), with a greater percent signal change for the left versus right side. For the fifth OT ROI, the main effects for Side were significant, $F(1, 48) = 12.21$, $p = 0.001$ ($\eta_p^2 = 0.20$), with a greater percent signal change for left versus right side. Taken altogether, these findings were consistent with the whole-brain analyses, revealing the expected patterns for TD as compared to DYS, that is, a higher signal response for processing words (see Fig. 2). S-RCDs showed BOLD signal changes in the central OT ROIs that are sometimes referred to as the Visual Word Form Area (VWFA); notably, S-RCD signal was significantly higher than DYS and similar to TD.

For AG and SMG, there were no significant main effects or interactions (all ps > 0.14), with the exception of Type for AG, which approached significance $F(1, 48) = 3.59$, $p = 0.06$ ($\eta_p^2 = 0.07$), with low-frequency words showing greater deactivation than high-frequency words.

For IFG, the side × group × condition interaction was significant, $F(2, 48) = 5.88$, $p = 0.005$ ($\eta_p^2 = 0.20$). *Post hoc* analyses revealed that differences were driven by the TD group showing significantly lower right hemisphere activity for high- as compared to low-frequency words ($p < 0.001$), whereas S-RCD showed a greater left- than right-hemisphere activity for low-frequency words. In contrast, DYS did not show hemispheric differences between word types (see Fig. 2). Taken together, these results suggest that both DYS and S-RCD show anomalies in IFG in terms of differential processing low-versus-high-frequency words in IFG.

FMRI ROI results: pseudowords

Exploratory analyses of pseudowords (as compared to baseline fixation) revealed similar patterns in the OT. For the first OT ROI, there was no significant difference among groups, or any other significant main effects or interactions (all ps > 0.24). For the second OT ROI, there was a significant difference among groups, $F(2, 48) = 4.06$, $p = 0.024$ ($\eta_p^2 = 0.15$), with TD showing greater activity than DYS ($p = 0.008$), and the S-RCD showing marginally significantly greater activity than DYS ($p = 0.08$), with no difference between TD and S-RCD ($p = 0.51$). There were also significant main effects for Side, $(1, 48) = 6.45$, $p = 0.014$ ($\eta_p^2 = 0.12$), with greater percent signal change for left versus right side. For the third OT ROI, there was a significant main effect of group, $F(2, 48) = 3.60$, $p = 0.035$ ($\eta_p^2 = 0.13$), with TD showing greater activity than DYS ($p = 0.01$), and no significant differences between S-RCD and DYS ($p = 0.15$) and S-RCD and TD ($p = 0.40$). For the fourth OT ROI, there again was a significant difference among groups, $F(2, 48) = 4.26$, $p = 0.02$ ($\eta_p^2 = 0.15$), with TD showing greater activity than DYS ($p = 0.006$), and the S-RCD showing marginally significantly greater activity than DYS ($p = 0.08$) and no significant differences from TD ($p = 0.49$). There were also significant main effects for side,

Table 2. Whole-Brain Analyses: GLM Group Comparisons

X coor	Y coor	Z coor	Peak T statistic	Cluster size	Side	Location	BA
TD > DYS							
−5	−95	11	5.14	532	Left	Cuneus	BA 18
6	−93	−8	4.56	532	Right	Lingual gyrus	BA 18
−14	−83	7	4.50	532	Left	Cuneus	BA 17
−55	−57	−9	4.87	100	Left	Inferior temporal gyrus	BA 37
−57	−54	2	4.60	100	Left	Middle temporal gyrus	BA 21
−16	−58	−1	4.79	470	Left	Lingual gyrus	BA 19
−36	−67	−19	4.59	470	Left	Fusiform gyrus	BA 19
−25	−75	−14	4.49	470	Left	Fusiform gyrus	BA 19
−43	−38	−24	4.38	66	Left	Fusiform gyrus	BA 36
8	−69	14	4.32	34	Right	Cuneus	BA 18
6	−62	0	4.28	35	Right	Lingual gyrus	BA 18
−33	22	31	4.20	119	Left	Middle frontal gyrus	BA 9
−44	16	36	4.17	119	Left	Middle frontal gyrus	BA 9
S-RCD > DYS							
−35	24	35	4.66	103	Left	Middle frontal gyrus	BA 9
−15	0	49	4.55	46	Left	Cingulate gyrus	BA 24
−22	−8	48	3.97	46	Left	Middle frontal gyrus	BA 6
−27	−73	−16	3.75	105	Left	Fusiform gyrus	BA 19
−40	−63	−19	3.27	105	Left	Fusiform gyrus	BA 37
−47	−44	−22	3.50	36	Left	Fusiform gyrus	BA 37
TD > S-RCD							
6	−95	−6	3.80	46	Right	Lingual gyrus	BA 18
−16	−83	7	3.32	44	Left	Cuneus	BA 17

BA, Brodmann area.

$F(1, 48) = 31.76$, $p < 0.001$ ($\eta_p^2 = 0.40$), with a greater percent signal change for left versus right side. For the fifth OT ROI, there were significant main effects for side $F(1, 48) = 4.87$, $p = 0.032$ ($\eta_p^2 = 0.09$), with a greater percent signal change for left versus right side. Taken altogether, these findings are consistent with the whole-brain analyses and main ROI analyses, revealing the general similar patterns of TD and S-RCD showing a higher signal response than DYS (see Supplementary Figure S1; Supplementary Data are available online at www.liebertpub.com/brain) for results for the five OT ROIs.

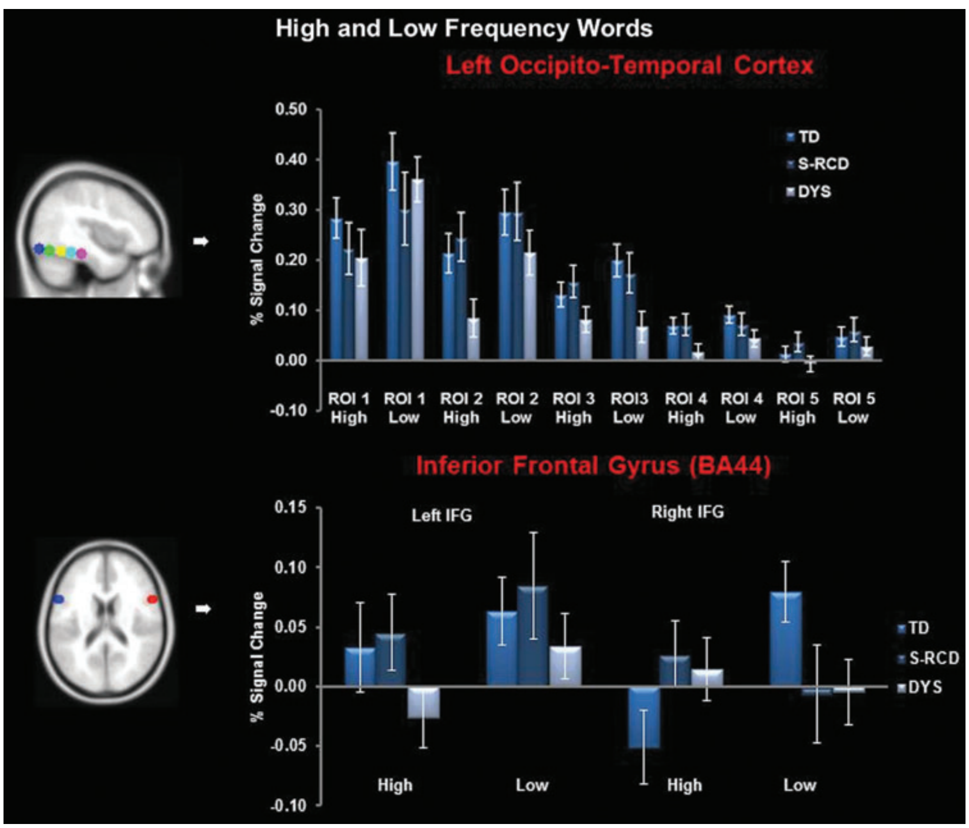

FIG. 2. ROI percent signal change for occipitotemporal cortex ROIs and IFG (BA 44) for high- and low-frequency words. IFG, inferior frontal gyrus; ROI, region of interest.

For the SMG, there was a significant difference among groups, $F(2, 48)=3.8$, $p=0.029$ ($\eta_p{}^2=0.14$), with TDs and S-RCD both showing greater activity than DYS ($p<0.031$), with the TD and S-RCD comparison not significant ($p=0.62$). No other main effects or interactions were significant (see Supplementary Figure S1).

For the AG, there was a significant group × side interaction, $F(2, 48)=3.9$, $p=0.027$ ($\eta_p{}^2=0.14$). Follow-up *post hoc* tests revealed that the S-RCD showed significantly greater deactivation on the left as compared to the right ($p=0.047$), whereas the same was not true for the TD and DYS groups ($p>0.12$) (see Supplementary Figure S1). No other main effects or interactions were significant.

For IFG, there were no significant main effects or interactions (all ps >0.19).

Psychophysiological interaction

PPI analyses using IFG (low- versus high-frequency words) as a seed region were conducted. Additionally, exploratory PPI analyses using AG (using pseudowords as compared to baseline fixation) as a seed region were conducted.

Results of the PPI analyses with right and left IFG as seed regions when processing low- versus high-frequency stimuli revealed a coactivation-by-reading group interaction for the S-RCD group as compared to TD (see Table 3 and Fig. 3). This context-dependent functional interaction was indicated by a widespread greater covariance between left IFG and a variety of subcortical and cortical regions, including left parahippocampal and hippocampal gyri, right thalamus, right putamen, and right middle frontal gyrus for S-RCD as compared to TD. In contrast, for DYS, the context-dependent functional interaction anomaly was most prominently seen in right IFG, as indicated by a widespread greater covariance between right IFG and right OT/VWFA areas, as well as bilateral medial frontal gyrus, as compared to TD.

Exploratory PPI analyses in AG revealed that DYS showed anomalous connectivity to right-hemisphere language homologs as compared to both the S-RCD and TD groups for pseudowords as compared to baseline. These findings were evident in both right and left AG, with right AG connectivity showing almost the identical area of anomalous connectivity in right middle/superior temporal gyri for DYS > TD and the DYS > S-RCD. Additionally, in right AG, TD showed greater connectivity than S-RCD for pseudowords than baseline to anterior and posterior cingulate regions (see Supplementary Table S1 and Supplementary Fig. S2).

Discussion

This study was designed to examine the neurobiology associated with word reading in adolescents with S-RCD, and how their patterns of neural activity compared to TD and those with DYS. Participants completed an fMRI lexical decision task that varied in word frequency, thus placing demands on lexical access to varying degrees. Overall, we hypothesized that we would see abnormalities in DYS as compared to TD in key left-hemisphere-reading regions. When examining patterns of activity for S-RCD, we hypothesized that, overall, we would see patterns of activity more analogous to TD than DYS, as S-RCD are characterized by the preservation of word-reading skills behaviorally. However, we hypothesized that when stimuli were broken into more fine-grained categories, differences would emerge. Specifically, consistent with the LQH, we hypothesized that we would continue to see evidence for a typically developing O-P system in S-RCD, as reflected by normal processing on all word and pseudoword stimuli in classic word recognition regions (left occipitotemporal/VWFA and SMG). However, we hypothesized that when stimuli placed greater demands upon lexical-semantic coding for accessing the representation for low frequency words, anomalies in other regions would be revealed due to lexical quality problems at the semantic level in this group.

Consistent with our hypotheses, findings revealed that overall TD and S-RCD showed comparable activity and had significantly greater activity than DYS in the typical reading-related regions, including OT, as seen by the results of the whole-brain analyses. Therefore, these whole-brain analyses indicated that in general, the source of reading comprehension deficits in S-RCD is not consistent with a

Table 3. Psychophysiological Interaction Group Comparisons of Low Versus High Words: Inferior Frontal Gyrus (BA 44)

X coor	*Y coor*	*Z coor*	*Peak T statistics*	*Cluster Size*	*Side*	*Location*	*BA*
Left DYS > TD							
−20	11	9	4.12	41	Left	Putamen	N/A
Left S-RCD > DYS							
19	−22	17	4.25	80	Right	Thalamus/lateral Posterior nucleus	N/A
Left S-RCD > TD							
−31	−21	−7	4.05	49	Left	Parahippocampal Gyrus/hippocampus	N/A
19	−18	19	3.9	158	Right	Thalamus	N/A
30	−14	11	3.17	158	Right	Putamen	N/A
19	−13	59	3.47	53	Right	Middle frontal gyrus	BA 6
24	−11	54	3.45	53	Right	Middle frontal gyrus	BA 6
Right DYS > TD							
36	−43	−3	4.10	52	Right	Fusiform/visual word form area	BA 19
36	−36	−8	3.91	52	Right	Fusiform/visual word form area	BA 36
−10	54	34	3.70	47	Left	Superior frontal gyrus	BA 9
3	54	31	3.67	57	Right	Superior frontal gyrus	BA 9

N/A, no cytoarchitectonic designation applicable.

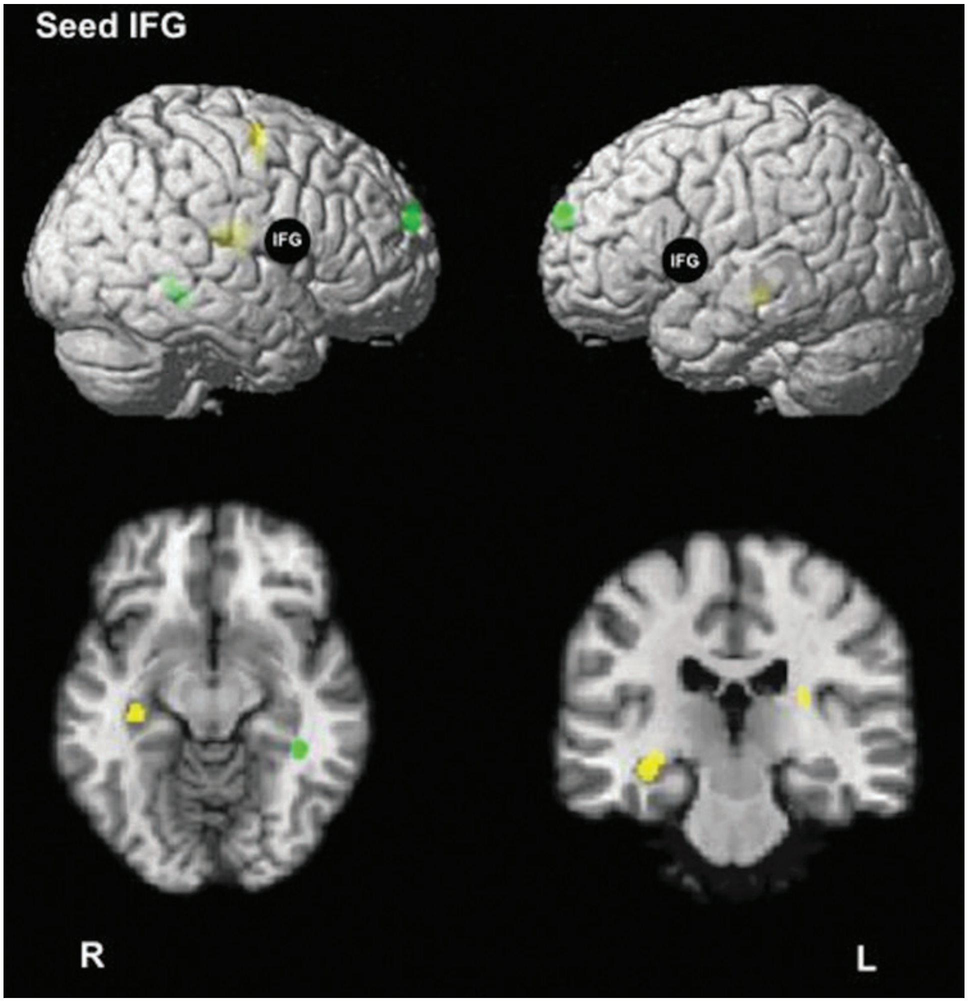

FIG. 3. Schematic summary of psychophysiological interaction analyses for low- versus high-frequency words in IFG (BA44). Activity for the DYS > TD contrast is in green, and activity for the S-RCD > TD contrast is in yellow. Activity in left IFG specifically increased its coupling for low- versus high-frequency words with hippocampus/ parahippocampus in the S-RCD group as compared to TD (see activation in yellow in coronal and axial slices). In contrast, activity in right IFG specifically increased its coupling for low- versus high-frequency words with right visual word-form area in the DYS group as compared to TD (see axial slice). Images are presented in neurological convention (L = L), $p < 0.001$, k = 34.

gross abnormality in word-level decoding skills, such as those that characterize DYS. Nevertheless, our whole-brain analyses, while important, could not comprehensively answer whether S-RCD may show subtle anomalies in specific regions for more difficult-to-process words, such as low-frequency words. The investigation of these questions was more suited to using ROI analyses in well-established reading-related regions [i.e., occipitotemporal, inferior frontal, and temporoparietal (angular and supramarginal) cortices (Pugh et al., 2000a; Richlan, 2012)].

The first area we examined was OT, which is associated with fast and efficient word processing (Dehaene and Cohen, 2011). This region, therefore, should be the most critical in terms of examining whether weaknesses are present in S-RCD that have to do with processing words quickly and efficiently, or the system supporting orthographic–phonological representations (O-P). In all comparisons, we saw reliable increases in the BOLD signal for both TD and S-RCD as compared to DYS, and no statistically significant differences between TD and S-RCD, thus supporting our hypothesis that the behavioral studies showing a normal O-P system in S-RCD would also be reflected neurobiologically. Specifically, progression along the posterior-to-anterior gradient revealed that TD and S-RCD both showed significantly greater BOLD signal than DYS for words, but no difference was found between TD and S-RCD; evidence for this same pattern was found with the pseudoword stimuli as well. This finding is not only consistent with previous DYS findings showing reduced OT activation, but also indicates that the fast and efficient reading observed behaviorally in S-RCD is also reflected neurobiologically. Consistent with our OT results were findings in SMG, a region where anomalous activation is typically seen in DYS and is thought to be important for phonological aspects of word processing (Richlan et al., 2011; Richlan et al., 2009). Here our exploratory analyses with our purest O-P stimuli, pseudowords, revealed that both TD and S-RCD showed a significantly higher BOLD signal than DYS in SMG, with no significant differences between TD and S-RCD, thus providing additional evidence that the central O-P neural systems known to be problematic for DYS are intact for S-RCD.

Results for S-RCD, however, became less clear-cut within other reading-related regions, suggesting that S-RCD do not have completely intact word recognition neural systems. Within IFG, a different pattern in neural responses began to emerge among high- and low-frequency word types. IFG (BA 44) is typically associated with phonological processing, while BA 45/47 is often linked with semantics; however, BA 44 has been additionally associated with semantic retrieval (Badre and Wagner, 2002) as well as selection and cognitive control during semantic tasks (Heim et al., 2009; Huang et al., 2012). In particular, Price et al. (2012) have noted in their recent synthesis of language and reading that BA 44 has been associated with strategic/executive/control processes that are required to access, retrieve, compare, and manipulate semantic knowledge (p. 11), as well as short-term memory. Given the executive function weaknesses in S-RCD (Locascio et al., 2010), these strategic executive processes in semantics may prove to be an important component in future studies for further understanding the anomalies found in the present study. In addition to BOLD anomalies for S-RCD in IFG, PPI analyses for low- versus high-frequency words revealed abnormal context-dependent functional interactions for between IFG and hippocampal and parahippocampal regions, as well as prefrontal regions (BA 6); these same anomalous patterns were not present when the DYS group was compared to TD. In contrast, the DYS group generally showed context-dependent connectivity anomalies from IFG to right-hemisphere homologs of left-hemisphere language circuits. These findings are consistent with previous reports in DYS (Stanberry et al., 2006). Therefore, our findings suggest that connectivity abnormalities related to modulation associated with the frequency of words in DYS are more constrained to contralateral regions homologous to left language regions, versus entirely different areas of the brain.

The fact that hippocampal and parahippocampal involvement is present in S-RCD suggests that this group may have anomalies in connections between basic language-related areas (BA 44) and declarative memory systems. This finding is not altogether surprising when considered in light of the fact that S-RCD show semantic deficits, which presumably would be intimately related to the declarative memory systems. Hippocampal and parahippocampal regions have been largely implicated in the encoding and subsequent retrieval of episodic and semantic memories (Eichenbaum, 2000; Moscovitch et al., 2005), which may support the supposition that S-RCD have deficits in declarative (semantic) memory systems, or a deficit in the lexical quality of semantic representations (Perfetti et al., 2007). Furthermore, linkages between IFG and hippocampal regions as related to semantic retrieval have been shown (Burianova et al., 2010, although in this study, the part of IFG linked to hippocampal regions was BA 47, not BA 44) thus providing a basis for the IFG–hippocampal link as related to semantics. One theory of memory formation posits that hippocampal and parahippocampal structures are needed in the early stages of memory formation, and once the memory is consolidated, it is then represented in cortical structures (Moscovitch et al., 2005). Although certainly highly speculative at this time, it could be that S-RCD may have difficulty with the consolidation of memory in cortical structures. Perhaps, it is the transition from encoding to a fully consolidated semantic memory that is problematic for S-RCD; alternatively, S-RCD may utilize IFG–hippocampal connections as a compensatory mechanism. The origin of these deficits and how they may relate to the other deficits observed in S-RCD (e.g., executive function) could be an interesting line of further inquiry, especially given the prefrontal abnormalities in connectivity that were observed as well. Interestingly, it has been proposed that DYS show deficits in procedural learning/memory (Preston et al., 2010), suggesting that S-RCD and DYS may represent a double disassociation across types of RD.

For the AG exploratory analyses with pseudowords, both DYS and S-RCD showed anomalies as compared to TD. Consistent with previous findings in DYS, our whole brain analysis showed anomalous functional connectivity between AG and brain regions traditionally associated with word stimuli (Pugh et al., 2000b). Specifically, DYS showed greater connectivity between left AG and right-hemisphere homologs of language-related brain regions than TD. However, while S-RCD, as compared to TD, did show atypical left-hemisphere BOLD deactivations in AG to pseudowords in ROI analyses, functional connectivity to the AG region was not different from TD. This suggests that, while AG may be recruited in an anomalous fashion for S-RCD, these anomalies do not necessarily reflect systemic abnormalities in co-activation of language-related regions during O-P processes. If we interpret the atypical functional connectivity in DYS as reflecting O-P deficits, the findings suggest that something other than O-P deficits underlie AG anomalies observed in S-RCD.

One could speculate further on a possible connection between this pattern of S-RCD findings to proposed semantic skills differences between S-RCD and TD. In the resting state fMRI literature, one hypothesis is that un-directed semantic activity (i.e., random thought) underlies the unevoked co-activation of a default mode network of brain regions that includes the left AG (e.g., Binder et al., 1999; Binder and Desai, 2011; Seghier et al., 2010). In this framework, the historically somewhat puzzling findings of BOLD deactivations associated with cognitive tasks during fMRI experiments can be explained by the interruption of this spontaneous default mode "semantic activity" in order to accomplish the specific cognitive task. Following this logic, perhaps S-RCD findings of atypical BOLD response correspond to an atypical semantic system that accomplishes word identification in the absence of semantic context, i.e., pseudowords, differently than TD.

Although our hypothesis regarding weaknesses in lexical-semantic representation appears to be supported, it is important to explore other potential explanations for our findings. The most obvious one is that S-RCD could be reflective of readers who are simply compensated DYS—that is, at one time, they showed weaknesses in word recognition skills, but have compensated enough to behaviorally read quickly and efficiently at the word-level but still show neurobiological abnormalities. While it is true that S-RCD showed neurobiological anomalies, they were not very similar to often-seen DYS patterns. If S-RCD had weak neural systems stemming from similar vulnerabilities as DYS, then one would expect abnormalities in regions that support the O-P system including OT regions and, perhaps less so, other regions thought to be associated with beginning reading (SMG, AG, and IFG). In fact, we saw the opposite—OT regions, which are a hallmark area of abnormality in DYS, showed *normal* levels of BOLD signal. One could postulate that the IFG abnormalities were compensatory in nature for S-RCD, as has been suggested in previous research with DYS (Hoeft et al., 2011); however, the fact that these abnormalities were confined to low-frequency words, were not present with pseudowords (a hallmark sign of DYS), and showed strikingly different patterns of connectivity suggests that the supposition that S-RCD is reflective of compensated DYS cannot be supported within the present study. It is also important to mention that even though both RD groups showed similar levels of verbal abilities behaviorally (Verbal IQ), only the S-RCD group showed IFG–hippocampal connectivity differences, suggesting that the abnormalities were not simply reflective of lower verbal abilities and were specific to S-RCD. Finally, the findings of the reading questionnaire also did not support a pattern suggesting compensated DYS. The questionnaire included questions about whether parents had ever been concerned about reading development, whether their child ever had trouble sounding out words, and whether their child had ever received tutoring. All of these questions were not significantly different between the S-RCD and TD group, while they were between the TD and DYS group, thus providing further suggestion that S-RCD are not simply compensated DYS.

Overall, our findings suggest that although the behavioral profiles of individuals with S-RCD are marked by the relative preservation of word-level skills related to the O-P aspect of the LQH, subtle abnormalities, which may be caused by impoverished lexical-semantic representations despite intact O-P, may be present when increased demands are placed on lexical access. These findings suggest that along with other weaknesses in their behavioral profile (e.g., executive function), the lexical-semantic representation aspect of word recognition posited by the LQH may not be neurobiologically intact for S-RCD. It is important to highlight that the causal mechanisms of any weaknesses in lexical access/semantic representations in S-RCD are in no way definitive: whether the anomalies are consequences or the cause of the disorder is not clear at this time. In particular, S-RCD were reported to read less on their own than TD, which is consistent with other reports (Cain and Oakhill, 2011). Whether their vocabulary weaknesses are a result of not reading (i.e., so called Matthew Effects) and/or whether the reason is neurobiological in genesis is not clear, and will need experimental versus the descriptive research presented in the present study, to disentangle.

In sum, while an extensive literature exists on the neurobiological correlates of DYS, our study is the first to examine the neurobiological profile of individuals with S-RCD. While future studies could benefit from larger sample sizes, more closely matched groups on IQ, particularly Verbal IQ, and paradigms that more directly capture semantic processing versus phonological processing/decoding (including those that exclude incorrect in-magnet trials and account for bigram frequency), our novel finding provides foundational insights into the nature of S-RCD, and sets the stage for future investigations of this common, but understudied, reading disorder. Specifically, findings reveal that S-RCD show a unique pattern of abnormalities in context-dependent (i.e., processing low versus high frequency words) connectivity to specific regions; this includes those neural systems involved in declarative memory and higher-level processing. Finding neurobiological correlates related to semantics is in line with previous behavioral findings in S-RCD. This is also consistent with what would be predicted by the LQH; namely, even though O-P connections are intact, if lexical-semantic representations are not, poor lexical quality will result. Future investigations should further examine structural connectivity and utilize experimental paradigms that manipulate semantics more directly in this poor reader group, as well as examine other sources of abnormality seen in S-RCD (e.g., executive function) to better elucidate the neurobiological correlates of the reading comprehension weaknesses in S-RCD.

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Author Disclosure Statement

The authors declare no conflicts of interest.

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