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Anomalous Gray Matter Patterns in Specific Reading Comprehension Deficits are Independent of Dyslexia

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Abstract

Specific reading comprehension deficits (SRCD) affects up to 10% of all children. SRCD is distinct from dyslexia (DYS) in that individuals with SRCD show poor comprehension despite adequate decoding skills. Despite its prevalence and considerable behavioral research, there is not yet a unified cognitive explanation of SRCD. While its neuroanatomical basis is unknown, SRCD could be anomalous in regions subserving their commonly reported cognitive weaknesses in semantic processing and/or executive function. Here we investigated, for the first time, patterns of gray matter volume difference in SRCD as compared to DYS and typical developing (TD) adolescent readers (N=41). A linear support vector machine algorithm was applied to whole brain gray matter volumes generated through voxel-based morphometry. As expected, analyses revealed that DYS differed significantly from TD in a pattern that included features from left fusiform and supramarginal gyri (DYS vs. TD: 80.0%, $p < 0.01$). SRCD was well differentiated not only from TD (92.5%, $p < 0.001$) but also from DYS (88.0%, $p < 0.001$). Of particular interest were findings of reduced gray matter volume in right frontal areas that were also supported by univariate analysis. These areas are thought to subserve executive processes relevant for reading, such as monitoring and manipulating mental representations. Thus, preliminary analyses suggest that SRCD readers possess a distinct neural profile compared to both TD and DYS readers and that these differences might be linked to domain-general abilities. This work provides a foundation for further investigation into variants of reading disability beyond DYS.

Keywords

magnetic resonance imaging; specific reading comprehension deficits; reading skill; voxel-based morphometry; multivariate pattern analysis

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Introduction

Nearly 1 in 3 fourth grade children in the United States have "below basic" reading comprehension skills (National Assessment of Educational Progress, 2013). One cause is impaired decoding, the ability to sound out words from letters, which in turn impedes reading comprehension (Hoover and Gough, 1990). This type of reading disability is often referred to as dyslexia (DYS) and affects 10–15% of children (Kirby and Savage, 2008). However, decoding problems do not explain poor reading comprehension in all individuals. Up to 10% of children have adequate word recognition skills yet fail to comprehend text (Aaron et al., 1999, Catts et al., 2003, Cutting et al., 2013, Leach et al., 2003, Locascio et al., 2010, Nation et al., 2004, Torppa et al., 2007), i.e. they have a specific reading comprehension deficit (SRCD). SRCD has received less attention from researchers than DYS, especially in terms of neurobiological studies, and a unifying cognitive profile is still under active investigation (Cain and Oakhill, 2006). SRCD is an impediment particularly in middle and later grades as children rely more on independent reading for content knowledge (Locascio et al., 2010, Snowling and Hulme, 2012).

Skilled reading comprehension requires the integration of language-specific skills (phonological processing, semantics and syntax) and domain-general executive function (EF) abilities (working memory, self-monitoring, and response inhibition) to generate a coherent representation of the text (Cutting and Scarborough, 2006, Daneman and Merikle, 1996, Gough and Tunmer, 1986, Kirby and Savage, 2008). Research on SRCD has implicated both language-specific skills and general cognitive abilities. For example, Nation and Snowling showed that individuals with SRCD are less sensitive to semantic information in semantic priming tasks than typically developing (TD) readers but perform similarly to them on a rhyme judgment task (Nation and Snowling, 1998, Nation et al., 1999). This suggests that while SRCD readers may have intact phonological representations of words, their semantic representations may not be as rich. A more recent large-scale analysis by Spencer, Quinn & Wagner is consistent with previous findings, revealing that most children with SRCD have weaker vocabularies than their TD counterparts (Spencer et al., 2014). These findings suggest that SRCD may arise from difficulty linking lexical to semantic information at the single-word level, despite intact mapping of orthography to phonology, which is impaired in DYS (Perfetti, 2007).

Poor comprehension in SRCD has also been linked to weaker EF abilities, such as working memory and response inhibition. EF has been shown to uniquely predict reading comprehension ability after accounting for oral language and decoding (Savage et al., 2006, Sesma et al., 2009), and deficits in EF have been reported in both DYS and SRCD (Lee Swanson, 2003, Locascio et al., 2010, Pimperton and Nation, 2010, Reiter et al., 2005). In one study, Cain found that many SRCD readers have poorer working memory than TD readers and are also less efficient at prioritizing information; that is, individuals with SRCD were more likely to recall material that was not relevant to overall text meaning than TD readers (Cain and Oakhill, 2006). Others have suggested that EF deficits in SRCD could be tied to the language domain, becoming more exacerbated with more complex language demands (Eason et al., 2012, Pimperton and Nation, 2010). Thus, the question of whether

SRCD arises primarily from language deficits, cognitive deficits, or both is still a matter of investigation.

Magnetic resonance imaging (MRI) has helped disentangle the neurocognitive differences in individuals with reading difficulties, particularly DYS. Studies have shown that poor fluent reading is marked by abnormal functioning in occipito-temporal cortex (Gabrieli, 2009, McCandliss and Noble, 2003). Whole-brain voxel-based morphometry (VBM) is one of the most widely used techniques for comparing brain structure between individuals. Although the exact source of VBM signal has not been identified, it has been linked to microstructural properties of the brain, such as neuronal size, cortical folding and dendritic arborization (Mechelli et al., 2005). Previous research has used VBM to characterize DYS, identifying deficit-related differences in brain areas associated with fast and efficient word and letter recognition (occipito-temporal cortex), phonological processing (temporo-parietal cortex) and the cerebellum (Linkersdörfer et al., 2012).

While the evidence suggests a specific neurobiological signature for DYS, the degree to which SRCD shows neural differences is mostly unexplored. In the first functional MRI (fMRI) study of SRCD, Cutting et al. found that, unlike readers with DYS, adolescents with SRCD showed normal responses to word stimuli in the left occipito-temporal region, an area implicated in DYS that is known to correlate with fast and efficient word recognition (Cutting et al., 2013). In contrast, DYS readers showed expected underactivation in the left occipito-temporal areas associated with efficient orthographic-phonological mapping. These findings indicate that, for readers with SRCD, the neural basis for rapid word identification in the phonological-orthographic route is intact. Nevertheless, SRCD readers did show some functional anomalies when processing words; specifically, the left inferior frontal gyrus correlated more highly with the hippocampus and parahippocampal areas in SRCD than TD for low versus high frequency words. This supports the hypothesis that access to low frequency words is harder for SRCD, possibly reflecting a semantic deficit, as low frequency words are more difficult to access. However, this study did not specifically target connectivity using prefrontal seeds regions, so it is unclear how regions that support domain-general abilities may play a role in the neurobiology of SRCD. One hypothesis (consistent with behavioral studies) is that whereas DYS involves deficits in mapping symbols to words, SRCD is deficient in accessing meaning from words (Cutting et al., 2013, Perfetti, 2007). This difficulty could either stem from problems fundamental to language (e.g. vocabulary) or from domain-general processes that guide lexical access under demanding conditions.

Here, for the first time, we use multivariate pattern analysis (MVPA) to characterize gray matter anomalies in SRCD readers. MVPA is a machine learning analytical approach that has been previously used to classify individuals from developmentally disabled populations, including autism (Ecker et al., 2010, Wee et al., 2014), fragile X syndrome (Hoeft et al., 2010), attention deficit hyperactivity disorder (Lim et al., 2013). Unlike VBM, which runs separate statistical tests on each voxel in the brain image, MVPA is a machine learning approach that analyzes the entire dataset simultaneously, producing a weighting map that for classification (Pereira et al., 2009). MVPA of neuroimaging data is sensitive to differences in reading ability, both on a continuum (He et al., 2013) and between classes of readers such as those with DYS (Hoeft et al., 2007, Tanaka et al., 2011). Given that reading comprehension

relies on a distributed set of brain areas (Price, 2012), MVPA may be more capable of differentiating between SRCD, DYS and TD adolescent readers than univariate VBM analysis.

In the current study, we sought to identify whether SRCD was characterized by abnormalities in gray matter volume in regions traditionally linked to language (left perisylvian cortex), suggesting a primary deficit in language-based processing, or in regions associated with executive functions (bilateral frontal areas), suggesting domain-general deficits, or both areas. We expected to replicate prior findings in DYS of gray matter reductions in left occipito-temporal cortex, known to be important for fast and efficient word recognition, consistent with their fundamental word-level weaknesses. However, based on our prior study showing that this region was functionally intact in SRCD when processing words, we did not expect SRCD to differ from TD in these regions. Instead, we hypothesized that we would see differences from TD in areas either associated with semantics (e.g., posterior middle temporal or dorsal inferior frontal gyrus), or with more domain-general processes (e.g. dorsolateral prefrontal cortex), depending on whether SRCD is primarily related to language or EF. Answers to these questions could be an important first step towards a neurobiological characterization of this less well-known reading disorder.

Methods

Participants

Data came from a larger study investigating the neural and behavioral bases of reading comprehension in a cross-section of adolescents (RO1 HD044073). These participants were recruited from the community via flyers, bulletins and the internet. (See Locascio et al. for complete recruiting information (Locascio et al., 2010).) Students who met the inclusion criteria were invited to participate in two days of behavioral testing, with an optional MRI scan on the second day (total N = 126; scanned N = 87). Of the participants who received MRI scans, 41 had sufficiently high quality structural MRI data to be included in the current study.

Inclusion Criteria—Participants had to have earned a standard score of at least 80 on the Wechsler Intelligence Scales Children Verbal Comprehension or Perceptual Reasoning Indices (4th Ed.) (Williams et al., 2003). Furthermore, 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.

Group Assignment—Participants were classified by their word-level and reading comprehension skills. The Basic Reading (BR) composite score from the Woodcock Reading Mastery Test - Revised/Normative Update, which consists of the Letter Word Identification (real word recognition) and Word Attack (pseudo-word reading) subtests, was used to measure word-level reading ability (Woodcock, 1998). Given the established variance in scores across reading comprehension measures (Cutting and Scarborough, 2006), four different tests were used to measure this domain (Karlsen and Gardner, 1995, MacGinitie et al., 2000, Wiederholt and Bryant, 2000, Woodcock, 1998). Participants in the

DYS group had to score at or below the 25th percentile rank for the BR standard score. SRCD participants had to score at least in the 37th percentile rank for BR, but below the 25th percentile on two or more reading comprehension measures. TD participants had to score at or above the 37th percentile rank for BR, as well as on the four reading comprehension measures or on three out of the four measures, with the fourth score being above the 25th percentile. In total, 14 participants met the criterion for DYS, 11 for SRCD, and 16 for TD (Table 1).

We also assessed symptoms of attention deficit hyperactivity disorder (ADHD), such as difficulty paying attention to details, organizing tasks and activities and remaining still when appropriate (American Psychiatric Association, 2013). Since these behaviors overlap with EF abilities hypothesized to be deficient in individuals with SRCD, in order to make sure we could not attribute our findings to ADHD, we examined the role of ADHD in two ways: (1) whether ADHD was differentially distributed across groups and (2) if ADHD status (hyperactive (H), inattentive (I) or both (H-I)) differentially impacted findings. No differences were found between groups on ADHD status ($\chi^2 = 2.25$, $p < 0.325$; DYS: 4 H-I and 1 I; SRCD: 2 H-I and 1 I; and TD: 2 H-I; see Locascio et al., 2010 for ADHD criteria). ADHD status also did not show any relationship to MVPA classification strength (see Table 2), suggesting that our findings were not unduly influenced by presence of ADHD.

MRI Acquisition and Preprocessing

A Philips Achieva 3.0 Tesla scanner (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 Brain Imaging at the Kennedy Krieger Institute in Baltimore, MD. For the T1-Turbo Field Echo structural scan, volumes were acquired with the following parameters: axial acquisition geometry; 200 slices; 8.052 ms TR; 3.68 ms TE; 8 degree flip angle; 1 mm slice thickness; 0 mm slice gap; 419 s scan duration; and 256x256 acquisition matrix.

Optimized voxel-based morphometry, a whole-brain analysis technique, was used to determine gray matter volume metrics for each subject. Specifically, we used the VBM8 toolbox running on SPM8 software (www.fil.ion.ucl.ac.uk/spm) for Matlab (Mathworks, Inc., Natick, MA). For VBM8 manual and further details, see www.dbm.neuro.uni-jena.de/vbm. Defaults settings were used for all toolbox options. After bias correction, T1 images were segmented into gray matter then spatially normalized to a DARTEL template. Then, non-linear Jacobian modulation was applied (preserving total gray matter volume), followed by smoothing with an isotropic Gaussian kernel with full width at half maximum of 8-mm (Ashburner and Friston, 2000).

Multivariate Pattern Analysis

A schematic of the MVPA analysis pipeline is shown in Figure 1. For pattern classification, a linear support vector machine, as implemented by an in-house MVPA toolbox, was used (Hoeft et al., 2011c, Hoeft et al., 2011b, Kesler et al., 2013). This toolbox (http://ncnl.stanford.edu/tools) adopted LIBSVM, a software library for support vector machines (Chang and Lin, 2011). The support vector machine algorithm utilizes a training set of data

(i.e., gray matter volume maps) to create an optimal weighting map of features to predict whether a novel dataset belongs in one group or another (Haynes and Rees, 2006, Hoeft et al., 2007, Hoeft et al., 2011a, Mourão miranda et al., 2006). Separate classifiers were built for each group comparison, i.e. "DYS vs. TD", "SRCD vs. DYS" and "SRCD vs. TD". The features used for classification were sub-threshold ($p < 0.30$, uncorrected) group differences in the training data. To further reduce the number of features, we performed recursive feature elimination. For this, the bottom 30% of the voxels based on the absolute value of their weights were iteratively excluded until the performance started degrading (De Martino et al., 2008, Formisano et al., 2008).

The validity of each classifier was tested using leave-one-out cross-validation (LOOCV) to minimize over-fitting and allow generalization of the model. Although superior cross-validation methods exist, including k-fold cross-validation testing classifiers on an independent dataset, our relatively small sample size was not large enough to implement these effectively. In LOOCV, each classifier uses a training set of m-dimensional feature vectors for N-1 subjects, where m was the number of voxels in the subject's gray matter volume map (with a fixed regularization parameter C=1). The resultant weighting map, or hyperplane, optimally bisected the two classes and was used to predict group classification for the Nth subject. This procedure was repeated for each subject, and the accuracy for the model was determined by the proportion of correct predictions (Hoeft et al., 2011a, Hosseini and Kesler, 2014, Tanaka et al., 2011). Unbalanced sample size for the classes was corrected by using equal group sizes within each training set. Classes were randomly permuted and the analyses were repeated 2000 times to obtain average measures of accuracy, specificity, sensitivity and predictive value for each comparison.

Each feature used in MVPA is assigned a weight and a direction (i.e. positive or negative). Features with high weights are considered important contributors to classification. The feature direction is arbitrarily chosen (e.g. in "SRCD vs. TD", if SRCD is positive then TD would be negative). MVPA predicts group involvement by determining the direction of the sum of all weighted features. The greater an individual's distance from the hyperplane, the more (or less) that individual resembles its group peers (e.g. if an individual is in the positive group but has a large negative hyperplane distance, that individual is much different than his or her peers). A correlation between an individual's distance from the hyperplane and their behavioral metrics would suggest that differences utilized by the classifier are related to behavioral differences and are not random. In the current study, Pearson correlations for distances and behavioral metrics were conducted using SPSS. Analyses were corrected for multiple comparisons using the Bonferonni method to $p < 0.05$.

Maps for each classifier were constructed by averaging each feature's (voxel) weight at all permutations. To display meaningful clusters (i.e., those with sufficiently large positive or negative weights), these maps were thresholded at an empirical threshold of $p < 0.05$ (2000 permutations). Further, to identify neuroanatomical patterns that were uniquely anomalous to SRCD, and to DYS, we performed a Boolean conjunction of each group's comparisons (e.g. "SRCD vs. TD" and "SRCD vs. DYS") taking the weight directions into account (i.e. clusters with only positive (or only negative) weights from both classifications were conjoined, whereas if a cluster showed a positive weight in one classification and negative in

the other, then these clusters were not considered). These operations resulted in three distinct maps: 1) regions where SRCD showed only positive (or only negative) weights compared to both DYS and TD; 2) regions where DYS showed only positive (or only negative) weights compared to both SRCD and TD; and 3) regions where TD showed only positive (or only negative) weights compared to both SRCD and DYS. Conjunctions were performed using tools from the Analysis of Functional NeuroImages (AFNI) toolbox.

Finally, we examined univariate differences in clusters of features (voxels) identified as having high weights in MVPA analyses of SRCD vs. TD and SRCD vs. DYS classification. This was done by performing one-way univariate analysis of variance with the average gray matter intensity across subject groups for each conjunction map (e.g. areas where SRCD was weighted negatively compared to both TD and DYS groups). Comparisons were Bonferonni-corrected to a confidence level of $p < 0.05$.

Results

All three classifiers ("SRCD vs. TD", "SRCD vs. DYS" and "DYS vs. TD") were able to distinguish between groups at a level significantly above chance (Figure 2). Note that each of the 2000 iterations of the support vector machine may produce a unique weighting map; however, when averaged, areas that most reliably identify one group over the other will emerge. Representative slices from these average weighting maps are shown in Figure 3.

Because a central aim of this investigation was to investigate which brain areas uniquely differentiated SRCD from both other types of readers, we performed a Boolean conjunction of the average weighting maps to show areas where the group was characterized by positive (or negative) weights in both comparisons (e.g. areas where "SRCD > TD" and "SRCD > DYS"). The major patterns for each of the groups are described below, and Figure 4 illustrates them.

Patterns in DYS

We identified patterns of features voxels that were uniquely different in DYS Compared to both TD and SRCD, based on the classifications "DYS vs. TD" (accuracy 80.0%, $p < 0.01$) and "DYS vs. SRCD" (accuracy 88.0%; $p < 0.001$). Cluster locations and the relative effect size (i.e. the magnitude of the cluster's effect on accurate classification over 2000 permutations, scaled to a proportion of the maximum) are reported in Table 3A. Regions represented with negative weights (voxels where comparison groups were both positively weighted) include language regions in the posterior occipito-temporal and temporo-parietal cortex, consistent with previously reported differences (Maisog et al., 2008, Richlan et al., 2013). DYS was also characterized by positive weights in the inferior cerebellum, and right parietal, temporal and frontal areas (Table 4A).

Patterns in SRCD

Neuroanatomical patterns of features (voxels) unique to SRCD were based on "SRCD vs. TD" (accuracy 92.5%; $p < 0.001$) and "SRCD vs. DYS" (accuracy 88.0%; $p < 0.001$) classifications. Negatively weighted voxels were centered in the right prefrontal region, which is associated with cognitive control processes, and the cerebellum (Table 3B). In

contrast to DYS, language regions, including the left inferior frontal gyrus and superior temporal gyrus, were characterized mostly, but not exclusively, by positive weights (Table 4B).

Patterns in TD

Neuroanatomical patterns of features (voxels) unique to TD, based on "SRCD vs. TD" (accuracy 92.5%; $p < 0.001$) and "DYS vs. TD" (accuracy 80.0%, $p < 0.01$) classifications, were more evenly distributed between left and right hemispheres (Table S2). The largest clusters of negative weights (voxels where comparison groups were both positively weighted) were found in the right insula, left postcentral gyrus, right inferior frontal gyrus and anterior cerebellum. Positive weights were also located on the inferior cerebellum and a number of right frontal areas.

Univariate Analysis

We performed univariate analysis to determine if the patterns described above were directly related to differences in gray matter volume (versus overall patterns). Results revealed that gray matter volume was significantly reduced for areas where "DYS < TD & SRCD" ($p = 0.006$) and "SRCD < TD & DYS" ($p = 0.002$). However, areas with positive weights in the reading disability groups did not reach statistical significance ("DYS > TD & SRCD", $p = 0.21$; "SRCD > TD & DYS", $p = 0.07$). Areas characterizing TD across comparisons were significant in both the positive ("TD > DYS & SRCD", $p = 0.001$) and negative ("TD < DYS & SRCD", $p = 0.005$) directions.

Hyperplane Correlation

For each comparison, multiple behavioral indices correlated with individual distances to the MVPA hyperplane. (See Table 2 for correlations and directionality of them.) As expected, word-level reading metrics were significantly correlated ($p < 0.01$) with hyperplane distance derived from classifiers "DYS vs. TD" and "SRCD vs. DYS" but not "SRCD vs. TD". Reading comprehension measures, on the other hand, were correlated with both classifiers involving TD readers but not in "SRCD vs. DYS". Individual variance in verbal intelligence was significantly related only to metrics of fit in the "SRCD vs. TD" classifier ($p < 0.05$).

Discussion

SRCD is estimated to affect up to 10% of school-aged children (Nation et al., 2004), yet most attention from the scientific community has been directed toward understanding issues with word decoding, or dyslexia (DYS). However, reading comprehension is a more complex construct than word decoding, and behavioral studies have been inconclusive as to whether a single neurocognitive profile underlies SRCD (Cain and Oakhill, 2006). In this study, we investigated whether adolescents with SRCD shared patterns of gray matter volume that distinguished them from typically developing (TD) and DYS readers. Multivariate pattern analysis (MVPA) discriminated between each group with a high degree of accuracy, especially in comparisons involving SRCD. Furthermore, classifier fit correlated with individual differences in reading ability, and areas characterized by negative classifier weights for each reading disability were directly related to gray matter differences.

These initial results suggest that adolescents with SRCD indeed possess a unique neurobiological signature compared to other readers and provide a new perspective for investigating the cognitive profile of SRCD.

Of central interest were the brain regions showing reduced gray matter volume in SRCD compared to both TD and DYS readers. Based on previous literature, we had three hypotheses: the cognitive deficits seen in SRCD would be related to gray matter reductions in language areas (left perisylvian cortex), in EF areas (bilateral prefrontal cortex) or both sets of regions. Regions traditionally involved in core language processing, including semantic processing (e.g., angular gyrus and inferior frontal gyrus (BA 45/47)), did not show reduced gray matter volume in SRCD. In fact, left perisylvian cortex was characterized mostly by positive classifier weights in primary language regions, including parts of the posterior middle temporal gyrus and inferior frontal gyrus. Nevertheless, there were two areas within the temporal lobe that were characterized by reduced gray matter volume, including a segment of the inferior temporal gyrus, which may play a role in semantic processes such as categorization (Devlin et al., 2002); however, it was distinctly anterior from occipito-temporal regions known to play a role in word decoding. A smaller contribution of auditory cortex (left superior temporal gyrus) was also observed.

The predominantly positive weighting of SRCD in language regions stand in contrast with the DYS profile, which was characterized by reduced gray matter volume in left inferior temporal gyrus, left supramarginal gyrus and left inferior frontal gyrus, consistent with previous structural studies (Maisog et al., 2008, Richlan et al., 2013). These regions are closely linked to the rapid word recognition and orthographic-phonological mapping that is deficient in DYS readers (Linkersdörfer et al., 2012, McCandliss and Noble, 2003). An additional finding was reduced gray matter volume in bilateral thalamus. A number of individual studies have reported abnormalities in thalamic function and structure in DYS (Brown et al., 2001, Fan et al., 2014, Maisog et al., 2008),although these areas were not implicated in recent meta-analyses (Linkersdörfer et al., 2012, Richlan et al., 2013). Overall, these results suggest that reading difficulties arising from reduced gray matter volume i n primary language areas, and possibly subcortical regions, are unique to DYS.

An alternative hypothesis is that impaired comprehension in SRCD stems from deficits in domain-general abilities. EF skills facilitate the construction, maintenance and enrichment of a reader’s mental representation of text. Our finding of multiple clusters of reduced gray matter volume in the right frontal cortex of individuals with SRCD supports this hypothesis. These areas encompass portions of the middle and superior frontal gyri, including regions functionally associated with cognitive control (i.e. rule maintenance) and response inhibition (Rajah et al., 2008, Zurawska Vel Grajewska et al., 2011). Previous lesion studies have shown that while the bilateral prefrontal cortex is important for the manipulation of cognitive representations, the right prefrontal cortex is especially important for goal-directed behavior and adaptive decision-making (Barbey et al., 2013). This is consistent with the report that SRCD readers were less accurate in response inhibition and planning/ organization than DYS or TD readers (Locascio et al., 2010). In particular, these prefrontal systems may underlie findings that SRCD tend to recall information not relevant to overall text meaning (Cain and Oakhill, 2006), a process that would require adaptive decision

making while reading. Overall, our findings support a model implicating a key role for EF in a neurocognitive model of SRCD, as well as to reading comprehension more generally. While additional research should be done to clarify the role of these skills in SRCD, reduced gray matter in prefrontal regions is a viable candidate for future biomarker studies.

The general hemispheric dissociation between language-related areas of reduced gray matter volume in DYS (left hemisphere showing negative weights compared to TD) and SRCD (right hemisphere showing negative weights compared to TD) may further support the hypothesis that, whereas DYS has deficits in primary language processes, SRCD is characterized by difficulty with non-linguistic skills facilitating comprehension. While damage to left-lateralized language regions has profound effects on language use (e.g. expressive or receptive aphasia), individuals with lesions in right hemisphere homologues have more subtle deficits in language comprehension (Bookheimer, 2002, Jung-Beeman and Chiarello, 1998). In fMRI studies, the right hemisphere contributes to comprehension of connected text but not to single-word reading tasks and is implicated in an "extended language network" which supports inferential contextualization of the text (Cutting and Scarborough, 2006, Ferstl et al., 2008, Vigneau et al., 2011). Xu et al. found that right hemisphere neural activity increases with the evolving development of a narrative, and suggested that the right hemisphere is involved in integrating story information with external knowledge (Xu et al., 2005). Other studies have reported greater right hemisphere activation when comprehending metaphors, drawing inferences or identifying syntax errors (Bottini et al., 1994, Mashal et al., 2005, Schmidt and Seger, 2009). Some studies have also suggested that right hemisphere language homologues take on more primary processing roles when left language counterparts are not fully functional (Pugh et al., 2000); for instance, dyslexic readers might engage right hemisphere homologues and bilateral prefrontal areas to compensate for phonological processing deficits (Shaywitz et al., 2002), although these findings have been disputed (Richlan et al., 2013). Thus, while left language areas are considered to be the primary language network, right hemisphere areas seem to support mental model building, enriching their representation and facilitating comprehension (Jung-Beeman, 2005). Given that intervention has been shown to increase gray matter volume (Krafnick et al., 2011), one possibility is that SRCD's gray matter reductions in the right hemisphere, especially in frontal areas, result from an inconsistent use of these extended language faculties, possibly stemming from impaired semantic access/processing. Specifically, during the early stages of reading, SRCD may place most of their attention on the decoding process, to the neglect of building and enriching a coherent mental model (Yuill and Oakhill, 1991). By adolescence, inconsistent exercise of this skill could result in a major obstacle to comprehension. To begin to address these speculations, however, we need more comprehensive longitudinal studies, as inferring the direction of causality between behavior and biology is difficult and not possible with the cross-sectional design in the current study.

Reduced gray matter volume in the cerebellum was also important for classifying SRCD. The cerebellum has traditionally been associated with making smooth movements and motor learning. Recent work, though, has shown that higher-level cognitive processes, including lexical and semantic processing tasks, also activate the cerebellum (Stoodley and Stein, 2011). In reading tasks, the cerebellum is associated with the temporal processing of stimuli

and sequencing as a story proceeds (Booth et al., 2007), and lesions to the cerebellum can result in acquired reading disability (Moretti et al., 2002). Ben-Yehudah and Fiez found that individuals with cerebellar lesions had more difficulty recalling lists of non-words than digits or familiar words, leading the authors to suggest that the cerebellum has a specific role in articulatory monitoring in addition to its role in error-monitoring (Ben-Yehudah and Fiez, 2008). Reduced gray matter in the cerebellum has been observed in multiple voxel-based morphometry studies of DYS (Brambati et al., 2004, Brown et al., 2001, Kronbichler et al., 2008). However, there is variability between studies in both presence and location of the deficits (Eckert et al., 2003, Stoodley and Stein, 2011). While it is conceivable then that reduced cerebellar gray matter could also affect semantic monitoring in SRCD, we are cautious in over-extending these interpretations. Nonetheless, these findings are intriguing and warrant further investigation into the cerebellar contributions to higher-level comprehension processes.

Future studies will benefit from larger sample sizes, especially for more precisely localizing the reductions in gray matter. We used leave-one-out cross-validation and permutation testing to reduce the bias to the training data and obtain descriptive statistics for our analyses; however, a larger number of subjects would allow researchers to estimate the viability for these biomarkers on an independent dataset. Additionally, SRCD and DYS groups were defined by decoding and reading comprehension ability so that we could investigate the neurobiological impact of basic reading skills and higher-level comprehension abilities. Imaging studies that carefully tease apart semantics and EF will help to disentangle the neurobiological profile of SRCD.

In summary, to the best of our knowledge, this study is the first to characterize neuroanatomical differences in individuals with SRCD, and the results suggest a neurobiological profile that is distinct from TD and DYS readers. These initial findings suggest that the pattern of differences is not in primary language areas but in domain-general areas that may support language processes, especially in the cognitively demanding context of reading comprehension. However, a more comprehensive understanding of the neurobiology of SRCD, similar to what has been developed for DYS in the past twenty years, will help answer questions as to how uniform this profile is across individuals with SRCD. Longitudinal studies that emphasize both behavior and neurobiology will be crucial for determining when and why readers with SRCD begin to differ, and how educators can best support them.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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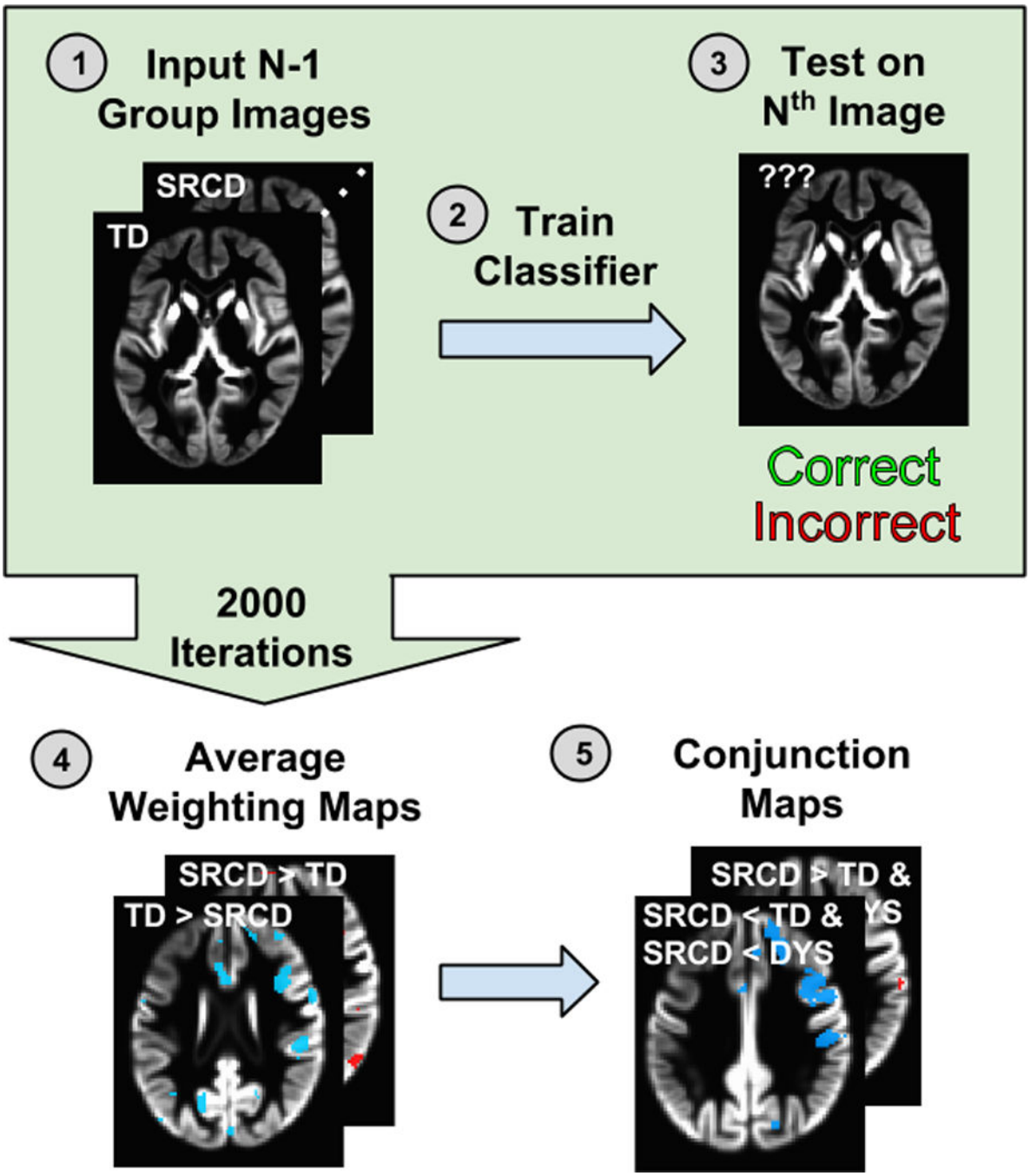

Figure 1.

Schematic of the MVPA analysis pipeline. 1) Label the gray matter volume maps from the groups of interest, leaving one out. 2) The MVPA algorithm computes an optimal weighting map that distinguishes the two groups from each other. 3) Test algorithm performance by feeding in the subject that was left out. The algorithm will either correctly or incorrectly identify the novel map. 4) Iterate 2000 times, leaving out a random subject each time. This results in performance metrics such as accuracy as well as an average map of areas

important for classification. 5) Conjoin multiple weighting maps to identify areas that uniquely classify each group from the other.

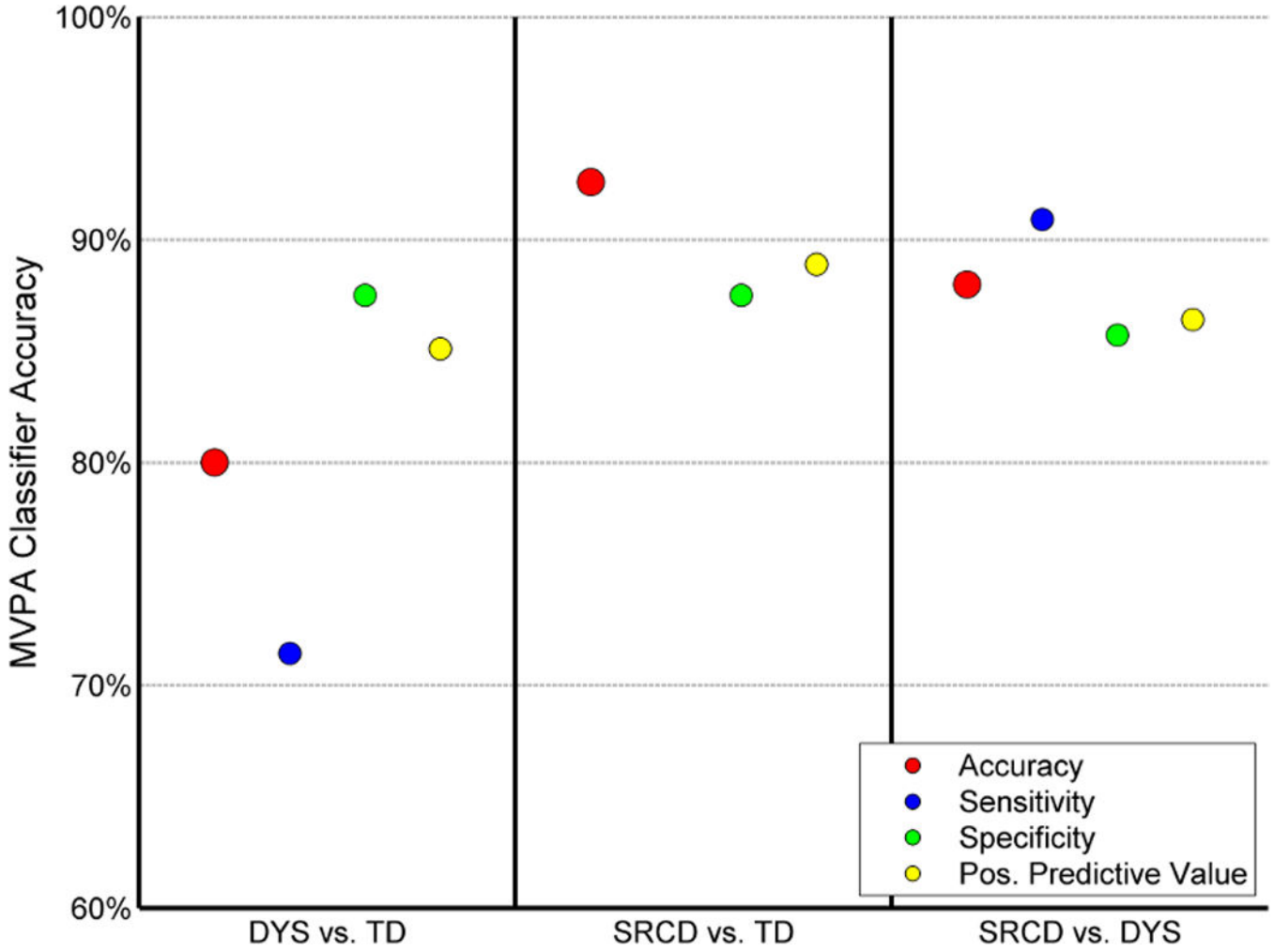

Figure 2.
All classifiers performed at levels significantly above chance (2000 permutations).

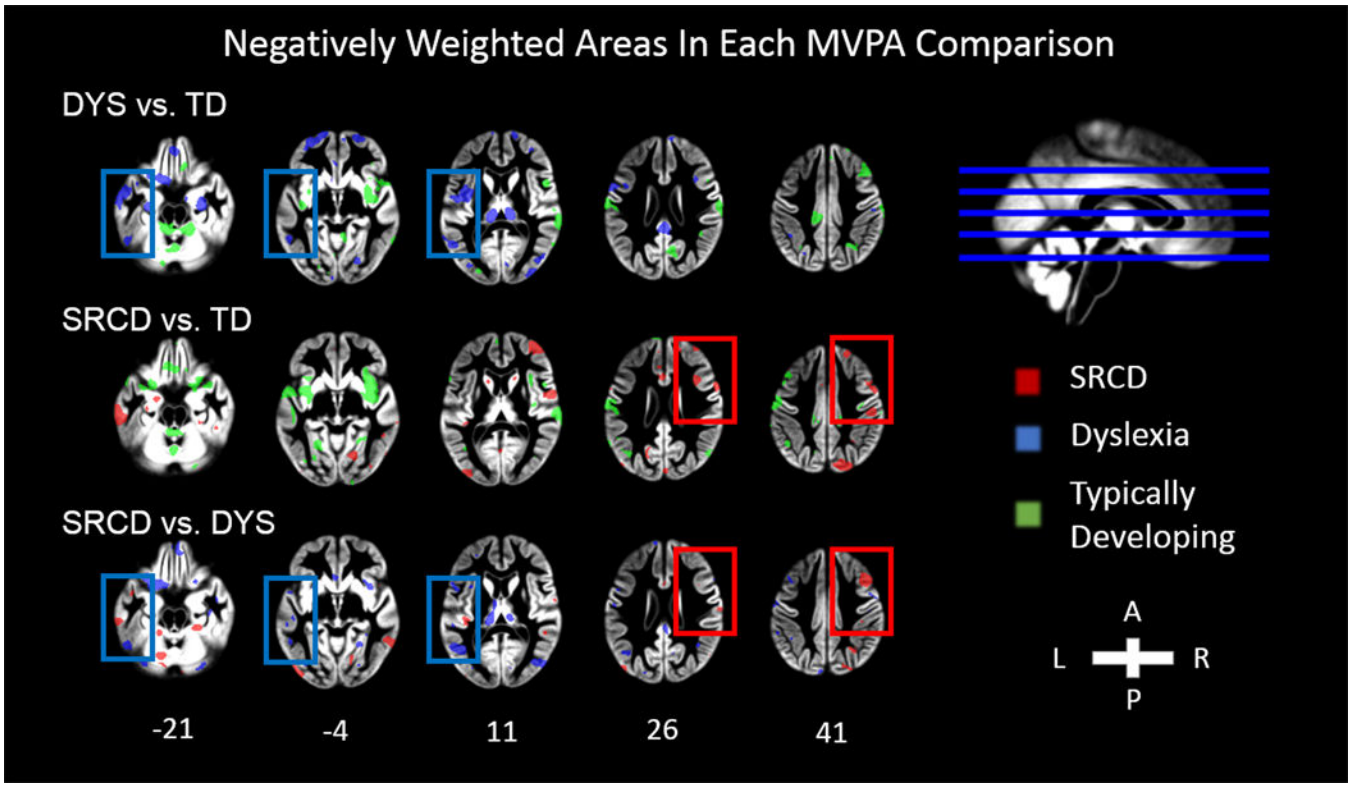

Figure 3.

Weighting maps for each MVPA classifier ($p < 0.05$, permutation-based correction) overlaid on the mean gray matter volume template for all subjects. Negatively weighted regions are those which contribute towards a positive classification of the comparison group (e.g. in "DYS vs. TD", high values in areas negatively weighted for SRCD would yield a prediction of TD). The blue boxes highlight negative weights in temporal language regions used in classifiers involving DYS. The red boxes highlight negative weights in right hemisphere regions contributing to classifiers involving SRCD.

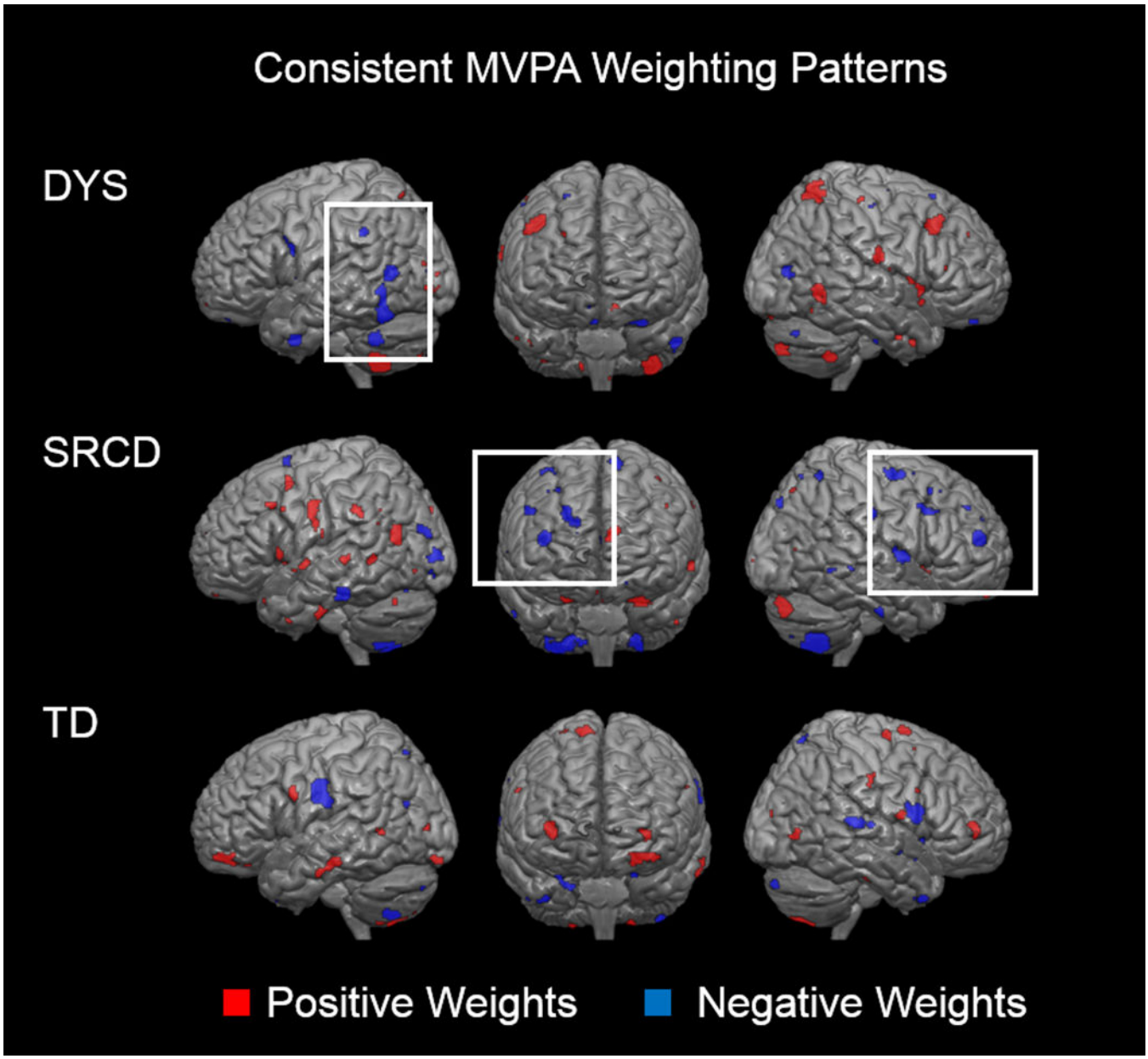

Figure 4.

Cortical areas of significant weighting for each conjoined set of classifier maps. Individual classifiers (e.g. "SRCD vs. DYS" and "SRCD vs. TD") were conjoined to find areas where each group was consistently characterized by increased or decreased gray matter volume relative to both comparison groups (e.g. "SRCD > TD & SRCD" and "SRCD < TD & SRCD"). Areas shown were significant in each classifier at $p < 0.05$ after permutation-based correction (2000 permutations).

Table 1
Group Demographics and Behavioral Profiles

Demographic information and mean behavioral scores for typically developing (TD), dyslexia (DYS) and specific reading comprehension deficits (SRCD) groups.

Demographics	TD	DYS	SRCD
Age	11.9 (1.1)	12.5 (1.3)	11.5 (1.3)
Gender	9 M, 7 F	10 M, 4 F	6 M, 5 F
General Intelligence			
WISC Verbal Comprehension Index*StS*	118.4 (11.9)[a]	96.7 (11.3)	95.0 (8.2)
WISC Perceptual Response Index*StS*	109.1 (7.8)[a]	96.9 (14.6)	92.5 (15.4)
Word Decoding			
WRMT Letter Word ID*StS*	104.9 (7.5)[b]	83.5 (5.4)	100.6 (6.2)[b]
WRMT Word Attack*StS*	105.1 (5.1)[b]	86.5 (5.6)	105.4 (4.9)[b]
Reading Comprehension			
Stanford Diagnostic Reading Test*P*	72.8 (29.3)[a]	26.3 (21.4)	19.4 (14.7)
Gates-MacGinitie Reading Test*P*	81.5 (18.7)[a]	27.1 (33.1)	19.1 (11.8)
Diagnostic Achievement Battery*ScS*	10.8 (0.77)[a]	7.6 (2.1)	6.4 (2.4)
GORT - Comprehension*ScS*	12.6 (2.1)[a]	8.8 (2.4)	8.8 (3.3)

WISC: Wechsler Intelligence Scale for Children - IV; WRMT: Woodcock Reading Mastery Tests – Revised; GORT: Gray Oral Reading Test;

StS standard score;

P percentile;

ScS scaled score;

[a] "TD > DYS & SRCD", $p < 0.05$;

[b] "TD and SRCD > DYS", $p < 0.05$.

Table 2

Coefficient of Determination (r^2) between Hyperplane Distance and Behavior

Linear relationships between behavioral metrics and distance from the classifier hyperplane. Word-level reading metrics significantly predicted DYS classification, and reading comprehension metrics significantly predicted both DYS and SRCD classification. All behavioral scores represent standard scores unless otherwise noted. All p-values were Bonferonni-corrected for multiple comparisons.

Demographics	**DYS vs. TD**	**SRCD vs. TD**	**SRCD vs. DYS**
Age	0.07	0.03	0.18
Gender	0.09	0.04	0.07
General Intelligence			
WISC Verbal Comprehension	0.18	0.26 *	0.01
WISC Perceptual Reasoning	0.10	0.13	0.04
ADHD Status	0.00	0.08	0.00
Word Decoding			
WRMT Letter Word ID	0.40 **	0.01	0.56 **
WRMT Word Attack	0.48 **	0.04	0.67 **
Reading Comprehension			
Stanford Diagnostic Reading Test^{P}	0.23 *	0.38 **	0.00
Gates-MacGinitie Reading Test^{P}	0.21	0.42 **	0.01
Diagnostic Achievement Battery^{SS}	0.18	0.10	0.06
GORT – Comprehension^{SS}	0.27 *	0.17	0.00

WISC: Wechsler Intelligence Scale for Children; WRMT: Woodcock Reading Mastery Test; GORT: Gray Oral Reading Test.

^{P}percentile;

^{S}scaled score;

* $p < 0.05$;

** $p < 0.01$

Table 3

Clusters of negative classifier weights characterizing DYS and SRCD: A)Clusters where “DYS < SRCD” and “DYS < TD”. B) Clusters where “SRCD < DYS” and “SRCD < TD”. Univariate analyses reveal that gray matter volume was significantly different from comparison groups in these clusters (see Results). Cluster effect size (i.e. the magnitude of the cluster’s effect on accurate classification over 2000 permutations) has been scaled to be a proportion of the maximum effect size in the comparison. All voxels are significant at an empirical threshold of $p < 0.05$; cluster extent (k) was set to a threshold of 20 voxels for presentation purposes. All coordinates are in MNI standard coordinate space.

A: Negative Classifier Weights for Dyslexia Relative to SRCD & TD						
k	***Rel. Effect Size***		***Center of Mass***			***Primary Brain Region***
	v. TD	***v. SRCD***	***X***	***Y***	***Z***	
Frontal						
455	0.46	0.24	−13	13	−20	L Inf. Frontal Gyrus
Temporal						
239	0.62	0.48	−52	−55	−16	L Inf. Temporal Gyrus
160	0.37	0.91	−52	−59	7	L Mid. Temporal Gyrus
90	0.40	0.08	−50	5	−37	L Mid. Temporal Gyrus
Parietal						
43	0.62	0.43	3	−39	24	R Post. Cingulate
21	0.44	0.53	−52	−41	35	L Supramarginal Gyrus
Occipital						
88	0.38	0.32	43	−77	10	R Mid. Occipital Gyrus
69	0.56	0.16	11	−84	5	R Lingual Gyrus
Subcortical						
428	0.84	0.30	−8	−23	13	L Thalamus
285	0.67	0.27	11	−21	13	R Thalamus
122	0.42	0.16	−46	−49	−37	L Cerebellum
21	0.16	0.25	40	−71	−31	R Cerebellum
B: Negative Classifier Weights for SRCD Relative to Dyslexia & TD						
k	*Rel. Effect Size*		*Center of Mass*			*Primary Brain Region*
	v. TD	*v. DYS*	*X*	*Y*	*Z*	
Frontal						
202	0.37	0.41	21	44	31	R Sup. Frontal Gyrus
140	0.46	0.40	38	52	16	R Mid. Frontal Gyrus

A: Negative Classifier Weights for Dyslexia Relative to SRCD & TD

k	*Rel. Effect Size*		*Center of Mass*			*Primary Brain Region*
	v. TD	*v. SRCD*	*X*	*Y*	*Z*	
112	0.51	0.45	36	−6	60	R Precentral Gyrus
112	0.38	0.34	−10	8	66	L Sup. Frontal Gyrus
95	0.47	0.50	1	21	19	R Ant. Cingulate
88	0.42	0.37	46	16	36	R Mid. Frontal Gyrus
73	0.50	0.60	25	3	50	R Mid. Frontal Gyrus
56	0.38	0.16	37	9	29	R Mid. Frontal Gyrus
21	0.40	0.45	30	18	48	R Mid. Frontal Gyrus
Temporal						
164	0.50	0.75	−61	−29	−22	L Inf. Temporal Gyrus
138	0.25	0.41	56	−1	5	R Sup. Temporal Gyrus
54	0.50	0.47	56	−16	−34	R Inf. Temporal Gyrus
26	0.28	0.15	−37	−33	12	L Sup. Temporal Gyrus
Parietal						
51	0.21	0.03	52	−20	33	R Postcentral Gyrus
Occipital						
157	0.40	0.29	−35	−91	4	L Mid. Occipital Gyrus
85	0.40	0.31	16	−70	−8	R Lingual Gyrus
82	0.43	0.33	22	−81	38	R Cuneus
80	0.27	0.14	−43	−84	20	L Mid. Occipital Gyrus
Subcortical						
1069	0.35	0.35	28	−56	−52	R Inf. Cerebellum
318	0.21	0.24	−23	−56	−53	L Inf. Cerebellum
158	0.34	0.31	20	−76	−44	R Inf. Cerebellum

Table 4

Clusters of positive classifier weights characterizing DYS and SRCD: A) Clusters where “DYS > SRCD” and “DYS > TD”. B) Clusters where “SRCD > DYS” and “SRCD > TD”. Cluster effect size (i.e. the magnitude of the cluster’s effect on accurate classification over 2000 permutations) has been scaled to be a proportion of the maximum effect size in the comparison. All voxels are significant at an empirical threshold of $p < 0.05$; cluster extent (k) was set to a threshold of 20 voxels for presentation purposes. All coordinates are in MNI standard coordinate space.

A: Positive Classifier Weights for Dyslexia Relative to TD and SRCD						
k	***Rel. Effect Size***		***Center of Mass***			***Primary Brain Region***
	v. TD	***v. SRCD***	***X***	***Y***	***Z***	
Frontal						
274	0.43	0.62	43	2	42	R Mid. Frontal
Temporal						
88	0.99	0.37	63	−54	−4	R Inf. Temporal Gyrus
33	0.39	0.50	−11	−80	−20	L Sup. Temporal Gyrus
Parietal						
534	0.61	0.37	21	−57	63	R Sup. Parietal Lobule
117	0.30	0.15	30	−61	39	R Angular Gyrus
107	0.30	0.38	64	−15	21	R Postcentral Gyrus
106	0.71	0.30	27	−37	55	R Postcentral Gyrus
Subcortical						
451	0.48	0.25	−34	−51	−52	L Ant. Cerebellum
284	0.36	0.42	28	−78	−40	R Inf. Cerebellum
111	0.25	0.41	36	−48	−47	R Ant. Cerebellum
24	0.45	0.39	10	−87	−19	R Sup. Cerebellum
23	0.39	0.27	−14	−42	−21	L Ant. Cerebellum
B: Positive Classifier Weights for SRCD Relative to TD and Dyslexia						
k	*Rel. Effect Size*		*Center of Mass*			*Primary Brain Region*
	v. TD	*v. DYS*	*X*	*Y*	*Z*	
Frontal						
77	0.55	1.00	5	−24	54	R Mid. Cingulate Cortex
69	0.26	0.28	−37	8	52	L Mid. Frontal Gyrus
43	0.20	0.21	−7	62	19	L Med. Frontal Gyrus
38	0.07	0.02	−53	14	5	L Inf. Frontal Gyrus

A: Positive Classifier Weights for Dyslexia Relative to TD and SRCD

k	*Rel. Effect Size*		*Center of Mass*			*Primary Brain Region*
	v. TD	*v. SRCD*	*X*	*Y*	*Z*	
21	0.21	0.11	−43	19	38	L Mid. Frontal Gyrus
Temporal						
458	0.39	0.32	35	13	−7	R Insula
330	0.30	0.33	−25	12	−23	L Sup. Temporal Gyrus
99	0.33	0.33	−45	−15	−37	L Inf. Temporal Gyrus
99	0.36	0.22	−53	−27	−2	L Mid. Temporal Gyrus
44	0.37	0.38	−60	−3	−2	L Mid. Temporal Gyrus
44	0.10	0.12	−33	11	2	L Insula
30	0.39	0.33	24	17	−25	R Parahippocampal Gyrus
29	0.44	0.40	26	−54	−5	R Fusiform Gyrus
25	0.26	0.65	−52	−48	1	L Mid. Temporal Gyrus
Parietal						
117	0.50	0.53	−56	−9	33	L Postcentral Gyrus
23	0.21	0.40	−6	−39	34	L Supramarginal Gyrus
Occipital						
360	0.52	0.77	−41	−64	17	L Mid. Occipital Gyrus
52	0.44	0.43	8	−55	51	R Precuneus
30	0.15	0.11	−10	−87	35	L Cuneus
Subcortical						
234	0.34	0.28	33	−80	−30	R Post. Cerebellum