Neuroscience

Changes in DTI Diffusivity and fMRI Connectivity Cluster Coefficients for Students with and without Specific Learning Disabilities In Written Language: Brain's Response to Writing Instruction

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Before and after computerized writing instruction, participants completed assessment with normed measures and DTI and fMRI connectivity scanning. Evidence-based differential diagnosis was used at time 1 to assign them to diagnostic groups: typical oral and written language (n=6), dysgraphia (impaired handwriting, n=10), dyslexia (impaired word spelling and reading, n=20), and OWL LD (impaired syntax construction, n=6). The instruction was aimed at subword letter writing, word spelling, and syntax composing. With *p* <.001 to control for multiple comparisons, the following significant findings were observed in academic achievement, DTI (radial diffusivity RD, axial diffusivity AD, and mean diffusivity MD), and graph cluster coefficients for fMRI connectivity. A time effect (pre-post intervention increase) in handwriting and oral construction of sentence syntax was significant; but diagnostic group effects were significant for dictated spelling and creation of word-specific spellings, with the dyslexia and OWL LD groups scoring lower than the typical control or dysgraphia groups. For RD a time effect occurred in anterior corona radiata and superior frontal. For AD a time effect occurred in superior corona radiata, superior frontal region, middle frontal gyrus, and superior longitudinal fasciculus. For MD a time effect occurred in the same regions as AD and also anterior coronal radiata. A diagnostic group effect occurred for graph cluster coefficients in fMRI connectivity while writing the next letter in alphabet from memory; but the diagnostic group x time interaction was not significant. The only significant time x treatment interaction occurred in right inferior frontal gyrus associated with orthographic coding. Compared to time 1, cluster coefficients increased at time 2 in all groups except in the dysgraphia group in which they decreased. Implications of results are discussed for response to instruction (RTI) versus evidence-based differential diagnosis for identifying students with SLDs in writing which may be best understood at both the behavioral and brain levels of analysis.

Differential Diagnosis of SLDs in Writing | Behavioral Response to Writing Intervention | Brain Response to Writing Intervention | DTI Diffusivity | Graph Analysis of fMRI Cluster Coefficients | Changes in White Matter-Gray Matter Correlations

Introduction

Epidemiological studies have shown that among school-age children and youth, different kinds of specific learning disabilities (SLDs) occur in oral language (1), reading (2), and writing (3). Compared to the reading disabilities, relatively less research has focused on writing disabilities (3); and despite considerable progress in understanding early writing development (4), less is understood about the persisting SLDs in oral and/or written language despite early intervention at and/or outside school. However, all of these SLDs may involve writing but at different levels (units) of language.

Although oral language disabilities emerge in the preschool years they often also involve oral and written language disabilities during the school years (1, 5, 6, 7). The hallmark impairment of those oral and written language disabilities has been shown to be syntax processing and production which can interfere with listening comprehension, oral expression, reading comprehension, and or written expression (8). Dyslexia is typically thought to be a disorder in phonological decoding, that is, pronouncing nonwords without meaning based on alphabetic principle; but the persisting hallmark impairment has been shown in many research studies to be written word spelling (9, 10). Dysgraphia is often thought to be a handwriting disorder related to motor dysfunction, but programmatic research has shown that it is a written language disorder in which the hallmark impairment is legible and automatic subword letter formation out of or in word context (11).

The goals of the current study were, therefore, to investigate whether (a) students with SLDs in writing disabilities at different levels of language (subword, word, or syntax) respond the same in response to writing instruction aimed at all levels of written language, and (b) students with these contrasting writing disabilities respond the same as typically developing writers without SLDs in writing. Both behavioral response to instruction (behavioral RTI) assessed with clinical measures and brain response to instruction (brain RTI) assessed with diffusion tensor imaging (DTI) and fMRI functional connectivity imaging were evaluated. White matter microstructure has previously been shown to change in response to short-term learning (12). In the current study writing instruction was provided during the study in multiple levels of writing, ranging from subword letter formation to word spelling to syntax construction; and RTI was evaluated for white matter microstructure change in both those with and without SLDs. Also, instead of examining changes in BOLD response in a region of interest (ROI) or from a seed with different regions in separate analyses, the current study applied complex network analysis based on graph theory to evaluate changes in fMRI connectivity. To apply complex network analysis/graph theory (13), functional networks were constructed based on correlation of the time-course of the BOLD signal. Finally, significant changes in gray matter-white matter correlations in response to writing instruction were also examined.

Conflict of interest: No conflicts declared.

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Research Questions Addressed

***Research Question 1*:** Is there evidence at the behavioral level that participants with and without specific learning disabilities (SLDs) affecting writing improved in writing and writing-related skills from before to after completing the computerized lessons aimed at all levels of language in the functional writing system?

***Research Question 2*:** If improvement is shown at the behavioral level, is there also evidence that participants changed at the neurological level in white matter integrity (research question 2a) and/or gray matter clustering coefficients (research question 2b) as well as the white matter-gray matter correlations (research question 2c)?

***Research Question 3*:** Do typical controls respond at the behavioral and brain levels of analysis to the same writing instruction? If so, this would show that simply analyzing RTI may be informative but is not sufficient alone to diagnose SLDs.

Methods

Ascertainment of Participants and Assignment to Diagnostic Groups

Prior to the first imaging session or intervention, all participants, who had been recruited for persisting writing disabilities in grades 4 to 9, had completed comprehensive diagnostic assessment and had been assigned to one of four groups based on absence or presence of hallmark impairments in cascading levels of written language as described in (14). These groups are typical oral and written language learner control, dysgraphia, dyslexia or oral and written language learning disability (OWL LD).

For both typically developing language learners (15) and those with dysgraphia, dyslexia, or OWL LD (16), Verbal Comprehension on a widely used normed measure of intellectual ability explained significant variance in writing and reading achievement. Likewise, a recent study that compared the verbally gifted with and without SLDs and the verbally average with and without SLDs supported the importance of including Verbal Comprehension Index on the Wechsler Scales in diagnostic assessment for SLDs in written language (17). None of these findings, however, support defining SLDs on the basis of discrepancy between Full Scale Scores on the Wechsler Scales and reading or writing achievement. Thus, the evidence-based procedures (14, 16) used in the current study required that Verbal Comprehension Index scores on the Wechsler Scale (18) fall at least within the lower limit of the normal range (--1 1/3 SD or standard score of 80). Exclusion criteria included developmental disabilities and brain injuries.

In addition, there was a further requirement for inclusion into an SLD diagnostic group. There had to be evidence that the hallmark impairment for an SLD diagnostic group had been persisting during middle childhood and early adolescence despite early literacy intervention; or for the typical controls, no evidence of having ever struggled in literacy learning. That is because prior research showed brain differences between students with persisting reading problems who were not treatment responders for early intervention in reading and the early responders who did respond readily (19). Furthermore, assignment to diagnostic group in the current sample was based on learning profiles for levels of language affected in hallmark writing impairment in dysgraphia (handwriting), dyslexia (spelling), or OWL LD (syntax) or lack of hallmark language impairment (typical writer controls). Such learning profiles contributed uniquely to writing and reading achievement over and beyond verbal comprehension and multiple components of working memory supporting language learning (16). The overall criteria for the four diagnostic groups are now summarized.

Typical writer control. There was no parent report of past or current struggles with handwriting, spelling, composing, or reading. There was no evidence on clinical normed measures of hallmark impairments in handwriting, spelling, composing, or reading.

Dysgraphia. There were parent reported past and current history of persisting struggles with handwriting but not with reading. On clinical normed measures there was evidence of hallmark impairments on at least two handwriting measures but not on reading measures.

***Dyslexia*.** There were parent reported past and current history of persisting struggles with spelling and word reading despite early intervention. On clinical normed measures there was evidence of hallmark impairments on at least two spelling measures (recognizing or producing correct spellings). Both on parent reported past and current history and normed measures there could not be indicators of oral language disabilities at the syntax or text level; however, consistent with the cascading levels of language differential diagnosis model (14), co-occurring handwriting problems (a lower level language skill than word- level spelling) were not an exclusion criterion.

***OWL LD*.** There were parent reported past history of early emergence of oral language problems during the preschool years, and despite early intervention, persisting oral and written language problems during the school years involving syntax (and text) such as listening comprehension, oral expression, reading comprehension, and/or written expression. On clinical normed measures there was evidence of hallmark impairments on at least two oral or written language measures involving syntax or text. Both on parent reported past and current history and on normed measures there had to be evidence of hallmark impairments at the syntax level of language. However, consistent with the cascading levels of language differential diagnosis model, co-occurring handwriting or spelling problems (lower level skills) were not exclusion criteria.

Research Design for the Current Imaging Study

After assignment to diagnostic groups, the participants completed the brain imaging study; measures of DTI white matter integrity and fMRI measures of functional connectivity, were obtained. After the first brain imaging session participants were enrolled in an instructional intervention study. A unique feature of these lessons was that instruction was aimed at all levels of language close in time to create a functional writing system: *subword* level letter production, *word* level decoding and spelling, and *syntax* level of composition. The learning activities included specialized instruction for (a) handwriting (strategies for letter formation and automatic retrieval of letters in alphabetic order from memory), (b) spelling (interrelationships among phonology, orthography, and morphology in the spelling direction for English, a morphophonemic orthography, 20, 21, 22, 23, 24), and (c) syntax composing, for example word order and content/function words; see (25). Thus, the lessons were designed to include not only learning activities for impaired writing skills for each of three specific SLD diagnoses (dysgraphia, dyslexia, and OWL LD) but also to facilitate writing of typically developing writers who also may benefit from teaching to all levels of language to create a functional writing system. After completing the 18 computerized

lessons, the participants completed a second imaging session, and the battery of achievement tests administered as part of the diagnostic assessment was also given again.

Sample Characteristics

Altogether 42 upper elementary and middle school participants (22 males and 20 females; grades 4 to 9; average age 11 years 10 months) completed brain imaging before and after they completed 18 lessons of specialized writing instruction. For DTI one participant did not have usable data at both time 1 and time 2 (N=41): control (n=6), dysgraphia (n=10), dyslexia (n=19), and OWL LD (n=6). For fMRI gray matter graph analyses, two did not have usable data at both time 1 and time 2 (N=40): controls (n=6), dysgraphia (n=10), dyslexia (n=20), and OWL LD (n=4).

Ethnicity was primarily European American (80.5%), but also Asian American (4.9%), and other/mixed (14.6%). Parents' level of education ranged from less than high school (mothers, 0%; fathers 2.4%), to high school (2.4%, mothers; 2.4% fathers), to more than high school, less than college (7.1%, mothers; 9.5%, father), to college (42.9%, mothers, 33.3%, fathers), to more than college (4.7%, mothers; 9.5%, fathers).

Imaging of White Matter and Gray Matter

All scans were acquired at the Diagnostic Imaging Sciences Center in collaboration with the Integrated Brain Imaging Center and had Institutional Review Board approval. First diffusion tensor imaging (DTI) scans and then functional magnetic resonance imaging (fMRI) scans were obtained for all 42 children on a Philips 3 T Achieva scanner (release 3.2.2 with the 32- channel head coil) to obtain measures of structural white matter integrity and functional connectivity, respectively. Participants practiced lying still before entering the scanner and were instructed to lie still throughout the scanning. They also practiced the tasks before scanning and had to achieve 90% accuracy to continue participation.

Each participant was screened for MRI safety before entering the scanner. Physiological monitoring was performed using the Philips pulse oximeter placed on the left hand index finger for cardiac recording; and respiration was recorded using the Philips bellows system where the air-filled bellows pad was placed on the abdomen. Head-immobilization was aided by using an inflatable head-stabilization system (Crania, Elekta).

MRI data acquisition. The following MRI series were scanned: 1) 3-plane scout view with gradient echo pulse sequence: TR/TE 9.8/4.6 ms; Field of view 250 × 250 × 50 mm; acquisition time 30.3 s; 2) reference scan (used in parallel imaging) with gradient echo pulse sequence: TR/TE 4.0/0.75 ms; Field of View 530 × 530 × 300 mm; acquisition time 44.4 s; 3) Resting State fMRI scan with echo-planar gradient echo pulse sequence (single shot): TR/TE 2000/25 ms; Field of view 240 × 240 × 99 mm; slice orientation transverse, acquisition voxel size 3.0 × 3.08 × 3.0 mm; acquisition matrix 80 × 80 × 33; slice thickness 3.0, SENSE factor in the AP direction 2.3; epi factor 37; bandwidth in the EPI frequency direction 1933 Hz, SoftTone factor 3.5, sound pressure 6.1 dB, 180 dynamic scans; 5 dummy scans; fold over direction AP, acquisition time 6:14 min/s; 4) B0 field map imaging with gradient echo pulse sequence and 2 echos; TR/TE 11/6.3 ms; delta TE 1.0 ms; slice orientation transverse, Field of view 240 × 240 × 129 mm; voxel size 1.5 × 1.5 × 3.0 mm; acquisition matrix 160 × 160 × 43, output image magnitude and phase, acquisition time 2:29 min/s; 5) MPRAGE structural scan: TR/TE 7.7/3.5 ms, Field of view 256 × 256 × 176 mm, slice orientation sagittal, voxel size 1 × 1 × 1 mm, inversion pulse delay 1100 ms, Sense factor 2 in the AP direction, acquisition time 5:33 min/s; 6) diffusion tensor imaging with echo-planar spin-echo diffusion pulse sequence: TR/TE 8593/78 ms, slice orientation transverse, Field of view 220 × 220 × 128 mm, voxel size 2.2 × 2.2 × 2.0 mm, bvalues 0 and 1000, output images 1 bvalue at 0 and 32 bvalues at 1000 with 32 different diffusion vector non-colinear directions, SoftTone factor 4.0, sound pressure 3.1 dB, bandwidth in the EPI frequency direction 1557.7 Hz, epi factor 57, acquisition time 9:35.7 min/s; and 7) fMRI during the writing tasks: same parameters as with the Resting State fMRI described above except with dynamic scans 387, acquisition time 13:08 min/s.

fMRI writing tasks. It was possible to study writing during imaging by using a novel MRI-compatible stylus, which allows participants to write while in the scanner and stores what they write concurrently and is registered in time with the fMRI data acquisition for subsequent analyses (27). Two kinds of writing tasks were compared. One involved only sublexical handwriting. One involved lexical spelling and sublexical handwriting.. Although planning was assessed during scanning, and the written compositions written after scanning, results for these tasks were reported earlier (28) and not in the current study. During the fMRI writing tasks, a mirror system enabled the participant in the scanner to see the instructions and task on a screen. The tasks and writing pad recordings were all programmed, timed, and coordinated with the scanner triggers using E-prime and in-house LabView software.

fMRI alphabet writing task. The task was to write the letter that sequentially follows a visually displayed letter in alphabet order. There were 6 seconds of instruction for the alphabet task. The alphabet writing task lasted for 4 min and was self-paced. After the visual display of the first letter, the child wrote the next letter in the alphabet. When the child lifted the pen off the tablet then visual display 2 appeared and the process repeated until the 4 minutes were completed.

fMRI spelling writing task. The task was to write the letter in the blank in a visually displayed letter string to create a correctly spelled word, that is, word-specific spelling based on an amalgamation of phonology, orthography, morphology, and semantics (29). There were 6 seconds of instruction for spelling followed by the spelling task that lasted for 4 minutes and was self-paced. After visual display 1, the child wrote a letter in the blank to complete the word spelling. When the child lifted the pen off the tablet, visual display 2 appeared and the process repeated until the 4 minutes were completed.

Brain Data Analyses

Diffusion tensor imaging analysis. Three kinds of diffusivity were analyzed (30, 31, 32): Radial Diffusivity (RD) for diffusivity in directions perpendicular to the principal axis of diffusion, which has been associated with the degree of myelination and number of branching, exiting fibers; Axial Diffusivity (AD) for diffusivity along and parallel to the principal axis, which has been associated with the axon diameter (33, 34, but see 31 for a critical interpretation of these indices); and Mean Diffusivity (MD). Mean diffusivity is a measure of water diffusion which is an average measure across all spatial directions from all angles measured by the diffusion-weighted gradient directions. In other words, MD is not specific for a certain diffusion direction. DTI data were processed with DTIPrep/GTRACT software to ensure quality control and generate the tensors (http://www.nitrc.org/projects/dtiprep). Then custom software (GFORTRAN) was used to

calculate the DTI parameters (axial diffusivity, radial diffusivity, mean diffusivity) from the tensors. FSL software (tract-based spatial statistics, TBSS) was used to co-register and prepare the DTI data for group analysis using a higher level design matrix to perform a voxel by voxel group map comparison between groups. FSL's randomise software, which robustly corrects for multiple comparisons with permutation methods (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/TBSS/UserGuide), was used to generate the group maps, which were co-registered to the FSL standard white matter atlas called JHU white matter atlas (26). A regional analysis was performed within each significant cluster. Altogether 16 brain regions were analyzed for each of the DTI parameters described above, all on the left: superior frontal gyrus, precentral gyrus, anterior corona radiata, superior corona radiata, cingulate gyrus, genu corpus callosum, body corpus callosum, superior frontal white matter, middle frontal white matter, precentral white matter, cortical spinal, cingulate white matter, forceps minor white matter, superior longitudinal fasciculus, uncinate, and mid corpus callosum. All of the brain regions studied were previously shown to be significant in connectivity studies (35-38).

***Functional connectivity analyses*.** Functional images were corrected for motion using FSL MCFLIRT (39), and then high-pass filtered at sigma = 20.83. Motion scores (as given in the MCFLIRT report) were computed for each subject and average motion score (mean absolute displacement) for each of the groups: control 1.31 ± 1.37 mm, dysgraphic 1.50 ± 1.23 mm, dyslexic 1.47 ± 1.03 mm, and OWL LD 1.32+/- 0.638 mm. Spikes were identified and removed using the default parameters in AFNI's 3dDespike. Slice-timing correction was applied with FSL's slicetimer, and spatial smoothing was performed using a 3D Gaussian kernel with FWHM = 4.0 mm. Time series motion parameters and the mean signal for eroded (1 mm in 3D) masks of the lateral ventricles and white matter (derived from running FreeSurfer's recon-all on the T1-weighted image) were analyzed. Co-registration of functional images to the T1 image was performed using boundary based registration based on a white matter segmentation of the T1 image through epi_reg in FSL. The MPRAGE structural scan was segmented using FreeSurfer software; white matter regressors were used to remove unwanted physiological components. Software was written in gfortran to compute a 68x68 correlation matrix which was used in the Brain Connectivity Toolbox. This 68x68 correlation matrix was made by finding the cross correlation between the fMRI time series signal between brain regions where each of the 68 brain regions was parcelled using the cortical regions of the MORI atlas (40). The individual space of the fMRI scan was coregistered to this atlas using FSL FLIRT software.

To conduct Graph Theory Analysis, we used matlab software called "Brain Connectivity Toolbox", https://sites.google.com/site/bctnet/construction in order to perform the complex network analysis/graph theory analysis as described in (13). Clustering coefficients for the nodes in the Cingulate Operculum (CO) network (13, 41) were calculated using this toolbox because of our ongoing programmatic research on self-regulated learning. For this regional analysis we chose brain regions in this network based on important prior research (42) demonstrating the importance of the cingulo-opercular (CO) network in language processing. The CO network is one of the reproducible functionally-connected resting-state networks, is thought to be involved in cognitive control during task performance, and is believed to detect errors in behavior, thereby signaling the possible need for cognitive strategy adjustment (43). The cingulo- opercular network displays increased activity during the performance of many complex cognitive tasks (44); and the strength of the within-network connectivity predicts cognitive performance (45, 46, 47), implying that this network is a "task-control" system that may underlie global cognition. In fact, these networks are hypothesized to represent a dual system of top- down control that supports cognitive ability, given their pattern of activation and connectivity during task performance (48). The CO network is thought to facilitate the maintenance of task-relevant goals and the incorporation of error information to adjust behavior (49).

Brain regions were identified based on the overlap of the 68 brains in this toolbox with the cingulo-operculum network brain regions. Altogether 8 regions of significant fMRI connectivity bilaterally were identified all of which were previously shown to be significant for multiple comparison corrections as processed using FSL software randomise: left and right cingulate gyrus, left and right superior frontal gyrus, left and right middle frontal gyrus, left and right inferior frontal gyrus, left and right superior temporal gyrus, left and right insula, left and right cingulum (cingulate) gyrus, and left and right cingulum (hippocampus). Results reported are for clustering coefficient measures informed by graph theory.

Graph theory-based approaches model the brain as a complex network represented graphically by a collection of nodes (50). In the virtual graph, nodes indicate anatomical elements (e.g., brain regions) and represent the relationships between nodes (e.g., connectivity). After the network modeling procedure, various graph theoretical metrics can be used to investigate the organizational mechanism underlying the relevant networks. The graph-based network analyses allow us not only to visualize the overall connectivity pattern among all the elements of the brain (e.g., brain regions) but also to quantitatively characterize the global organization. In addition, this approach also gives insight into the topological reconfiguration of the brain in response to external task modulation, ageing, disorders, or disease (51, 52, 53, 54, 55). Moreover, this approach provides a vital framework to elucidate the relationship between brain structure and function (57). Both structural and functional brain networks have been demonstrated to organize intrinsically as highly modular small-world architectures capable of efficiently transferring information at a low wiring cost as well as formatting highly connected hub regions (58, 59, 60, 61, 62, 63, 64). Furthermore, the utility of graph-based techniques has been proven by an increasing number of studies to probe potential mechanisms involved in normal development (65, 66, 67, 68), aging (53, 69, 70), and various brain disorders (71, 72, 73, 74, 75).

In graph theory, a clustering coefficient is a measure of the degree to which nodes in a graph tend to cluster together (76, 77). Evidence suggests that in most real-world networks, and in particular social networks, nodes tend to create tightly knit groups characterized by a relatively high density of ties; this likelihood tends to be greater than the average probability of a tie randomly established between two nodes (78, 79). Two versions of this measure exist: the global and the local. The global version was designed to give an overall indication of the clustering in the network, whereas the local gives an indication of the embeddedness of single nodes (80). The main graph theory values reported are the local clustering coefficients which come from a vertex (node) from our set of 68 cortical brain regions (in which case each brain region is tested as a node) and quantifies how close its neighbors are to being a clique (complete graph). Figure 1 is an example of a correlation matrix which was used in the graph theory analysis from one of the typical writers in the control group. Figure 2 is an example of functional brain network from a single participant in the control group.

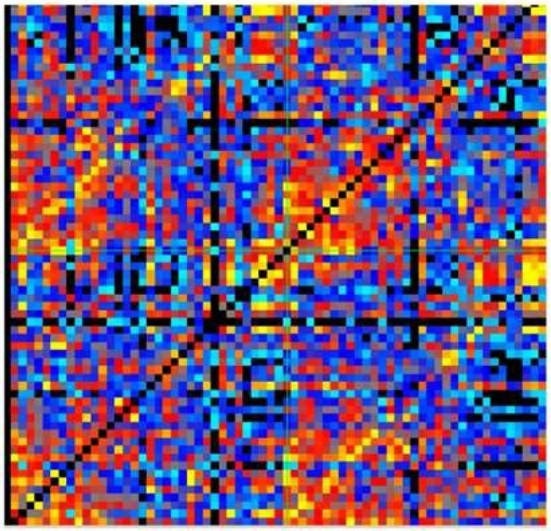

Figure 1. This correlation matrix map of 68x68 dimensions was made from the 68 cortical brain regions during the writing spelling task of a typical writer in the control group.

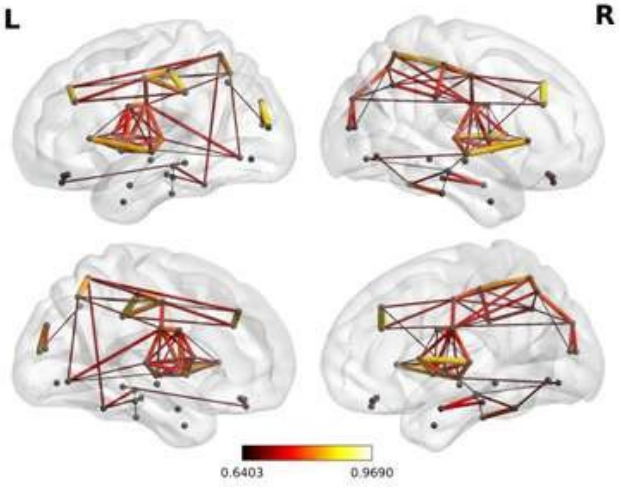

Figure 2. A representative functional brain network in a single participant (typical writer in control group), thresholded at 10% sparsity. Colors correspond to r-values. This figure was generated using BrainNet viewer (https://www.nitrc.org/ projects/bnv).

Results

To control for multiple comparisons for a particular brain region, p was set at a conservative $\leq .001$ for drawing conclusions about DTI indicators or cluster coefficients in the current study. However, to stimulate future research that evaluates if findings replicate to provide converging evidence across studies (81), results significant at p<.05 or .01 are reported in Tables 1-5 notes for comparison with findings in future research studies with larger samples and other samples of students with persisting SLDs-WL beyond the beginning years of elementary school.

Research Question 1: Behavioral Assessment Results for Response to Writing Instruction (RTI)

Only one handwriting measure—copying in one's best handwriting a sentence-- met the p-value criterion set for controlling for multiple comparisons for a significant time effect, F (1, 37)=46.21, p<.001, eta^2=.56, that is, evidence of response to instruction. The measure of oral sentence syntax construction also met the p-value criterion set for controlling for multiple comparisons for a significant time effect, F (1, 37)=15.60, p<.001, eta^2=.30, that is, evidence of response to instruction, and a diagnostic group effect, F (3, 37)=8.04, p<.001, eta^2=.40. Both the measure of dictated spelling, F (3, 37)=11.57, p<.001, eta^2=. 49, and the measure of creating a correct word-specific spelling, which is an analog of the fMRI spelling task, F (3, 28)=8.85, p<.001, eta^2=. 49, also showed a significant diagnostic group effect. On the dictated spelling measure the dyslexia group showed the least improvement from before to after instruction; on the creating a word-specific spelling measure (by adding a letter), only the dyslexia group did not improve. See means in Table 1. However, the diagnostic group x time interaction was not significant. See Table-1 note for indicators of response to instruction based on time effects significant at p <.05 or p<.01.

Research Question 2a: Results for White Matter Diffusion Tensor Imaging (DTI) RTI

For DTI results for different indicators of white matter integrity, see Table 2 for Radial Diffusivity (RD), Table 3 for Axial Diffusivity (AD), and Table 4 for Mean Diffusivity (MD).

Radial Diffusivity (RD). Two brain regions——anterior corona radiata, F(1, 37)=12.15, p<.001, eta^2= .25, and superior frontal region, F(1, 37)=7.85, p<.001, eta^2= .18,——showed significant time effects, that is, evidence of response to instruction. See Table 2 for the means at time 1 and at time 2 for each of the diagnostic groups in these regions. However, no diagnostic group x time interactions were significant for RD. See Table 2 note for seven time effects for RD that were significant at p <.05 or p<.01 but not p<.001.

Axial Diffusivity (AD). Four brain regions——superior corona radiata, F(1, 37)=22.04, p<.001, eta^2= .42, superior frontal region, F(1, 37)=21.81, p<.001, eta^2= .37, middle frontal region, F(1, 37)=17.01, p<.001, eta^2= .32, and superior longitudinal fasciculus, F(1, 37)=20.70, p<.001, eta^2= 1.00,—— showed significant time effects, that is, evidence of response to instruction. See Table 3 for the means at time 1 and at time 2 for AD in each of the diagnostic groups in these regions. However, none of diagnostic group x time interactions were significant at p<.001. See Table 3 note for six diagnostic group x time interactions that were significant at p<.05 or p<.01.

Mean Diffusivity (MD). Five brain regions——anterior corona radiata, F(1, 37)=13.29, p<.001, eta^2= .26, superior corona radiata, F(1, 37)=12.81, p<.001, eta^2= .25, superior frontal region, F(1, 37)=18.28, p<.001, eta^2= .33, middle frontal region, F(1, 37)=13.80, p<.001, eta^2=.40, and superior longitudinal fasciculus, F(1, 37)=15.38, p<.001, eta^2= .29,—— showed significant time effects, that is, evidence of response to instruction. See Table 4 for the means at time 1 and at time 2 for MD in each of the diagnostic groups in these regions. However, no diagnostic group x time interactions were significant at p<.001. See Table 4 note for four diagnostic group x time interactions that were significant at p<.05 or p<.01.

Table 1. Means (Standard Deviations) for Written (Handwriting and Spelling) and Oral (Sentence Formulation) Language Achievement from Before to After Computerized Lessons.

Test	Time 1				Time 2			
	Control	Dysgraphia	Dyslexia	OWL LD	Control	Dysgraphia	Dyslexia	OWL LD
Alphabet 15z (a)	-.98 (.67)	-1.57 (.41)	-1.46 (.62)	-1.54 (.47)	-.09 (.54)	-1.42 (.87)	-.98 (.91)	-1.57 (.26)
Copy Best (b)	12.43 (2.70)	8.10 (3.28)	8.88 (3.59)	8.29 (4.50)	12.43 (3.16)	9.40 (2.78)	10.53 (3.39)	8.14 (4.56)
WIAT Spell (c)	106.86 (14.92)	96.00 (20.17)	82.59 (11.11)	70.86 (9.63)	109.43 (14.27)	101.00 (19.87)	83.71 (8.48)	73.00 (6.14)
TOC Spell (d)	9.00 (3.16)	10.81 (3.09)	9.20 (2.44)	6.40 (2.30)	10.00 (3.56)	11.75 (4.33)	9.00 (2.36)	7.20 (.84)
Form Sent	11.14 (4.38)	8.90 (3.81)	11.77 (1.86)	5.86 (1.57)	12.00 (1.83)	11.60 (2.68)	12.29 (1.36)	9.43 (2.64)

Note. Effects not significant at $p<.001$.
(a) Time Effect, F (1, 36)=7.61, $p<.01$, $eta^2=.17$; Diagnostic Group Effect, $F(3, 36)=5.35$, $p<.01$, $eta^2=.31$.
(b) Diagnostic Group Effect, $F(3, 37)=3.05$, $p<.05$, $eta^2=.20$.
(c) Time Effect, F (1, 37)=6.01, $p<.05$, $eta^2=.14$.
(d) Time Effect, F (1, 28)=4.51, $p<.05$, $eta^2=.14$.

Table 2. Means (Standard Deviations) for Radial Diffusivity (RD) in Left Brain Regions

Brain Region	Time 1				Time 2			
	Control	Dysgraphia	Dyslexia	OWL LD	Control	Dysgraphia	Dyslexia	OWL LD
Superior Frontal Gyrus LGM (a)	4.75 (.26)	4.87 (.19)	4.70 (.47)	4.89 (.32)	4.79 (.26)	4.67 (.34)	4.67 (.32)	4.56 (.24)
Anterior Corona Radiata	5.37 (.57)	5.35 (.61)	5.33 (.58)	5.51 (.41)	5.13 (.41)	5.09 (.55)	5.12 (.48)	5.27 (.37)
Superior Corona Radiata (b)	5.32 (.42)	5.46 (.40)	5.46 (.39)	5.68 (.39)	5.29 (.48)	5.25 (.43)	5.41 (.45)	5.43 (.29)
Body Corpus Callosum (c)	4.59 (.45)	4.72 (.50)	4.69 (.33)	4.87 (.39)	4.49 (.37)	4.54 (.35)	4.54 (.40)	4.78 (.28)
Superior Frontal Region	4.65 (.32)	4.80 (.22)	4.75 (.42)	4.87 (.35)	4.62 (.25)	4.60 (.24)	4.66 (.31)	4.67 (.07)
Middle Frontal Region (d)	5.42 (.52)	5.50 (.41)	5.57 (.42)	5.82 (.24)	5.41 (.63)	5.30 (.34)	5.47 (.38)	5.58 (.30)
Superior Longitudinal Fasciculus (e)	4.95 (.29)	5.04 (.28)	5.01 (.36)	5.18 (.25)	4.94 (.34)	4.94 (.34)	4.95 (.28)	4.94 (.11)
Uncinate Tract (f)	5.61 (.59)	5.71 (.46)	5.66 (.50)	5.99 (.59)	5.48 (.92)	5.48 (.50)	5.64 (.43)	5.71 (.56)
Mid Corpus Callosum (g)	4.59 (.45)	4.72 (.50)	4.69 (.33)	4.87 (.39)	4.49 (.37)	4.54 (.35)	4.54 (.39)	4.78 (.28)

Note. Effects not significant at $p<.001$. When the label has region in the name, it also includes white matter.
(a) Time Effect, F (1, 37)=4.96, $p<.05$, $eta^2=.12$.
(b) Time Effect, F (1, 37)=5.75, $p<.05$, $eta^2=.13$.
(c) Time Effect, F (1, 37)=5.21, $p<.05$, $eta^2=.12$.
(d) Time Effect, F (1, 37)=5.57, $p<.05$, $eta^2=.13$.
(e) Time Effect, F (1, 37)=5.15, $p<.05$, $eta^2=.12$.
(f) Time Effect, F (1, 37)=4.18, $p<.05$, $eta^2=.10$.
(g) Time Effect, F (1, 37)=5.26, $p<.05$, $eta^2=.13$.

Table 3. Means (Standard Deviations) for Axial Diffusivity (AD) in Left Brain Regions

Brain Region	Time 1				Time 2			
	Control	Dysgraphia	Dyslexia	OWL LD	Control	Dysgraphia	Dyslexia	OWL LD
Superior Frontal Gyrus (a)	9.93 (.74)	11.03 (.69)	10.26 (.51)	10.43 (.46)	.97 (.92)	10.27 (.47)	10.26 (.50)	10.29 (.95)
Precentral Gyrus (b)	9.79 (.95)	10.93 (.59)	10.15 (.74)	10.38 (.81)	9.74 (.91)	10.04 (.51)	10.06 (.68)	10.16 (.29)
Superior Corona Radiata	10.57 (.44)	10.50 (.51)	10.41 (.44)	10.88 (.55)	10.40 (.42)	10.14 (.54)	10.24 (.21)	10.36 (.40)
Body Corpus Callosum (c)	12.63 (.77)	12.76 (.37)	12.47 (.70)	12.82 (.55)	12.51 (.54)	12.14 (.41)	12.19 (.57)	12.50 (.27)
Superior Frontal Region (d)	11.04 (.58)	11.30 (.41)	10.82 (.44)	11.41 (.52)	10.90 (.57)	10.77 (.52)	10.71 (.45)	11.01 (.47)
Middle Frontal Region	10.79 (.27)	10.52 (.57)	10.32 (.55)	11.09 (.93)	10.51 (.67)	10.23 (.62)	10.16 (.38)	10.42 (.48)
Precentral Region (e)	10.07 (.64)	11.17 (.54)	10.50 (.45)	10.58 (.73)	10.10 (.60)	10.36 (.47)	10.41 (.48)	10.28 (.37)
Cortical Spinal Tract (f)	10.07 (.69)	11.14 (.47)	10.47 (.51)	10.56 (72)	10.06 (.65)	10.32 (.50)	10.39 (.49)	10.24 (.36)
Cingulum Tract (g)	12.54 (.70)	12.40 (.41)	12.05 (.90)	12.57 (.67)	12.84 (.22)	11.71 (.56)	11.84 (.59)	12.36 (.43)
Forceps Minor (h)	13.25 (.91)	13.13 (.77)	12.59 (1.29)	13.39 (.69)	13.72 (.28)	12.32 (.83)	12.46 (.83)	13.24 (.53)
Superior Longitudinal Fasciculus (i)	10.35 (.36)	10.72 (.28)	10.21 (.37)	10.75 (.40)	10.33 (.48)	10.17 (.37)	10.14 (.35)	10.35 (.36)
Uncinate Tract (j)	10.47 (.30)	10.11 (.94)	10.00 (.71)	10.52 (.49)	10.26 (.50)	9.74 (.82)	9.96 (.52)	10.09 (.41)
Mid Corpus Callosum (k)	12.61 (.76)	12.75 (.37)	12.46 (. 70)	12.81 (.55)	12.50 (.53)	12.12 (.41)	12.17 (.57)	12.49 (.27)

Note. Effects not significant at $p<.001$. When the label has region in the name, it also includes white matter.
(a) Time Effect, F (1, 37)=4.66, $p<.05$, $eta^2=.11$; Time x Diagnostic Group, $F(3, 37)=4.24$, $p<.01$, $eta^2=.26$.
(b) Time Effect, F (1, 37)=5.73, $p<.05$, $eta^2=.13$; Time x Diagnostic Group, $F(3, 37)=2.89$, $p<.05$, $eta^2=.19$.
(c) Time Effect, F (1, 37)=7.45, $p<.01$, $eta^2=.17$.
(d) Time x Diagnostic Group, F (3, 37)=3.00, $p<.05$, $eta^2=.20$.
(e) Time Effect, F (1, 37)=8.51, $p<.01$, $eta^2=.19$; Diagnostic Group Effect, F (3, 37)=3.23, $p<.05$, $eta^2=.21$; Time x Diagnostic Group, F (3, 37)=4.24, $p<.01$, $eta^2=.26$.
(f) Time Effect, F (1, 37)=7.98, $p<.01$, $eta^2=.18$; Diagnostic Group Effect, F (3, 37)=2.98, $p<.05$, $eta^2=.20$; Time x Diagnostic Group, F (3, 37)=3.79, $p<.05$, $eta^2=.24$.
(g) Diagnostic Group Effect, F (3, 37)=3.71, $p<.05$, $eta^2=.23$.
(h) Diagnostic Group Effect, F (3, 37)=3.36, $p<.05$, $eta^2=.21$.
(i) Time x Diagnostic Group, $F(3, 37)=6.06$, $p<.01$, $eta^2=.33$.
(j) Time Effect, F (1, 37)=5.27, $p<.05$, $eta^2=.13$.
(k) Time Effect, F (1, 37)=7.50, $p<.01$, $eta^2=.17$.

Table 4. Means (Standard Deviations) for Mean Diffusivity (MD) in Left Brain Regions

Brain Region	Time 1				Time 2			
	Control	Dysgraphia	Dyslexia	OWL LD	Control	Dysgraphia	Dyslexia	OWL LD
Superior Frontal Gyrus (a)	6.48 (.26)	6.93 (.23)	6.55 (.21)	6.74 (.21)	6.52 (.30)	6.53 (.32)	6.53 (.23)	6.47 (.31)
Precentral Gyrus (b)	6.60 (.31)	6.88 (.21)	6.54 (.33)	6.73 (.38)	6.54 (.25)	6.53 (.32)	6.15 (.27)	6.50 (.10)
Anterior Corona Radiata	7.59 (.29)	7.53 (.42)	7.47 (.45)	7.69 (.21)	7.53 (.35)	7.18 (.36)	7. 21 (.35)	7.48 (.34)
Superior Coronal Radiata	7.07 (.31)	7.14 (.16)	7.11 (.29)	7.35 (.39)	6.99 (.34)	6.88 (.28)	7.02 (.27)	7.08 (.26)
Body Corpus Callosum (c)	7.27 (.35)	7.40 (.41)	7.28 (.33)	7.52 (.30)	7.16 (.34)	7.07 (.23)	7.09 (.31)	7.35 (.23)
Superior Frontal Region	6.78 (.20)	6.94 (.18)	6.97 (.27)	7.05 (.29)	6.71 (.16)	6.65 (.26)	6.68 (.19)	6.78 (.16)
Middle Frontal Region	7.21 (.33)	7.17 (.21)	7.15 (.37)	7.58 (.34)	7.11 (.40)	6.94 (.35)	7.03 (.29)	7.19 (.25)
Precentral Region (d)	6.54 (.28)	6.86 (.22)	6.59 (.29)	6.76 (.37)	6.55 (.20)	6.55 (.28)	6.52 (.21)	6.48 (.13)
Cortical Spinal Tract (e)	6.57 (.28)	6.87 (.19)	6.58 (.29)	6.76 (.36)	6.55 (.21)	6.54 (.29)	6.54 (.22)	6.48 (.11)
Cingulate Tract (f)	7.54 (.43)	7.50 (.56)	7.40 (.45)	7.81 (.22)	7.60 (.29)	7.20 (.45)	7.21 (.32)	7.64 (.33)
Superior Longitudinal Fasciculus (g)	6.74 (.20)	6.94 (.18)	6.75 (.28)	7.03 (.25)	6.74 (.23)	6.68 (.26)	6.68 (.23)	6.75 (.12)
Uncinate Tract (h)	7.23 (.37)	7.18 (.38)	7.10 (.38)	7.50 (.51)	7.08 (.54)	6.90 (.35)	7.08 (.32)	7.17 (.43)
Mid Corpus Callosum (i)	7.27 (.35)	7.40 (.40)	7.28 (.33)	7.52 (.30)	7.16 (.34)	7.07 (.23)	7.08 (.31)	7.35 (.23)

Note. Effects not significant at $p<.001$. When the label has region in the name, it also includes white matter.
(a) Time Effect, F (1, 37)=8.55, $p<.01$, eta^2=.19; Time x Diagnostic Group, F(3, 37)=4.11, p<.01, eta^2=.25.
(b) Time Effect, F (1, 37)=11.19, $p<.01$, eta^2=.23; Time x Diagnostic Group, F(3, 37) 2.93, $p<.05$, eta^2=.19.
(c) Time Effect, F (1, 37)=8.61, $p<.01$, eta^2=.19.
(d) Time Effect, F (1, 37)=10.73, $p<.01$, eta^2=.23.
(e) Time Effect, F (1, 37)=11.59, $p<.01$, eta^2=.24; Time x Diagnostic Group, F(3, 37)=3.00, $p<.05$, eta^2=.20.
(f) Time Effect, F (1, 37)=4.78, $p<.05$, eta^2=.29.
(g) Time x Diagnostic Group, F(3, 37)=3.02, $p<.05$, eta^2=.20.
(h) Time Effect, F (1, 37)=6.42, $p<.05$, eta^2=.15.
(i) Time Effect, F (1, 37)=8.68, $p<.01$, eta^2=.19.

Table 5. Means (Standard Deviations) for Graph Cluster Coefficients in fMRI Connectivity (Gray Matter) on Writing Tasks

Brain Task/Brain Region	Time 1				Time 2			
	Control	Dysgraphia	Dyslexia	OWL LD	Control	Dysgraphia	Dyslexia	OWL LD
Handwriting-Writing Next Letter in Alphabet								
Left Lateral Cingulate Gyrus (a)	.024 (.026)	.057 (.016)	.022 (.04)	.086 (.09)	.028 (.06)	.074 (.18)	.011 (.02)	.539 (.65)
Spelling-Fill in Blank								
Left Lateral Cingulate Gyrus (b)	.024 (.025)	.075 (.103)	.022 (.050)	.341 (.636)	.089 (.138)	.017 (.040)	.017 (.026)	.152 (.108)
Left Inferior Cingulate Gyrus (Hippocampus) (c)	.016 (.04)	.000 (.000)	.002 (.06)	.000 (.000)	.000 (.000)	.000 (.000)	.000 (.000)	.074 (.148)
Right Inferior Frontal Gyrus (d)	.202 (.208)	.191 (.143)	.148 (.169)	.030 (.035)	.220 (.136)	.099 (.138)	.175 (.182)	.648 (.328)

Note. Effects not significant at $p<.001$.
(a) Time Effect, F (1, 36)=6.77, $p<.01$, eta^2=.16; Time x Diagnostic Group, F(3, 36)=4.55, $p<.01$, eta^2=.27.
(b) Time Effect, F (1, 36)=4.99, $p<.01$, eta^2=.29.
(c) Group Effect, F (3, 36)=3.04, p<.05, eta^2=.20; Time x Diagnostic Group, F(3, 36)=3.72, $p<.05$, eta^2=.24.
(d) Time Effect, F (1, 36)=9.85, $p<.01$, eta^2=.22.

Research Question 2b: Results for Gray Matter fMRI Connectivity Clustering Coefficient RTI

fMRI alphabet writing task. The diagnostic group effect was significant, F(3, 36)=10.02, $p<.001$, eta^2=46, in left lateral cingulate gyrus. See Table 5 for means. See Table 5 note for a diagnostic group x time interaction on fMRI alphabet writing task that is significant at p<.01.

fMRI spelling task. For this task which requires creating a word-specific spelling by writing a missing letter, the diagnostic group x time effect was significant, F (3, 36)=8.62, $p<.001$, eta^2=.42, in right inferior frontal gyrus. See Table 5 for means. See Table 5 note for graph cluster coefficient results significant at $p<.05$ or .01 in three brain regions on the spelling fill in the blank task.

Research Question 2c: Correlations between DTI and fMRI Connectivity Clustering Coefficient Measures

Correlations were performed between fMRI connectivity cluster coefficients and DTI parameters for RD, AD, or MD at both time 1 and time 2 brain scanning. Neural networks draw on the joint maturation of white matter and gray matter (83) and so may the brain's response to instruction during learning. The DTI parameter measures for these analyses were selected based on the analyses related to research questions 2a, 2b, and 2 c. For the fMRI clustering coefficient, one target region was left lateral cingulate which had shown significant effects at $p<.01$ on both the alphabet handwriting task and the spelling fill in the blank task, which requires writing a letter, and the right inferior frontal gyrus for which there was a significant diagnostic group x time interaction at $p<.001$.

The target DTI parameters, which were not task dependent, remained the same for all correlations. For the RD indicator of white matter integrity, the two target regions were left anterior corona radiata and left superior frontal region. For the AD indicator of white matter integrity, the four target regions were left superior corona radiata, left superior frontal region, left middle frontal region, and left superior longitudinal fasciculus. For the MD the five target regions were left anterior corona radiata, left superior corona radiata, left superior frontal region, left middle frontal region, and left superior longitudinal fasciculus. The correlations were performed on the whole sample because the power was not sufficient for correlations for single diagnostic groups. Of interest were the correlations at time 1 and at time 2 between gray matter fMRI clustering coefficients and the target DTI indicators of white matter integrity.

Alphabet Handwriting fMRI Task

Results of the correlational analyses between the fMRI gray matter clustering coefficient in left lateral cingulate gyrus for this handwriting task (see Table 5) and a target DTI indicator of white matter integrity showed that at Time 1 the only significant gray matter-white matter correlations for alphabet writing were between left lateral cingulate gyrus and MD in left superior frontal white matter, r=.35, p=.03, or MD in left superior longitudinal fasciculus, r=.35, p=.03. At Time 2, however, the only significant correlation between the same gray matter fMRI clustering coefficient (left lateral cingulate gyrus) and a target DTI indicator was with MD in left superior frontal white matter. Following writing instruction the magnitude of the correlation and significance level improved, r=.40, p=.01.

Spelling - Fill in the Blank fMRI Task

Results of the correlational analyses showed that at time 1 the gray matter clustering coefficient in the right inferior frontal gyrus was significantly correlated with AD in left superior frontal white matter, r=.37, p=.02, and at time 2 the same graph cluster in right inferior frontal gyrus was still significantly correlated with AD in left superior frontal white matter, r=.32, p=.05. However, after instructional intervention, three other gray matter-white matter correlations emerged at time 2 for graph cluster in right inferior frontal gyrus with MD in left anterior corona radiata, r=.43, p=.006; with MD in left superior corona radiata, r=.34, p=.03; and with MD in left middle frontal region, r=.33, p=.047. Of these, the magnitude of the correlation and level of significance was greater for right inferior frontal gyrus graph cluster and MD in anterior corona radiata. Brain imaging studies, for example (84), have reported converging evidence for the orthographic coding of written words in right inferior frontal gyrus for students with and without SLDs-WL.

Research Question 3

That more of the time effects than the diagnostic group x time effects were significant at p<.001 shows that all the diagnostic groups including the typical controls often responded to the same instruction aimed at all levels of language. These levels included the ones with hallmark impairments associated with each of the specific learning disabilities included in the current study — dysgraphia (subword), dyslexia (word), and OWL LD (syntax).

Discussion

Research Question 1

Overall the behavioral results support RTI at the behavioral level of analysis for one's best handwriting on a copy task and creation of oral sentence syntax, but less so for spelling in dyslexia. The technology supported instruction was specially designed to teach to all levels of language involved in writing close in time—ranging from subword letter formation, to word spelling, to syntax construction. It was also uniquely tailored to the learning needs of specific kinds of writing disabilities in that at least one set of learning activities in each lesson set was directed to a hallmark impairment of one of the specific diagnoses (25). Some learning activities were designed to help students with dysgraphia focus on the sequence of forming component strokes in letters and sequence of retrieving letters in alphabetic order. Some learning activities were designed to help students with dyslexia develop awareness of different units of sequential sounds in heard and spoken words, units of sequential letters in read and written words, and units of morphology (bases and affixes before and after bases) and then on cross-code interrelationships among phonology, orthography, and morphology in spelling words. Some learning activities were designed to help students with OWL LD order written words to construct word sequences in sentence syntax (both oral and written). Not only the OWL LD group but also the dysgraphia group may have scored lower on oral sentence formation because of difficulty with ordering items, which those with dysgraphia may experience beyond just sequencing strokes in forming letters; they may also experience difficulty in sequencing letters to spell words and sequencing words to create syntax.

Research Questions 2a, 2b, and 2c

During the past 25 years, beginning with the Decade of the Brain in 1990, many imaging studies have shown changes following instruction in brain locations (regions of interest) or connectivity from a seed with another brain region. However, in this study the overall results (significant at p<.001 and in the Tables 1-5 notes) show effects of instruction on changes in DTI (three white matter integrity indicators) and gray matter clustering coefficients on specific fMRI writing tasks. So do the correlations between gray matter clustering coefficients and DTI white matter integrity indicators both before and after the specialized writing instruction but more so after. Of interest, differences in three indicators of white matter integrity (RD, AD, and MD) were found in the left superior frontal region; and two indicators of white matter integrity (RD and MD) in left anterior corona radiata, and (AD and MD) in left superior corona radiata, left middle frontal region, and left superior longitudinal fasciculus. That is, changes in white matter integrity indicators occurred across DTI indicators in the same brain regions. Also of interest, significant diagnostic group effects were observed on both alphabet letter writing and creation of word- specific spelling during scanning in the left lateral cingulate gyrus, a brain region associated with executive functions and self-regulation. Collectively, the findings show that brain white matter integrity and gray matter clustering coefficient measures may show response to writing instruction.

Furthermore, following instruction, the functional network clustering coefficient in left lateral cingulate gyrus during the fMRI alphabet writing task (an index of orthographic loop of working memory) became significantly correlated at conventional levels with MD in superior frontal gyrus. In addition, following instruction, the right inferior frontal gray matter graph clustering coefficient during the fMRI spelling fill in the blank task (an index of word- specific spelling) became significantly correlated at conventional levels with MD in left anterior corona radiata. Although neither of these correlations met the p <.001 criterion of significance, they do provide suggestive evidence to pursue in future research regarding effects of writing instruction on brain RTI. Also, these correlations suggest a relationship between gray matter brain RTI and white matter RTI but do not prove causal relationships. Nevertheless, they provide clues about the brain bases for cognitive writing research findings supporting the mind (cognition)-hand (writing) link (82).

Research Question 3

Results showing main effects for time without any main effects for diagnostic group or time by diagnostic group interaction provide support for the prediction that computerized lessons designed to teach to all levels of language close in time can help all students——not only those with different kinds of SLDs affecting different levels of writing impairment but also typical writers. At a time in education when teachers are expected to optimize the achievement of all students and resources for individualizing

instruction may be limited, it is encouraging that teachers can meet the instructional needs of both those with and without SLDs in writing with specially designed instruction grounded in the language levels of the functional writing system.

Conclusion

The results also have implications for current controversies regarding the identification of students with SLDs and assessing their progress. One view is that identification should be based on assessing who does and does not respond to instruction provided for all students. However, the current results show that evaluating response to instruction (RTI) on both behavioral and brain data provides a richer understanding of the complexities involved in processing and producing written language. Alternative views are that comprehensive behavioral assessment should be administered and that evidence-based assessment should be performed for differential diagnosis of SLDs, for example, using a model of cascading levels of language impairment (14). The current findings raise the issue that a student may appear to be responding visibly to instruction at the behavioral level of analysis (see results in Table 1) but have invisible problems in white matter integrity (see Tables 2, 3, and 4) or in gray matter functional connectivity (see Table 5). That is, documenting visible behavioral RTI alone does not guarantee invisible brain RTI or even that brain RTI is comparable for white matter or gray matter or their relationships. These findings and their implications are significant for both educational/clinical practice and basic science. Hopefully the current study will stimulate future research on this issue in students with and without specific writing disabilities who otherwise are typically developing learners.

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1. Stoeckel, R.E., Colligan, R.C., Barbaresi, W.J., Weaver, A.L, Killian, J.M., Katusic S. 2013. Early speech-language impairment and risk for written language disorder: a population-based study. *Journal Developmental Behavior Pediatrics*. 34:38-44.
2. Katusic, S.K., Colligan, R.C., Barbaresi, W.J, Schaid, D.J., Jacobsen, S.J. 2001. Incidence of reading disability in a population-based birth cohort, 1976-1982, Rochester, Minnesota. *Mayo Clinic Proceedings*. 76:1081-92.
3. Katusic, S. K., Colligan, R.C., Weaver, A.L., Barbaresi W.J. 2009. The forgotten learning disability – Epidemiology of written language disorder in a population-based birth cohort (1976-1982) Rochester, Minnesota. *Pediatrics.* 123:1306-1313.
4. Treiman, R., Kessler, B. 2014. How children learn to write words. New York: Oxford University Press.
5. Catts, H.W., Adlof, S.M., Hogan, T., Weismer, S.E.. 2005. Are specific language impairment and dyslexia distinct disorders? *Journal of Speech, Language, and Hearing Research.* 48:1378–1396.
6. Paul, R., Murray, C., Clancy, K., Andrews, D. 1997. Reading and metaphonological outcomes in late talkers. *Journal of Speech, Language, and Hearing Research*. 40:1037–1047.
7. Thal, D.J., Bates, E., Goodman, J., Jahn-Samilo, J. 1997. Continuity of language abilities: An exploratory study of late-and early-talking toddlers. *Developmental Neuropsychology*. 13:239–273.
8. Silliman, E, Berninger V. 2011. Cross-disciplinary dialogue about the nature of oral and written language problems in the context of developmental, academic, and phenotypic profiles. *Topics in Language Disorders*. 31:6-23.
9. Berninger, V., Nielsen, K., Abbott, R., Wijsman, E., Raskind, W. 2008. Writing problems in developmental dyslexia: Under-recognized and under-treated. *Journal of School Psychology*. 46:1-21.
10. Lefly, D., Pennington, B. 1991. Spelling errors and reading fluency in dyslexics. *Annals of Dyslexia.* 41:143−162.
11. Berninger, V. 2009. Highlights of programmatic, interdisciplinary research on writing. *Learning Disabilities. Research and Practice*. 24:68-79.
12. Hofsteller, S., Tavor, I., Moryosef, S., Assaf, Y. 2013. Short-term learning induces white matter plasticity in the fornix. *Journal of Neuroscience*. 31:12844-12850.
13. Rubinov M., Sporns O. 2010. Complex network measures of brain connectivity: Uses and interpretations. *Neuroimage*. 52:1059-1069.
14. Berninger, V., Richards, T., Abbott, R. 2015**.** Differential diagnosis of dysgraphia, dyslexia, and OWL LD: Behavioral and neuroimaging evidence. *Reading and Writing. An Interdisciplinary Journal*. 28:1119-1153.
15. Niedo, J., Abbott, R., Berninger, V. 2014. Predicting levels of reading and writing achievement in typically developing, English-speaking 2nd and 5th graders. *Learning and Individual Differences.* 32C:54-68.
16. Sanders, E., Abbott, R., Berninger, V. 2017. Sequential prediction of literacy achievement for specific learning disabilities contrasting in impaired levels of language in grades 4 to 9**.** *Journal of Learning Disabilities*. In Press.
17. Lyman, R., Sanders, E., Abbott, R., Berninger, V. 2017. Translating interdisciplinary research on language learning into identifying specific learning disabilities in verbally gifted and average children and youth. *Journal of Behavioral and Brain Research*. Special issue on Learning Disorders. In Press.
18. Wechsler, D . (2003). *Wechsler intelligence scale for children, 4th edition* (WISC-IV). San Antonio, TX: The Psychological Corporation.
19. Leonard, C., Eckert, M., Given, B., Berninger, V., Eden, G. 2006. Individual differences in anatomy predict reading and oral language deficits. *Brain*. 129:3329-3342.
20. Cahill, L., Tiberius, C., Herring J. 2013. PolyOrth: Orthography, phonology, and morphology in the inheritance lexicons. *Written Language and Literacy*. 16:146-185.
21. Nunes, T., Bryant, P. 2009. *Children's reading and spelling. Beyond the first steps*. Oxford UK: Wiley-Blackwell.
22. Nunes, T., Bryant, P., Bindman M. 1997. Morphological spelling strategies: Developmental stages and processes. *Developmental Psychology*. 33:637–649.
23. Venezky, R. 1970. *The structure of English orthography*. The Hague: Mouton.
24. Venezky, R. 1999. *The American way of spelling*. New York: Guilford.
25. Tanimoto, S., Thompson, R., Berninger, V., Nagy, W., Abbott, R. 2015. Computerized writing and reading instruction for students in grades 4 to 9 with specific learning disabilities affecting written language. *Journal of Computer Assisted Learning*. 31:671-689.
26. Hua, K., Zhang, J., Wakana, S., Jiang, H., Li, X., Reich, D.S., Calabresi, P.A., Pekar, J.J., van Zijl, P.C., Mori, S. 2008. Tract probability maps in stereotaxic spaces: Analyses of white matter anatomy and tract-specific quantification. *NeuroImage*. 39:336-347.
27. Reitz, F., Richards, T., Wu, K., Boord, P., Askren, K., Lewis, T., Berninger, V. 2013. A low-cost, computer-interfaced drawing pad for fMRI studies of dysgraphia and dyslexia. Sensors. 13:5099-5108.
28. Wallis, P., Richards, T., Boord, P., Abbott, R., Berninger, V. 2017. Relationships between translation and transcription processes during fMRI connectivity scanning and coded translation and transcription in writing products after scanning in children with and without transcription disabilities. *Creative Education*. In Special Issue on Teaching and Learning Language. In Press.
29. Ehri, L. 1980. The role of orthographic images in learning printed

words. In J. F. Kavanaugh, & R. Venezky (Eds.), *Orthographic reading and dyslexia* (pp. 307-332). Baltimore, MD: University Park Press.
30. Basser, P. J., Pierpaoli, C. 1996. Microstructural and physiological features of tissues elucidated by quantitative-diffusion-tensor MRI. *Journal Magnetic Resonance Series B.* 111(3):209-219.
31. Mori, S. 2007. *Introduction to diffusion tensor imaging*. Amsterdam: Elsevier.
32. Wheeler-Kingshott, C.A., Cercignani, M. (2009). About 'axial' and 'radial' diffusivities. *Magnetic Resonance Medicine*. 61:1255-1260.
33. Song, S.K., Sun, S.W., Ramsbottom, M.J., Chang C., Russell, Cross A.H. 2002. Dysmyelination revealed through MRI as increased radial (but unchanged axial) diffusion of water. *Neuroimage.* 17:1429-1436.
34. Song, S.K. Yoshino, J., Le, T.Q., Lin, S.J., Sun, S.W., Cross, A.H., Armstrong, R.C. 2005. Demyelination increases radial diffusivity in corpus callosum of mouse brain. *Neuroimage*. 26:132-140.
35. Sporns, O. 2013. The human connectome: Origins and challenges. *Neuroimage*. 80: 53–61.
36. Van den Heuvel, M., Sporns, O. 2011. Rich-club organization of the human connectome. *The Journal of Neuroscience*. 31:15775–15786.
37. Purcell, J., Turkeltaub, P.E., Eden, G.F., Rapp B. 2011. Examining the central and peripheral processes of written word production through meta-analysis. *Frontiers in Psychology*. 2:1-16.
38. Richards, T.L., Grabowksi, T., Askren, K., Boord, P., Yagle, K., Mestre Z., Robinson, P., Welker, O., Gulliford, D., Nagy, W., et al. 2015. Contrasting brain patterns of writing-related DTI parameters, fMRI connectivity, and DTI-fMRI connectivity correlations in children with and without dysgraphia or dyslexia. *Neuroimage Clinical*. 8:408-421.
39. Jenkinson, M., Bannister, P., Brady, M., Smith, S. 2002. Improved optimization for the robust and accurate linear registration and motion correction of brain images. *Neuroimage.* 17:825-841.
40. Oishi, K., Faria, A., Jiang, H., Li, X., Akhter, K., Zhang, J., Hsu, J.T., Miller, M.I., van Zijl, P.C., Albert, M., et al. 2009. Atlas-based whole brain white matter analysis using large deformation diffeomorphic metric mapping: application to normal elderly and Alzheimer's disease participants. *Neuroimage.* 46(2):486-499.
41. Horowitz-Kraus, T., Toro-Serey, C., DiFrancesco, M. 2015. Increased resting-state functional connectivity in the cingulo-opercular cognitive-control network after intervention in children with reading difficulties. *PLOS ONE*. 10(7): e0133762.
42. Vaden, K.I., Kuchinsky, S.E, Cute, S.L., Ahlstrom, J.B., Dubno, J.R., Eckert, M.A. 2013. The cingulo-opercular network provides word-recognition benefit. *Journal of Neuroscience.* 33:18979-18986.
43. Dosenbach, N.U., Visscher, K.M., Palmer, E.D., Miezin, F.M., Wenger, K.K., Kang, H.C., Burgund, E.D., Grimes, A.L., Schlaggar,B.L., Petersen, S.E. 2006. A core system for the implementation of task sets. *Neuron*. 50:799-812.
44. Dosenbach, N.U., Fair, D.A., Miezin, F.M., Cohen, A.L., Wenger, K.K., Dosenbach, R.A., Fox, M.D., Snyder, A.Z., Vincent, J.L., Raichle, M.E., et al. 2007. Distinct brain networks for adaptive and stable task control in humans. *Proceedings of National Academy of Science USA*.104(26):11073-11078.
45. Rypma, B., Berger, J.S., Prabhakaran, V., Bly, B.M., Kimberg, D.Y., Biswal, B.B., D'Esposito, M. 2006. Neural correlates of cognitive efficiency. *Neuroimage*. 33:969-979.
46. Seele, W.W., Menon, V., Schatzberg, A.F., Keller, J., Glover, G.H., Kenna, H., Reiss, A.L., Greicius, M.D. 2007. Dissociable intrinsic connectivity networks for salience processing and executive control. *Journal of Neuroscience*. 27:2349-2356.
47. Song, M., Zhou, Y., Li, J., Liu, Y., Tian, L., Yu, C., Jiang, T. 2008. Brain spontaneous functional connectivity and intelligence. *Neuroimage*. 41:1168-1176.
48. Dosenbach, N.U., Fair, D.A, Cohen, A.L., Schlaggar, B.L., Petersen, S.E. 2008. A dual-networks architecture of top-down control. *Trends in Cognitive Science*. 2:99-105.
49. Cocchi, L., Zalesky, A., Fornito, A., Mattingley, J.B. 2013. Dynamic cooperation and competition between brain systems during cognitive control. *Trends in Cognitive Science*. 17:493-501.
50. Eguiluz, V.M., Chialvo, D.R., Cecchi, G.A, Baliki, M., Apkarian, A.V. 2005. Scale-free brain functional networks. *Physical Review Letters*. 94:018102.
51. Bassett, D.S., Bullmore, E.T., Meyer-Lindenberg, A., Apud, J.A., Weinberger, D.R., Coppola, R. 2009. Cognitive fitness of cost efficient brain functional networks. *Proceedings of the National Academy of Sciences U.S.A*. 106:11747-11752.
52. Wang, J., Zuo, X., He, Y. 2010. Graph-based network analysis of resting-state functional MRI. *Frontiers in Systems Neuroscience*. 4(16):1-16.
53. Micheloyannis, S., Vourkas, M., Tsirka, V., Karakonstantaki, E., Kanatsouli, K., Stam, C.J. 2009. The influence of ageing on complex brain networks: a graph theoretical analysis. *Human Brain Mapping*.30:200-208.
54. Pachou, E., Vourkas, M., Simos, P., Smit, D., Stam, C. J., Tsirka, V., Micheloyannis, S. 2008. Working memory in schizophrenia: an EEG study using power spectrum and coherence analysis to estimate cortical activation and network behavior. Brain Topography. 21:128-137.
55. He, Y., Chen, Z., Gong, G., Evans A. 2009. Neuronal networks in Alzheimer's Disease. *Neuroscientis*t. 15:333-350.
56. Bassett, D.S., Bullmore, E.T. 2009. Human brain networks in health and disease. *Current Opinion Neurology*. 22: 340□347.
57. Honey, C.J., Thivierge, J.P., Sporns, O. 2010. Can structure predict function in the human brain? *NeuroImage.* 52:766-776.
58. Salvador, R., Suckling, J., Coleman, M.R., Pickard, J.D., Menon, D., Bullmore, E. 2005, Neurophysiological architecture of functional magnetic resonance images of human brain. *Cerebral Cortex*.15:1332-1342.
59. Achard, S., Bullmore, E.T. 2007. Efficiency and cost of economical brain functional networks. *PLoS Computational Biology*. 3(e17):174-183.
60. He, Y., Chen, Z.J., Evans, A.C. 2007. Small-world anatomical networks in the human brain revealed by cortical thickness from MRI, *Cerebral Cortex*. 17:2407-2419.
61. He, Y., Wang, J., Wang, L., Chen, Z.J., Yan, C., Yang, H., Tang, H., Zhu, C., Gong, Q., Zang, Y., et al. 2009. Uncovering intrinsic modular organization of spontaneous brain activity in humans. *PLoS ONE*. 4:e5226.
62. Chen, Z.J., He, Y., Rosa-Neto, P., Germann, J., Evans, A.C. 2008. Revealing modular architecture of human brain structural networks by using cortical thickness from MRI. *Cerebral Cortex*. 18:2374-2381.
63. Hagmann, P., Cammoun, L., Gigandet, X., Meuli, R., Honey, C.J, Wedeen, V.J., Sporns, O. 2008. Mapping the structural core of human cerebral cortex. *PLoS Biology*. 6:e159.
64. Gong, G., He, Y., Concha, L., Lebel, C., Gross, D.W., Evans, A.C., Beaulieu, C. 2009. Mapping anatomical connectivity patterns of human cerebral cortex using in vivo diffusion tensor imaging tractography. *Cerebral Cortex*.19: 524-536.
65. Fair, D.A., Dosenbach, N.U., Church, J.A, Cohen, A.L., Brahmbhatt, S., Miezin, F. M., Barch, D.M., Raichle, M.E., Petersen, S.E., Schlaggar, B.L. 2007. Development of distinct control networks through segregation and integration. *Proceedings National Academy of Sciences U.S.A*. 104:13507-13512.
66. Fair, D.A, Cohen, A.L., Dosenbach, N.U., Church, J.A,, Miezin, F.M., Barch, D.M., Raichle, M.E., Petersen, S.E., Schlaggar, B.L. The maturing architecture of the brain's default network. *Proceedings National Academy of Science. U.S.A*. 105:4028-4032.
67. Fair, D.A., Cohen, A.L., Power, J.D., Dosenbach, N.U., Church, J.A., Miezin, F. M., Schlaggar, B.L., Petersen, S.E. 2009. Functional brain networks develop from a "local to distributed" organization. *PLoS Computational Biology*. 5:e1000381.
68. Supekar, K., Musen, M., Menon, V. 2009. Development of large-scale functional brain networks in children. *PLoS Biology. 7*:e1000157.
69. Gong, G., Rosa-Neto, P., Carbonell, F., Chen, Z.J., He, Y., Evans, A.C. 2009. Age- and gender-related differences in the cortical anatomical network. *Journal of Neuroscience*. 29:15684-15693.
70. Meunier, D., Achard, S., Morcom, A., Bullmore, E.T. 2009. Age related changes in modular organization of human brain functional networks. *Neuroimage*. 44:715-723.
71. Stam, C.J., Jones, B.F., Nolte, G., Breakspear, M., Scheltens, P. 2007. Small-world networks and functional connectivity in Alzheimer's disease. *Cerebral Cortex*. 17:92-99.
72. He, Y., Chen, Z., Evans, A. 2008. Structural insights into aberrant topological patterns of large-scale cortical networks in Alzheimer's disease, *Journal of Neuroscience.* 28:4756-4766.
73. Buckner, R.L., Sepulcre, J., Talukdar, T., Krienen, F.M., Liu, H.,

Hedden, T., Andrews-Hanna, J.R., Sperling, R.A., Johnson, K.A. 2009. Cortical hubs revealed by intrinsic functional connectivity: mapping, assessment of stability, and relation to Alzheimer's disease. *Journal of Neuroscience*. 29:1860-1873.

74. Liu, Y., Liang, M., Zhou, Y., He, Y., Hao,Y., Song, M., Yu, C., Liu, H., Liu, Z., Jiang, T. 2008. Disrupted small-world networks in schizophrenia. *Brain*. 131:945-961.
75. Wang, L., Zhu, C., He, Y., Zang, Y., Cao, Q., Zhang, H., Zhong, Q., Wang, Y. 2009. Altered small-world brain functional networks in children with attention-deficit/hyperactivity disorder. *Human Brain Mapping*. 30:638-649.
76. He, Y., Evans A. 2010. Graph theoretical modeling of brain connectivity. *Current Opinions in Neurology*. 4:341-350.
77. Watts, D.J, Strogatz..S. 1998. Collective dynamics of 'small-world' networks. *Nature*. 393: 440–442.
78. Wang, J., Wang, L., Zang, Y., Yang, H., Tang, H., Gong, Q., Chen, Z., Zhu, C., He, Y. 2009. Parcellation-dependent small-world brain functional networks: a resting-state fMRI study. *Human Brain Mapping*. 30:1511-1523.
79. Chen, S., Ross, T.J., Zhan, W., Myers, C.S., Chuang, K.S., Heishman, S.J., Stein, E.A., Yang, Y. 2008 Group independent component analysis reveals consistent resting-state networks across multiple sessions. *Brain Research*. 1239:141–151.
80. Holland, P.W., and Leinhardt, S. 1971. Transivity in structural models of small groups, *Comparative Group Studies*. 2:107-124.
81. Tukey, J. 1980. We need both exploratory and confirmatory. *American Statistics*. 34:23–25.
82. Fayol, M., Alamargot, D., and Berninger, V. (Eds.) 2012. Translation of thought to written text while composing: Advancing theory, knowledge, methods, and applications. New York: Psychology Press/Taylor Francis Group.
83. Olesen, P., Nagy, Z., Westerberg, H., and Klingberg, T. 2003. Combined analysis of DTI and fMRI data reveals a joint maturation of white and grey matter in a fronto-parietal network. *Cognitive Brain Research. 18*:48-57.
84. Aylward, E., Richards, T., Berninger, V., Nagy, W., Field, K., Grimme, A., Richards, A.L., Thomson, J.B., Cramer, S.C. 2003. Instructional treatment associated with changes in brain activation in children with dyslexia. Neurology. 61:212-219.
85. Barnett, A., Henderson, L., Scheib, B., and Schulz, C. 2007. *Detailed Assessment of Speed of Handwriting (DASH) Copy Best and Fast*. London: Pearson.
86. Pearson. 2009. *Wechsler Individual Achievement Test, 3rd Ed*. San Antonio, TX.
87. Mather, N., Roberts, R., Hammill, D., Allen, E. 2008. *Test of Orthographic Competence (TOC)*. Austin, TX: Pro-Ed.
88. Semel, E., Wiig, E. H., Secord, W.A. 2003. *Clinical Evaluations of Language Fundamentals 4th Edition: Examiner's Manual. San Antonio,TX: Harcourt Assessment, Inc.*