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Gray matter volume changes following reading intervention in dyslexic children

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ABSTRACT

Studies in children and adults with the reading disability developmental dyslexia have shown behavioral improvements after reading intervention. In another line of work, it has been shown that intensive training in a variety of cognitive and sensorimotor skills can result in changes in gray matter volume (GMV). This study examined changes in GMV following intensive reading intervention in children with dyslexia using voxel-based morphometry (VBM). Eleven dyslexic children underwent an eight week training focused on mental imagery, articulation and tracing of letters, groups of letters and words, which resulted in significant gains in reading skills. This was followed by an eight week null period (control) where no intervention was administered and no further significant gains in reading were observed. Structural scans were obtained before the intervention, after the intervention and after the null period. GMV increases between the first two time points were found in the left anterior fusiform gyrus/hippocampus, left precuneus, right hippocampus and right anterior cerebellum. However these areas did not change between time points two and three (control period), suggesting that the changes were specific to the intervention period. These results demonstrate for the first time that (1) training-induced changes in GMV can be observed in a pediatric sample and (2) reading improvements induced by intervention are accompanied by GMV changes.

Introduction

Developmental dyslexia is a neurobiologically-based learning disability in which individuals have difficulty with word decoding, word recognition and spelling and these in turn may negatively impact other reading abilities such as reading comprehension and vocabulary growth (Lyon et al., 2003). These deficits exist even though the individual has the intelligence, educational opportunity and motivation to learn to read (Lyon et al., 2003; Eckert, 2004; Vellutino et al., 2004). Dyslexia is more commonly observed in males than females and estimated to affect between 5.3% and 11.8% of school aged children (Katusic et al., 2001). Given this high incidence of dyslexia and the critical role of reading in the acquisition of knowledge and successful academic outcome, improving reading abilities in these children is an important priority for educators, policy makers and scientists. Over the past decade there has been increased interest amongst neuroscientists to quantify and characterize changes in brain structure, usually gray matter volume (GMV) following controlled learning experiences. These efforts, especially those focusing on the relationship between changes in brain structure and academic achievement in a formal learning environment (Draganski et al., 2006), have important implications for better understanding learning and skill acquisition in the classroom, especially in those children who encounter challenges in their efforts to acquire literacy. To date, no attempts have been made to measure changes in the brain's gray matter in children with dyslexia following a formal, structured learning experience. Here we address this gap and make the connection between behavioral intervention for reading disabilities and measures of brain morphometry, to inquire about the nature of GMV changes following intensive tutoring of children with dyslexia. The results, in conjunction with current understanding of brain-behavioral relationships, will help inform both educators and researchers in an effort to better understand the neural basis for successful reading intervention and potentially to develop programs to best help children who have trouble reading.

There exists now a significant corpus of work characterizing the neuroanatomical profile of dyslexia (for a review see Eckert, 2004). This research includes post mortem studies (Galaburda et al., 1985) and *in vivo* magnetic resonance imaging (MRI) research comparing dyslexic with non-dyslexic populations. The initial MRI research involved manual tracing of a variety of brain regions implicated in language and reading, however more recent research has quantified the neuroanatomical differences in dyslexic children and adults by using a technique known as voxel-based morphometry (VBM) (Ashburner and Friston, 2000). Using this automated method, a

Abbreviations: VBM, voxel based morphometry; GMV, gray matter volume; fMRI, functional MRI; PET, positron emission tomography; ALE, activation likelihood estimate; FA, fractional anisotropy; MRS, magnetic resonance spectroscopy.

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variety of brain structures have been shown to have smaller gray matter volume (GMV) in dyslexics as compared to controls. VBM studies comparing adult dyslexic to age matched control groups shave shown less left temporal GMV (Brown et al., 2001; Vinckenbosch et al., 2005) and less bilateral temporal GMV for the dyslexic groups (Brambati et al., 2004; Steinbrink et al., 2008). Brambati et al. (2004) found less bilateral GMV for dyslexics in the cerebellar nuclei and Brown et al. (2001) also found less left inferior frontal and right cerebellar GMV in the dyslexics. The only two studies of children with dyslexia employing VBM have shown less GMV in bilateral inferior parietal lobule and temporal gyri and left inferior frontal gyrus (Hoeft et al., 2007) and less bilateral lingual gyrus GMV compared to controls as well as left supramarginal gyrus and left posterior cerebellar lobe (Eckert et al., 2005). These regions are consistent with those implicated in studies using other structural analysis methods as described in Eckert (2004).

In parallel, functional brain imaging technologies (functional magnetic resonance imaging: fMRI; positron emission tomography: PET) have been used to investigate reading and language processing in the dyslexic brain. From these Pugh et al. (2001) has proposed a model describing the neural circuitry for reading in normal and disabled readers (2001). The model proposes that three left hemisphere regions are relied upon for typical reading: an inferior frontal region involved in phonological output, a temporo-parietal region involved in rule-based orthographic to phonological processing as well as semantic analysis, and an occipito-temporal region involved in single word identification. These areas are commonly found to be less activated in individuals with dyslexia during paradigms involving reading or reading-related skills. Specifically, temporo-parietal and occipito-temporal regions consistently show hypoactivation for children and adults with dyslexia compared to normal readers in phonologically demanding (real and pseudoword reading) tasks; the inferior frontal cortex is sometimes hyperactive in dyslexics compared to controls on similar tasks (Shaywitz and Shaywitz, 2008). A recent activation likelihood estimate (ALE) meta-analysis of predominantly adult studies of functional brain imaging in dyslexics compared to controls found left hemisphere temporal and parietal areas were most likely to be less active in dyslexics than controls, although support for inferior frontal hyperactivation was not found (Maisog et al., 2008).

In a study of dyslexic children, different results were found in comparisons with reading matched vs. age matched controls. When compared to both control groups the posterior network hypoactivation was found for dyslexics, however the hyperactivation in the frontal network was only found when compared to age matched controls, suggesting that the posterior hypoactivation represents a functional deficit of dyslexia, while the frontal hyperactivation is more representative of reading ability (Hoeft et al., 2007). Together these studies in children and adults point to a left hemisphere network that is impacted by an individual's reading disability. Notably these brain regions overlap with those that have demonstrated anatomical differences, as described above.

Most recently these functional brain imaging methodologies have been used to investigate whether the differences observed between dyslexic and normal readers change when the investigators intervene and improve reading ability in dyslexic individuals. Intervention studies in dyslexic children have shown changes in behavioral measures (i.e. increased performance in reading) and physiological changes measured using fMRI (Shaywitz et al., 2004; Aylward et al., 2003, Temple et al., 2003). While different types of interventions were given in these studies, similar patterns of increased activity were observed in bilateral frontal and temporo-parietal regions. An intervention study in adult dyslexics showed increases in activation in bilateral temporal and parietal areas as well as the right inferior frontal gyrus (Eden et al., 2004).

While these studies speak to physiological changes in brain function following intensive training regimens focused on reading, it is not yet known if there are parallel changes in cortical anatomy. Several longitudinal studies using VBM analysis have shown changes in subjects' GMV after training. Draganski et al. (2004) followed a group of adults who were scanned before and after learning to juggle, and after not juggling for 3 months. An increase in GMV in area V5/MT (known to be integral to visual motion processing) was observed following the training, yet after the third scan, following a period of no training, there appeared to be a reversal of this pattern in the form of GMV decrease (although it was not significant over the time observed). Other longitudinal VBM studies have examined GMV change after a variety of tasks including more juggling tasks (Driemeyer et al., 2008; Boyke et al., 2008; Scholz et al., 2009), medical students studying for an exam (Draganski et al., 2006), mirror reading (Ilg et al., 2008), as well as repetitive transcranial magnetic stimulation (rTMS) on the left superior temporal gyrus (May et al., 2007), cognitive behavioral therapy (CBT) in a chronic fatigue syndrome population (de Lange et al., 2008) and pharmacological (quetiapine) treatment of a schizophrenic population (Stip et al., 2009).

Taken together, this literature has provides insight into the plasticity of the adult brain during learning. Increases in gray matter density seen early on (i.e. within one week after onset of training) (Driemeyer et al., 2008), suggest changes in spine/synapse density or cell body increases rather than neuronal or glial genesis. Longer term increases in hippocampal gray matter (Draganski et al., 2006) are more likely to reflect this slower process of neurogenesis. Anatomical changes after training have been observed in adults ranging from their early 20's (Draganski et al., 2004) to early 60's (Boyke et al., 2008), but has yet to be studied in a pediatric population.

To this point, changes in GMV after reading intervention have not been shown in children or adults with dyslexia. However, the above studies of training-induced changes in GMV and the fact that brain anatomy varies as a function of reading status (as shown for dyslexic versus non-dyslexic comparisons as well as in studies of illiterates; Castro-Caldas et al., 1998), suggest the possibility that such changes in the cortex might be measurable.

The current study was designed to investigate whether children with dyslexia who receive a reading intervention over an eight week period show changes in GMV. A longitudinal VBM analysis comparing GMV before the intervention, after the intervention and after an equal time period of non-intervention was performed to examine if any changes in gray matter could be observed as a result of the training. This three time point design follows the original Draganski et al. (2004) juggling studies. Based on the anatomical differences known to distinguish dyslexics from non-dyslexics (Eckert, 2004), the physiological changes previously reported following successful reading interventions (Aylward et al., 2003; Shaywitz et al., 2004; Eden et al., 2004) and the nature of the intervention used in the current study (visual imagery of words, multisensory integration and development of the sound representation of words) areas for which GMV changes were predicted included left hemisphere ventral visual, parietal and frontal cortices.

Materials and Methods

Subjects

The eleven dyslexic children (8 male, 3 female) whose data were submitted to this analysis were recruited as part of a larger study from a private school specializing in students with dyslexia. The school records were used to identify students with Woodcock-Johnson III Letter-Word Identification (W-J WID; Woodcock et al., 2001) scores less than 92. Average age of the eleven subjects was 9.1 years (Range 7 yrs 5 months-11 yrs 11 months). IQ scores were obtained prior to the intervention using the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999) which measures verbal (VIQ), performance (PIQ) and full scale (FSIQ) IQ. To be included in the study subjects had to score greater than 80 on these measures. Table 1 presents average scores and standard deviations for this group. Average IQ scores for this group all fell within the normal range (85-115), whilst reading of real words on the Letter-Word Identification fell well below the normal range. All subjects were reported to be free of any other developmental disabilities, congenital or acquired neurological disorders or any injury or disease affecting brain function. Other exclusion criteria included diagnosed language or psychiatric disorders, hearing disorders, diagnosis of any major medical condition and any metallic implants, severe claustrophobia or any other contraindications to MRI scanning.

Behavioral Tests

A battery of behavioral tests were administered prior to and after the intervention as well as after the period of no intervention. Researchers acquiring the behavioral data were blind to the child's status of intervention. Woodcock-Johnson Word Identification (W-J WID; single real word reading; Woodcock et al., 2001), Woodcock-Johnson Word Attack (W-J WA; single pseudo-word reading; Woodcock et al., 2001), and Woodcock-Johnson Passage Comprehension (W-J PC; Woodcock et al., 2001) were used as direct measures of reading ability. The Lindamood Auditory Conceptualization Test (LAC-3; Lindamood and Lindamood, 1971), which measures phonemic awareness, Rapid Automatized Naming (RAN L&N; Denckla and Rudel, 1976a,b), which measures naming fluency for letters and numbers, and Digit Span (Wechsler, 1999), which measures working memory, all measure skills that support reading acquisition and were therefore of interest to this study (Wagner and Torgesen, 1987). Symbol Imagery (Bell, 2010) which measures visual memory for letters and orthographic patterns was used because of the strong imagery component of the reading intervention. All test scores are reported as standard scores (Mean = 100, SD = 15) except Symbol Imagery where the raw score is reported. The measures of single word reading, pseudoword reading and passage comprehension used multiple test forms (in an alternating A/B schedule). While the other tests did not include multiple forms, these are highly reliable tests and should reflect actually changes in score as opposed to test/retest effects. Fig. 1 presents the behavioral data acquired over the three time points.

Reading Intervention

The reading intervention, *Seeing Stars* (Bell, 1997), focuses heavily on imaging/visualization starting with single letters and increasing in difficulty to image one syllable and up to two and three syllable words. In addition, the intervention also has a tactile/motor aspect in which the students finger trace visualized letters, as well as a language production aspect in which they say the letter or sound name out loud while they are tracing the letter in the air. Thus, the intervention utilizes multiple sensory modalities in order to help integrate internal visual and phonological representations. The use of imagery as a focus of the intervention is aligned with several studies relating the use of imagery in reading including a self report study of imagery during reading (Long et al., 1989), use of imagery in semantic retrieval (Kosslyn, 1976), and more direct measures of relating imagery during reading to improved processing and comprehension (Sadoski, 1983; Linden and Wittrock, 1981). The intervention was administered at the subjects' school by employees of Lindamood-Bell Learning Processes who were specifically trained to administer the program. Subjects underwent eight weeks of this intervention followed by an eight week period of no intervention to serve as a control period. All behavioral testing prior to and following the intervention was conducted by research assistants who were members of the research team who were blinded to condition.

Table 1
Behavioral profile, n = 11 mean (sd).

Age	9.1 (1.3) years
WASI	
VIQ	110 (3.5)
PIQ	102 (11.3)
FSIQ	107 (6.5)
WJ Word ID	77 (8.9)

Imaging Procedures

Anatomical scans were obtained at the following three time points of the study: before the reading intervention (T1), after the reading intervention (T2) and after the period of no intervention (T3). At each of these three time points, three 3D T1-weighted MPRAGE images were obtained using a 3 Tesla Siemens Trio whole-body MRI system (TE = 4.38 ms, TR = 1600 ms, TI = 640 ms, FOV = 256 mm, 160 slices, slice resolution 1 mm, voxel size 1 mm^3). A blind image rating system using two raters was used to select the highest quality image from this set of three scans for each subject at each time point. This allowed for the selection of the image with the least amount of motion artifact, a problem that frequently occurs in this age group. An analysis of variance (ANOVA) was performed on the rating scores of the scans used for the three time points to ensure that there were no differences in rating scores across the three time points. As a precaution for avoiding head motion artifacts, children underwent training in a mock scanner prior to the acquisition of MRI data to help acclimate them to the MRI environment (i.e. confined space and noise). Additionally, to ensure fluctuations in the quality of the image was not a contributing factor in the results of this study, noise outside of the brain was measured in two spherical ROIs and shown to be stable across the three time points.

Analysis

To evaluate the efficacy of the reading intervention on standardized measures of reading and skills known to support reading acquisition, a one-way repeated measures ANOVA was conducted on all of the behavioral measures for the three time points, followed by post-hoc t-tests.

For the analysis of the MRI data, those images selected for analysis (one per subject at each time point) were processed according to the optimized VBM protocol (VBM2 toolbox pipeline) described by Good et al. (2001) in SPM2 (Statistical Parametric Mapping, Wellcome Department of Cognitive Neurology, London). This analysis created a GMV template that is specific to this group using the first scan for each subject. Images were then segmented into gray matter, white matter and cerebral spinal fluid. The gray matter images were spatially normalized using the first time point as the source image for each subject. Although the VBM2 toolbox does not automatically modulate images, images were modulated here in order to make volume inferences from the results. The segmented/normalized/modulated images were smoothed using a default setting of 8 mm FWHM. An absolute intensity threshold of 0.2 was used to remove voxels of low gray matter intensity from the analysis.

Statistical analysis for the VBM data was performed using the VBM2 toolbox. In order to determine clusters that significantly changed at any point during the study a one-way within-subjects ANOVA was performed at a height threshold of $p<0.001$ uncorrected, with an extent threshold of $p<0.05$. This height threshold has been used in previous VBM studies of dyslexia (Eckert et al., 2005) as well as other longitudinal VBM studies (Boyke et al., 2008; Driemeyer et al., 2008; Ilg et al., 2008). The cluster extent threshold here utilized the non-stationarity correction toolbox for SPM that allows for cluster level statistics on VBM data. Paired t-tests were then computed using

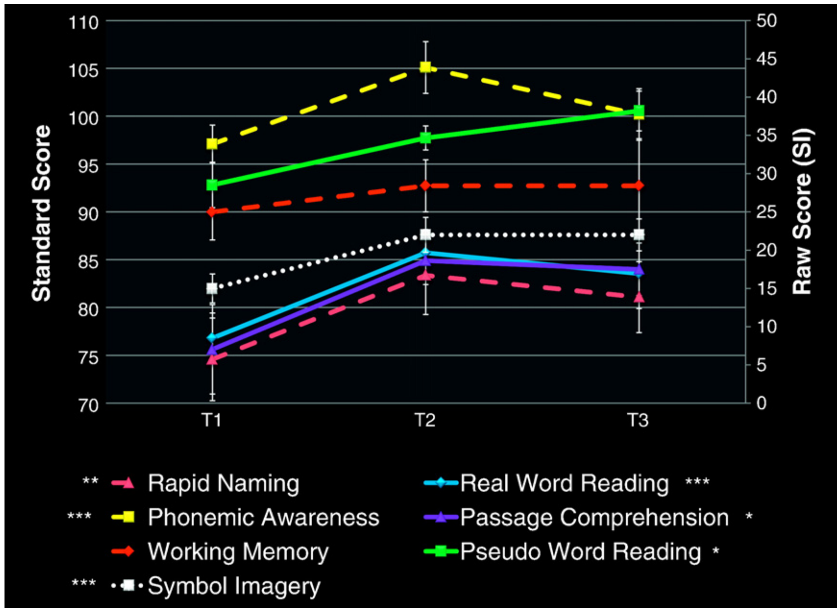

Fig. 1. Behavioral Score Changes Over the Course of Reading Intervention: Test scores for each of the three time periods: before intervention (T1), after intervention (T2) and after the period of no intervention (T3). Solid lines represent direct measures of reading ability and dotted lines represent skills predictive of reading ability (as discussed in text). Symbol Imagery (in white) corresponds with the y-axis on the right because unlike the other measures the scores are raw and not standardized. Significant increases in score between T1 and T2 are noted (* $p<0.05$ ** $p<0.01$ *** $p<0.001$) as tested by post hoc t-tests run after a one way repeated measures ANOVA. No significant changes were seen between time points 2 and 3.

the statistical analysis through the VBM2 toolbox to examine the direction of the effects (T2>T1, T3>T2 and T3>T1).

Average GMV signal (in arbitrary units) from these clusters was extracted using the MarsBaR toolbox (Brett et al., 2002). Average percent change in GMV for the clusters shown to increase significantly during the intervention was determined.

In addition to our main question about GMV changes brought about by reading intervention, we also wanted to explore whether the amount of reading improvement correlated with the amount of GMV change. To address this, a correlation matrix of GMV increases between T1 and T2 in regions identified by the above VBM analysis and behavioral test score changes between T1 and T2 was generated to obtain Pearson's correlation coefficients. The behavioral tests included: single real word reading (W-J WID), pseudoword reading (W-J Word Attack), reading comprehension (W-J PC), phonemic awareness (LAC-3), rapid naming of letters and numbers (RAN) and Symbol Imagery (SI).

Results

Behavioral Results

One-way repeated measures ANOVAs showed significant within-subjects effects over the three time points for all behavioral measures with the exception of working memory (Digit Span). Specifically, there were significant increases in the scores for single real word reading (W-J WID) $F(2,20)=10.77$, $p=0.001$; pseudoword reading (W-J Word Attack) $F(2,20)=6.321$, $p=0.007$; reading comprehension (W-J PC), $F(2,20)=5.420$, $p=0.013$; phonemic awareness (LAC-3) $F(2,20)=5.150$, $p=0.016$; rapid naming (RAN), $F(2,20)=7.655$, $p=0.003$; and Symbol Imagery (SI), $F(2,20)=30.723$, $p<0.001$. Working memory as measured by the Digit Span tests did not show significant changes, $F(2,20)=0.444$, $p=0.648$.

Post hoc t-tests were run on all behavioral measures (except Digit Span) to compare scores between T1 and T2, T1 and T3 as well as between T2 and T3. For the comparisons of scores between T1 and T2, single real word reading (W-J WID), phonemic awareness (LAC-3), and Symbol Imagery (SI) were each significant at $p<0.001$. Rapid Naming of letters and numbers (RAN) was significant at $p<0.01$. Pseudoword reading (W-J Word Attack) and reading comprehension (W-J PC) were both significant at $p<0.05$. Each of these measures was still significant when comparing T3 with T1 except for phonemic awareness (LAC-3). However, there were no significant changes in performance when comparing the scores between T2 and T3. A graphic representation of these behavioral score changes over the three Time Points are shown in Fig. 1.

Anatomical Results: ANOVA

The F test (2,20) employed in theVBM2 toolbox identified seven regions with significant changes in GMV during the course of the study. In the left hemisphere, the anterior fusiform gyrus extending into the hippocampus (BA 20; x = -36, y = -11, z = -24; F = 55.58), the superior frontal gyrus (BA 10; x = -11, y = 58, z = -12; F = 22.92) and the precuneus (BA 7; x = -17, y = -60, z = 31; F = 18.32) were identified. In the right hemisphere, the hippocampus (x = 32, y = -12, z = -16; F = 20.54), the anterior cerebellum (x = 8, y = -45, z = -10; F = 16.18), the precuneus (BA 7; x = 4, y = -60, z = 30; F = 15.95) and the caudate (x = 9, y = 16, z = 9; F = 14.96) were significant. Details for these clusters can be found in Table 2.

Anatomical Results: Paired t-tests

Post hoc t-tests performed using the VBM2 toolbox showed that each of the clusters identified by the ANOVA represented a significant increase in GMV over the course of the study. Specifically, the clusters which increased significantly between T1 and T2 (during the reading intervention) were: the left anterior fusiform gyrus extending into the hippocampus (BA 20; x = -36, y = -11, z = -24), left precuneus (BA 7; x = -17, y = -60, z = 31) right hippocampus (x = 31, y = -14, z = -15), and right anterior cerebellum (x = 7, y = -46, z = -11). Clusters from the ANOVA that demonstrated a significant increase between T1 and T3 were: the left anterior fusiform gyrus (BA 20; x = -36, y = -11, z = -24), right hippocampus (x = 32, y = -12, z = -16), left precuneus (BA 7; x = -17, y = -60, z = 31), right caudate (x = 9, y = 16, z = 9) and right anterior cerebellum (x = 8, y = -45, z = -10). Details for these

Table 2
VBM Results.

Hemisphere	Talairach Coordinates	Cluster Size	F statistic	Z Score	BA	Anatomical Description
Significant Clusters Identified by One Way ANOVA (within subjects)						
L	x = -36 y = -11 z = -24	369	55.58	5.68	20	Anterior Fusiform Gyrus
L	x = -11 y = 58 z = -12	344	22.92	4.58	10	Superior Frontal Gyrus
R	x = 32 y = -12 z = - 16	182	20.54	4.19	-	Hippocampus
L	x = -17 y = -60 z = 31	289	18.32	4.01	7	Precuneus
R	x = 8 y = -45 z = -10	56	16.18	3.82	-	Anterior Cerebellum
R	x = 4 y = -60 z = 30	85	15.95	3.80	7	Precuneus
R	x = 9 y = 16 z = 9	239	14.96	3.70	-	Caudate
Significant Clusters Identified by T2-T1 Contrast						
L	x = -36 y = -11 z = -24	372	7.83	5.24	20	Anterior Fusiform Gyrus
R	x = 31 y = -14 z = - 15	281	5.72	4.35	-	Hippocampus
L	x = -17 y = -60 z = 31	656	5.37	4.17	7	Precuneus
R	x = 7 y = -46 z = -11	114	5.34	4.16	-	Anterior Cerebellum
Significant Clusters Identified by T3-T1 Contrast						
L	x = -36 y = -11 z = -24	618	10.47	6.05	20	Anterior Fusiform Gyrus
R	x = 32 y = -12 z = - 16	460	6.21	4.58	-	Hippocampus
L	x = -17 y = -60 z = 31	679	5.64	4.32	7	Precuneus
R	x = 9 y = 16 z = 9	748	5.46	4.22	-	Caudate
R	x = 8 y = -45 z = -10	249	5.23	4.11	-	Anterior Cerebellum

clusters can be found in Table 2. The only regions shown to increase significantly during the null period (between T2 and T3) were the left superior frontal gyrus and right precuneus.

Anatomical Results: % GMV Change

For those clusters that were identified as showing an increase in GMV during the intervention (between T1 and T2), the percent change in GMV signal across the three time points was determined using the GMV data extracted using the MarsBaR toolbox (Brett et al., 2002). For these four clusters the average percent GMV signal increases were: 3.40% in the left anterior fusiform, 3.15% in the right hippocampus, 3.51% in the left precuneus and 2.55% in the right cerebellum. Fig. 2 pictures these four clusters and graphs the increase in GMV percentage over the three time points.

Anatomical-Behavioral Correlations

Correlation analysis between the change in behavioral scores and the GMV increase in the four clusters identified by the VBM analysis revealed two significant correlations. The amount of change in phonemic awareness (LAC-3) correlated positively with GMV change in the left precuneus ($R = 0.688$, $p < 0.05$) and the changes in pseudoword reading (Word Attack) correlated positively with GMV change in the right cerebellum ($R = 0.748$, $p < 0.01$) (see Fig. 3 for the scatter plots of these correlations). However, these correlations do not survive correction for multiple comparisons and were not significant comparing T1 to T3.

Discussion

This study followed eleven children with dyslexia who underwent reading intervention and examined if there were increases in GMV along with any intervention-induced gains in reading performance. From an educational standpoint, the intervention was successful, as it resulted in behavioral gains for measures of reading ability as well as for skills that are associated with good reading acquisition. These gains may be due to the multi-sensory approach used in the intervention (integration of phonology and visual imagery), but future studies will need to determine which components of programs such as the one employed here are critical in driving these increases in reading performance. Following the experimental design used in previous training-induced plasticity studies examining changes in GMV (Draganski et al., 2004, 2006) MRI scans were obtained before and after the intervention as well as after a null period where no intervention was given. We predicted increases in GMV in left hemisphere ventral visual, parietal and frontal cortices as these are brain areas that (1) subserve the skills targeted by the intervention program, (2) are known to be involved in the process of reading, (3) have been shown to be under-activated in dyslexic readers, and (4) have been shown to increase in activity following a successful reading intervention. The students showed significant gains in reading (as well as reading-related measures) following the intervention and GMV increases specific to the intervention period (T2 compared to T1) were observed in four areas: left anterior fusiform (extending into the hippocampus), left precuneus, right cerebellum and right hippocampus. Importantly, all of the behavioral gains (except for phonemic awareness) and the changes in these four regions were still significant when comparing T3 with T1, but were not significant when comparing T3 with T2, demonstrating that both behavioral and GMV changes observed on the second scan were associated with the period of intervention. The maintenance of these gains through the null period is encouraging in terms of the in classroom benefit for these children. The left fusiform and precuneus findings support our original predictions based on the nature of the intervention and what is known about the neural signature for reading and reading disability, while the increases in GMV in bilateral hippocampus and the right cerebellum may suggest that a more general learning network was engaged during the intervention period. Importantly, the GMV increases reported here provide evidence that the learning associated with the intervention has structural brain correlates. Understanding how specific changes in behavior relate to specific structural changes in the brain after intensive intervention may be useful in understanding which regions of the brain are targeted by specific interventions and, if the focus of the intervention is further tailored with this knowledge, it might eventually provide a better understanding of how children successfully learn in the general classroom and in special education settings.

Increased GMV in Left Anterior Fusiform/Hippocampus and Right Hippocampus

The peak of the cluster in the left anterior fusiform gyrus falls within the predicted changes for the ventral visual pathway. However, a significant portion of this cluster extended into the left hippocampus. This along with the cluster identified in the right hippocampus suggest a bilateral increase in hippocampal GMV. These

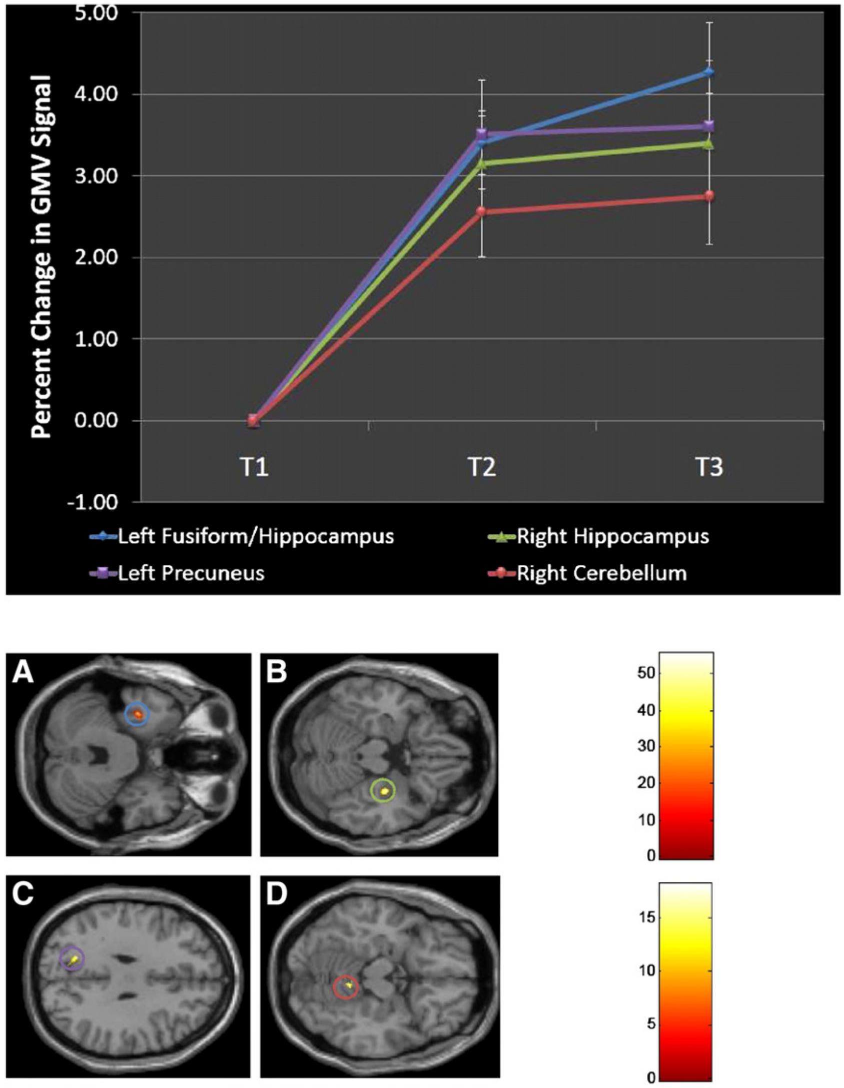

Fig. 2. Gray Matter Volume Increases Over the Course of Reading Intervention: Top) Percent change in GMV signal for the four clusters identified in the VBM2 toolbox pipeline. Bottom) Statistical parametric maps showing the four clusters. Ovals around clusters correspond to the color scheme in the top of the figure. A = left fusiform/hippocampus B = right hippocampus C = left precuneus D = right cerebellum. Scales represent the F score. Top scale corresponds to the left fusiform/hippocampal cluster, bottom scale corresponds with the right hippocampus, left precuneus and right cerebellum.

changes may reflect general learning that is occurring during the intervention period as has been demonstrated in the right hippocampus for students preparing for a medical exam (Draganski et al., 2006). Each of these regions will be discussed in turn.

The cluster with the peak in the left anterior fusiform is part of the ventral visual stream. However, it is more anterior than regions known to be involved in the processing of single words (the so called "visual word form area"; Cohen et al., 2002) and closer to regions that have been implicated in object naming/processing rather than word processing. Renvall et al. (2003) found this region to be more active for naming objects in a complex scene compared to naming colored circles. In a study looking at both naming and viewing of words and objects, multiple regions of the anterior fusiform were identified (Moore and Price, 1999). One peak in BA 20/37 was found to be more active for words and objects (over meaningless stimuli) irrespective of the task, and another peak (slightly anterior and superior in BA 20) was found to be more active specifically during object naming but not word naming (Moore and Price, 1999). The students in the current study were required to make connections between a letter or groups of letters and the sound they make. A possible interpretation is that students with dyslexia are relying on anterior located regions traditionally associated with object processing in order to compensate for regions in the posterior ventral stream that are not supporting word processing in ways that are typical for normal readers. Additionally, Anderson et al. (2000) showed a region in the anterior fusiform that was more active during encoding than retrieval during a word pair association task. Hence another possibility is that the intervention placed increased demand on this region in encoding the connections between letters/groups of letters and sounds, resulting in an increase in GMV. Future studies using functional imaging may be able to address both of these possibilities more directly.

Turning to the hippocampus, it is notable that a GMV study of learning in medical students found hippocampal gray matter to increase over all time points of the study (Draganski et al., 2006). The authors suggest that this could be due to the fact that neurogenesis occurs in the hippocampus, while it does not in other areas where GMV increases have been observed. However, in the current study both the left and right hippocampi showed a significant increase only during the intervention period while increases during the null period did not meet statistical significance. Hence we cannot reinforce the

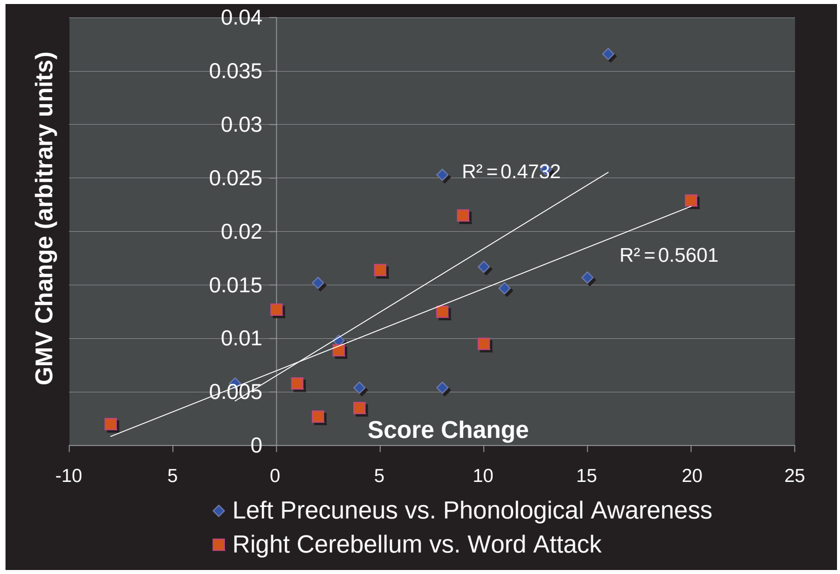

Fig. 3. Correlations of Behavioral Score Change with GMV Change: Scatter plot of GMV change in arbitrary units vs. score change. Blue diamonds represent GMV change in the left precuneus cluster vs. score change on the phonological awareness test (LAC-3). The Pearson's correlation coefficient for this association is R = 0.688 (R^2 = 0.4732) and was significant at $p < 0.05$. Red squares represent GMV change in the right cerebellum cluster vs. score change on the pseudo word reading (Word Attack) test. The Pearson's correlation coefficient for this association is R = .7484 (R2 = 0.5601) and was significant at $p < 0.01$.

interpretation offered by Draganski and colleagues, although we do not rule out the possibility that future studies could show a more robust increase during the control period.

Increase in GMV in the Left Precuneus

An increase in GMV in the left precuneus is consistent with predictions made for the study, based on the fact that the intervention has a strong emphasis on visual imagery. The precuneus has been implicated in various functions including visuo-spatial imagery and memory retrieval (for a review see Cavanna and Trimble, 2006). The left precuneus has been implicated in visual imagery of letters, specifically the visuo-spatial aspects of the imagery (Raij, 1999). Thompson et al. (2009) found bilateral precuneus activation during a spatial location task compared to a spatial-transformation task. In their study subjects viewed an arrangement of letter stimuli and later were primed with a letter and trisected circle; subjects had to decide which third of the trisected circle would be facing the middle of the screen if it was in the position of the primed letter (Thompson et al., 2009). In addition to these studies in typical populations linking letter imagery to the left precuneus, there is also evidence of differences the precuneus in dyslexic readers. A meta-analysis by Maisog et al. (2008) found the left precuneus to be less likely to be active in dyslexic adults compared to controls. In another study, the right precuneus was found to have less GMV in dyslexic adults compared to controls (Menghini et al., 2008).

Further, the amount of GMV increase in the left precuneus in our study showed a positive correlation with score change for the phonemic awareness test (LAC-3). As this is one of the skills targeted by the intervention (in addition to visual imagery), it is encouraging to find a direct relationship between the amount of GMV increase and the amount of improvement in this skill. However, a correlation between visual imagery, another integral part of the intervention, and precuneus GMV increases was not found and as mentioned in the results section, the correlations reported for this study did not survive a correction for multiple comparisons, suggesting these results are somewhat tentative.

Increase in GMV in the Right Cerebellum

The right anterior cerebellum also contained a cluster of increased GMV after the reading intervention. While we did not predict a change here, the findings are notable given the theoretical model linking the cerebellum and dyslexia (Nicolson et al., 2001; Stein and Walsh, 1997; Fawcett and Nicolson, 2007; Laycock et al., 2008), specifically in ways that account for the sensorimotor problems that have been reported in individuals with reading disability. For example, using PET, Nicolson et al. (1999) showed that dyslexic adults had lower right cerebellum activation compared to controls while learning a motor sequence and also when later performing that learned motor sequence. The cerebellum has also been included in a number of reports investigating GMV differences in dyslexic subjects using VBM (Eckert et al., 2005; Brown et al., 2001; Brambati et al., 2004) and other methods used to evaluate anatomical aberrations (reviewed by Eckert, 2004). For example, the right anterior lobe of the cerebellum has been shown to have less overall volume in dyslexic children compared to controls (Eckert et al., 2003). Further, a magnetic resonance spectroscopy (MRS) study showed male dyslexic adults to have biochemical asymmetry in the cerebellum that was suggestive of differences in the cellular density of dyslexics compared to controls (Rae et al., 1998). In a later study by these investigators using anatomical measures, dyslexic adults were found to have abnormally symmetric cerebellar gray matter compared to controls; controls had less left hemisphere gray matter than the dyslexic group (Rae et al., 2002).

It is notable that the amount of increase in GMV observed in the right anterior cerebellum following the intervention showed a positive correlation with the change in score on the pseudoword reading (Word Attack) measure. There is previous evidence for a relationship between phonological decoding skills (e.g. pseudoword reading) and the anterior cerebellum. Subjects characterized as phonological dyslexics (pseudoword decoding scores <90) were shown to have a leftward asymmetry in the anterior cerebellum (Leonard et al., 2001). It is possible that an increase in the right anterior cerebellum reflects a shift to a less asymmetrical anterior cerebellum. However, the subjects in our study were not as weak in their pseudoword reading abilities as the subjects reported by Leonard et al. (2001) (our subjects' weakness was most prominent for real word reading) and asymmetry of the anterior cerebellum prior to the intervention was not investigated. Also, as previously mentioned, the evidence for a relationship between GMV increases in the right cerebellum and pseudoword reading advancement is tentative (the correlation did not survive a correction for multiple comparisons).

Learning and Structural Plasticity

While our study design followed that employed by Draganski et al. (2004) who measured GMV prior to and following a training period (during which subjects learned to juggle) and again following by a period where no practice occurred, there is an important difference in our study, in that reading interventions should provide a lasting improvement (and it did) and subjects do not cease to read. In other words, the skill learned by the participants in the juggling studies (Draganski et al., 2004; Boyke et al., 2008; Driemeyer et al., 2008) was entirely novel to the subjects and the importance of maintaining long-term improvements was not of the same value as reading gains are to a dyslexic student. However, in this regard our study bears some resemblance to another study by Draganski and colleagues (Draganski et al., 2006) in which they followed medical students while they studied for an exam before the semester break. The type of learning the medical students did for their exam and the learning the children did in this study represent skills that are useful and more likely to be used regularly than those used in the juggling studies.

The pattern of GMV change (except for the hippocampus) for both the jugglers and the medical students showed an initial increase during the learning phase followed by a small but non-significant decrease during the null period (Draganski et al., 2004, 2006; Boyke et al., 2008; Driemeyer et al., 2008). This trend suggests that practice may be necessary to maintain the structural changes achieved while learning. The GMV change in the current study shows significant increases during the intervention and non-significant increases in the period after the intervention. This pattern is consistent with the behavioral data, where the scores showed significant improvement during the intervention, followed by non-significant changes in the eight weeks afterward. This is an important finding for educational purposes as it suggests these children are maintaining their behavioral gains without the intervention, but it raises an interesting question as to what cortical mechanisms support these sustained gains. May and Gaser (2006) offer a thorough review of the morphometry and plasticity literature including the possible neuronal correlates of the GMV changes. Importantly, while it is possible to speculate on the nature of these GMV changes after various interventions, it is not possible to determine from the current study or the previous longitudinal VBM literature whether these changes are due to learning or practice effects. Additional experimental groups including those varying in length of interventions and control groups including but not limited to those matched for cognitive effort and baseline behavior would be necessary in order to make more definitive conclusions.

Another important distinction from previous longitudinal VBM studies (Draganski et al., 2004, 2006; May et al., 2007; Boyke et al., 2008; Driemeyer et al., 2008; Ilg et al., 2008; de Lange et al., 2008; Scholz et al., 2009) is that the subjects here are children. The participants in the previous studies range from young adults through elderly subjects, but no subjects below the age of 20 have been studied as of yet. One might predict that changes in GMV in pediatric populations may be especially pronounced, since GMV is already undergoing dramatic changes as part of typical development (Sowell et al., 1999a,b). Even though GMV has not yet been investigated in the context of intervention in children, white matter integrity has been studied. Keller and Just (2009) showed that increases in phonological decoding ability correlated with increased fractional anisotropy (FA) in the left anterior centrum semiovale. While these changes do not correspond with the GMV changes reported in this study, this is not unexpected as both the tissue type analyzed and interventions used are different. Specifically, the duration, intensity and approach of the intervention may modulate which brain regions are impacted. Future studies examining a variety of anatomical measures and addressing different types of interventions will be able to assess the more integral relationships between anatomical changes and reading intervention. Further, because gray matter undergoes significant changes during development from childhood through adulthood (Sowell et al., 1999a, b) these studies will also need to include a wider age range.

Limitations

There are a few important considerations to take into account while interpreting the results of this study. The group was made up of eleven dyslexic children, and while this is similar to group sizes used in previous studies examining GMV changes following training (Draganski et al., 2004) and studies comparing dyslexic subjects to controls (Brambati et al., 2004; Vinckenbosch et al., 2005; Steinbrink et al., 2008), it should be noted that the sample size is small. It is also important to appreciate that we did not have a dyslexic control group that did not receive the intervention to compare with the dyslexic sample receiving the intervention. Instead, the null period following the reading intervention was used as a within subject developmental control period, which is typical in studies in the field of education, where it is difficult to withhold intervention from students who have significantly fallen behind on their academic skills. Further research into the nature of these changes and their relation to reading skills will help translate what is learned in the research environment to helping children directly in the classroom.

Conclusions

This study showed gains in reading skills and increased GMV in dyslexic children after an eight week reading intervention. GMV increases were observed in the left hemisphere in anterior fusiform/hippocampus and precuneus. The left anterior fusiform region is commonly engaged in tasks involving object processing and object naming and may suggest that the dyslexic students are relying on this region to help improve their processing of words. The left precuneus has been implicated in visual imagery and specifically in tasks involving imagery of individual letters. Right hemisphere GMV changes following the intervention were found in the cerebellum and hippocampus. There is a theoretical framework implicating the cerebellum in dyslexia and this study adds a novel contribution to this theory. Finally, the GMV increases in the left hippocampus (extending from the cluster reported for the anterior fusiform gyrus) and right hippocampus may reflect more general learning that is occurring during the intervention. The increases in GMV were restricted to the intervention period and were not observed after the intervention ended, suggesting that these increases in GMV are related to the intervention. This is the first longitudinal VBM analysis in children and demonstrates that changes in brain structure are brought about by intervention. These findings provide encouragement that learning can result in both lasting behavioral and structural changes in children who struggle in learning to read. Further investigation will improve understanding not only for how the brain responds to learning, but in how these findings may be translated into refining interventions and improve the learning experience.

Conflict of Interest

Since the completion of this study Dr. Lynn Flowers has retired from Wake Forest University, and is now employed by Lindamood-Bell Learning Processes.

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