RESEARCH ARTICLE

The Impact of Reading Intervention on Brain Responses Underlying Language in Children With Autism

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Deficits in language comprehension have been widely reported in children with autism spectrum disorders (ASD), with behavioral and neuroimaging studies finding increased reliance on visuospatial processing to aid in language comprehension. However, no study to date, has taken advantage of this strength in visuospatial processing to improve language comprehension difficulties in ASD. This study used a translational neuroimaging approach to test the role of a visual imagery-based reading intervention in improving the brain circuitry underlying language processing in children with ASD. Functional magnetic resonance imaging (MRI), in a longitudinal study design, was used to investigate intervention-related change in sentence comprehension, brain activation, and functional connectivity in three groups of participants (age 8–13 years): an experimental group of ASD children (ASD-EXP), a wait-list control group of ASD children (ASD-WLC), and a group of typically developing control children. After intervention, the ASD-EXP group showed significant increase in activity in visual and language areas and right-hemisphere language area homologues, putamen, and thalamus, suggestive of compensatory routes to increase proficiency in reading comprehension. Additionally, ASD children who had the most improvement in reading comprehension after intervention showed greater functional connectivity between left-hemisphere language areas, the middle temporal gyrus and inferior frontal gyrus while reading high imagery sentences. Thus, the findings of this study, which support the principles of dual coding theory [Paivio 2007], suggest the potential of a strength-based reading intervention in changing brain responses and facilitating better reading comprehension in ASD children. ***Autism Res*** *2016, 9: 141–154*. © 2015 International Society for Autism Research, Wiley Periodicals, Inc.

Keywords: autism; intervention; high imagery; low-imagery; language comprehension; functional MRI; functional connectivity; reading comprehension

Introduction

Impairment in language and communication is a major clinical feature of autism spectrum disorders [ASD; American Psychiatric Association, 2013]. Despite general deficits in language, some studies have found that individuals with ASD perform similarly to typically-developing (TD) individuals on language tasks that have a visual component [Kamio & Toichi, 2000; Moseley et al., 2013 Sahyoun et al., 2009; Toichi & Kamio, 2001]. Behavioral studies have consistently found that children and adolescents with ASD have intact, sometimes enhanced, visuospatial skills in tasks such as the embedded figures test [de Jonge, Kemner, & Engeland, 2006; van Lang et al., 2006; White & Saldaña, 2011] and visual search [Joseph et al., 2009; Manjaly et al., 2007]. In addition, reliance on perceptual processes to support higher-order cognitive and linguistic skills has also been identified as a phenotype of ASD [Belmonte et al., 2004]. However, an increased use of visuospatial processing in individuals with ASD may lead to overreliance on primary processing [Belmonte et al., 2004; Goldstein, Minshew, & Siegel, 1994; Minshew & Goldstein, 1998], with deficits in in language processing emerging when more complex skills are needed [Goldstein et al., 1994]. Additionally, many children with ASD have better reading fluency accompanied by poor comprehension [e.g., Jones et al., 2009; Lindgren et al., 2009; Nation et al., 2006; Newman et al., 2007; Norbury & Nation, 2011]. Jones et al. [2009] found that children with ASD exhibited basic reading skills that were equivalent to their full scale IQ (both of which were in the low average range), accompanied by statistically poorer reading comprehension. Reading comprehension was also found to be inversely correlated with social and communication deficits. Several earlier accounts also indicate that age-equivalent scores for children with ASD are typically lower for reading comprehension than for reading accuracy [Bartak & Rutter, 1973; Lockyer & Rutter, 1969; Nation et al., 2006;

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Snowling & Frith, 1986]. Thus, the discrepancy between reading ability and comprehension in children with ASD is an important issue that needs to be better understood to develop more effective interventions.

Neuroimaging provides a unique framework for investigating the brain mechanisms underlying this complex profile of language in ASD. Functional MRI (fMRI) studies of language comprehension in adults with ASD have found the recruitment of additional/alternative neural routes outside the typical language network [Baron-Cohen, et al., 2001; Kana & Wadsworth, 2012; Mason et al., 2008; Tesink et al., 2011; Wang et al., 2006]. For instance, adults with ASD tend to recruit additional right-hemisphere (RH) brain areas as well as parietal and occipital areas in language comprehension tasks [Kana & Wadsworth, 2012; Kana et al., 2006, Mason et al., 2008]. While neural deficits in language comprehension in adults with ASD are well documented, far fewer neuroimaging studies have addressed this in children with ASD. It appears that early in development, toddlers with ASD have abnormally high activation response in temporal lobe regions in the RH [Eyler, Pierce, & Courchesne, 2012; Redcay & Courchesne, 2008] compared with left-hemisphere (LH) activation in typical children. Thus, brain response to language may be altered in ASD fairly early in development. Reduced activation in core language areas like the left inferior frontal gyrus (LIFG) has also been reported in children with ASD when reading sentences that required higher-order integration [Groen et al., 2010]. Furthermore, children with ASD had increased reliance of visuospatial brain regions, including occipital, parietal, and ventral temporal areas, and reduced activation in frontal language areas when linguistic mediation was needed during a pictorial problem solving task [Sahyoun et al., 2010].

Thus, similar to the findings in adults, atypical recruitment of visual and RH regions in processing language may also be seen in children with ASD. A recent meta-analysis [Samson et al., 2012] found greater reliance on mental imagery and visualization to process words and sentences, specifically the fusiform gyrus and medial parietal cortex. These results were coupled with stronger RH activity for reading tasks in individuals with ASD. To our knowledge, there have been no studies assessing whether increased visuospatial reliance to comprehend language can be utilized as an appropriate avenue for interventions targeting language deficits in ASD children. This is especially pertinent given the plasticity of the developing brain on higher-order language skills Mody & Belliveau (2013). Neuroimaging studies of children with reading comprehension difficulties have not only found increased activity after reading intervention in LH language regions, but also in the RH, such as right inferior frontal gyrus (RIFG) [see Barquero, Davis, & Cutting, 2014 for review]. However, very little research has addressed neurological changes in response to targeted reading intervention in children with ASD. Behavioral findings from reading interventions in children with ASD are also limited, with a recent meta-analysis [El Zein et al., 2014] reporting results from only 12 studies, of which the majority were single-subject case studies. This suggests a dearth of translational studies and a greater need for testing the efficacy of potential reading interventions for children with ASD.

The current study examines the impact of language remediation training on brain responses in children with ASD. The intervention used in this study [Bell, 1991a,1991b] was developed specifically to tap into the visual imagery skills of children with language disabilities to help them develop critical thinking skills to improve both oral and reading comprehension, with the ultimate goal of improving the relation between imagery and language. Despite its significant implications for children with ASD, this intervention has never been applied to study ASD. This study used fMRI in a longitudinal design before and after a reading intervention to compare brain responses between high-functioning children with ASD who received the intervention and those with ASD who received no language-based intervention. Brain activity and functional connectivity were examined in response to a sentence task, the comprehension of which requires the integration of imagery and language. We hypothesized that children with ASD who participated in the intervention would show improvement in sentence comprehension, both increased brain activity in regions underlying language comprehension, such as LIFG and LSTG as well as compensatory strategies such as recruitment of RH or relatively posterior regions. The unique aspect of this study is its focus on translational neuroimaging with the goal of increasing our understanding of established neural networks in children with ASD and translating this knowledge to develop targeted behavioral interventions.

Materials and Methods

Participants

Participants were 26 children with ASD (mean age = 10.9 ± 1.34) and 19 age and IQ-matched TD children (mean age = 10.6 ± 1.59; see Table 1). All children with ASD underwent two fMRI sessions, 10 weeks apart. Thirteen randomly selected children with ASD participated in Visualizing and Verbalizing for Language Comprehension and Thinking (V/V) Intervention Program between imaging sessions (experimental group; ASD-EXP). The other 13 children with ASD received the same V/V intervention after the two imaging sessions were completed (wait-list control group; ASD-WLC). The TD control group underwent one fMRI session and did not participate in the intervention. ASD diagnosis was determined by a licensed clinical psychologist using the Autism Diagnostic

Table 1. Participant Demographics

Characteristic	EXP group (n = 13)	WLC group (n =13)	TD group (n = 19)
Age[a]	10.9 ± 1.53	11.0 ± 1.19	10.6 ± 1.59
Gender			
Male	11	10	14
Female	2	3	5
Self-Identify			
Caucasian	10	6	10
Black		1	9
Asian	3	5	
Hispanic		1	
WASI FSIQ[b]	94.1 ± 11.23	97.9 ± 15.91	96.2 ± 10.89
WASI VIQ[c]	91.0 ± 8.91	92.1 ± 13.70	96.1 ± 12.31
GORT-4 comprehension[d]	76.4 ± 12.0	86.1 ± 11.27	105.3 ± 20.68
SORT-R reading score[e]	105.2 ± 5.73	105.7 ± 8.43	107.1 ± 8.24

Note. value ± standard deviation.
[a] Age in decimal years at first imaging session.
[b] Wechsler abbreviated scale of intelligence, full scale intelligence quotient.
[c] Wechsler abbreviated scale of intelligence, verbal intelligence quotient.
[d] Gray oral reading test—forth edition comprehension subtest at the first imaging session in standard scores.
[e] Slosson Oral Reading Test—revised (SORT-R) reading score at the first imaging session in standard scores.

Observation Schedule [Lord et al., 2000] and/or the Autism Diagnostic Interview-Revised [Lord, Rutter, & Le Couteur, 1994; see Supporting Information for more details regarding additional inclusion criteria]. No statistically significant differences between the ASD group and the TD group were observed for age ($t(43) = 0.70$, $P = 0.487$), verbal IQ (mean ASD = 91.6 ± 11.35; mean TD = 96.1 ± 12.31; $t(43) = 1.26$, $P = 0.264$), or Full-Scale IQ (mean ASD = 96.0 ± 13.67; mean TD = 96.2 ± 10.89; $t(43) = 0.044$, $P = 0.965$). In addition, the ASD-EXP and ASD-WLC groups did not differ on reading comprehension level prior to the first fMRI session, as measured by the Gray Oral Reading Tests—4th Edition (GORT-4; see Supporting Information for details on the GORT-4): Comprehension Score (mean EXP = 76.43 ± 12.0; mean WLC = 86.07 ± 11.27; $t(43) = 1.99$, $P = 0.06$). Among the 26 children with ASD, 5 were female (2 in the ASD-EXP group and 3 in the ASD-WLC group), and all were right-handed. In the TD group, five were female, and all were right-handed. Data from five children with ASD and three TD children were discarded due to artifacts from excessive head motion.

Reading Intervention: Visualizing and Verbalizing for Language Comprehension and Thinking (V/V) Intervention Program

The V/V intervention is a well-established language intervention, based on dual coding of language and imagery, designed by Dr. Nanci Bell, and developed by the Lindamood-Bell Learning Processes [Bell, 1991b; Johnson-Glenberg, 2000; Lindamood & Bell, 1997]. This intervention is based on the use of nonverbal sensory input, in the form of imaged gestalts, to develop oral and written language comprehension, establish vocabulary, and develop higher order thinking skills [Bell, 1991a,b]. It is designed to teach children to form imaged gestalts, or concept imagery, as they read and hear language. Through the sequential teaching methods of the program, the imaged gestalt helps develop the imagery-language connection and improve oral and reading comprehension. The conceptual basis of V/V intervention is the dual coding theory (DCT) which posits that cognition involves the activity of two distinct subsystems, a verbal system specialized for dealing directly with language, and a nonverbal (imagery) system specialized for dealing with nonlinguistic objects and events [Paivio, 2007; Sadoski & Paivio, 2001]. This intensive intervention took place in 4-hr sessions, 5 days a week for 10 weeks, conducted at a Lindamood-Bell Learning Processes center closest to the family. Trained clinicians administered the program in a standardized manner, and were monitored by an experienced supervisor who gives constant feedback to the clinicians. Implementation of V/V intervention to the participants was done one-on-one in a distraction-free setting, with a primary clinician working with the student and an experienced supervisor rotating every hour to monitor progress. The clinical teaching method is a guided approach, as opposed to immediately correcting the participant when he/she makes a mistake (see Supporting Information for more details).

Experimental Paradigm

The experimental task was adapted from a previous design [Kana, et al., 2006], and included sentences involving high-imagery (e.g., *An H on top of an H on top of another H looks like a ladder*) and low-imagery (e.g., *Addition, subtraction, and multiplication are all math skills*). There were 24 high-imagery sentences and 24 low-imagery sentences, which were further divided into true or false categories, such that 12 of the high-imagery sentences and 12 of the low-imagery sentences were true statements, and the other 12 from each category were false statements. Prior to the scan, each participant practiced a shorter version of the task on a laptop. A unique set of stimuli were used during the practice version of the task, and were not included in the longer version of the task presented during the scan. During the scan, participants determined, by button press, whether each sentence was true or false. Each sentence was displayed for 8000 msec with an interstimulus interval of 2000 msec. Each block consisted of three high-imagery or three low-imagery sentences in rotating order, for a total of 16 blocks, 8 low-imagery blocks, and 8 high-imagery blocks, with a 6000 msec rest period between each block of three sentences. In addition, a 24-sec fixation was presented before the start of the task, and after every four blocks, for a total of five, to provide a baseline measure of brain activation. The experiment was presented in the scanner through the stimulus presentation software E-Prime 1.2 (Psychology Software Tools, Pittsburgh, PA) (see Supporting Information for more details).

MRI Data Acquisition

Structural and functional MRI data were acquired at each of the two scanning sessions. The MRI data were collected using a Siemens 3.0 Tesla Allegra Scanner (Siemens Medical Inc., Erlangen, Germany). For the high resolution anatomical scan, T1- weighted scans were acquired using a 160-slice 3D MPRAGE (Magnetization Prepared Rapid Gradient Echo) volume scan with TR = 200 msec, TE = 3.34 msec, flip angle = 7, FOV = 25.6 cm, 256 × 256 matrix size, and 1 mm slice thickness. Functional Magnetic resonance (MR) images were acquired using a single-shot T2*-weighted gradient-echo Echoplanar Imaging (EPI) pulse sequence. We used TR= 1000 msec, TE = 30 msec, and a 60° flip angle for 17 oblique axial slices 5 mm slice thickness with a 1 mm slice gap, a 24 × 24 cm field of view (FOV), and a 64 × 64 matrix, resulting in an in-plane resolution of 3.75 × 3.75 × 5 mm^3.

fMRI Data Analyses

Data were preprocessed using the SPM8 software (Wellcome Department of Imaging Neuroscience, London, UK). Functional images were slice time-corrected to the onset of the middle slice and spatially realigned using *INRIAlign*, a motion correction algorithm unbiased by local signal changes [Freire, Roche, & Mangin, 2002]. During realignment, a mean functional image was computed for each run and then matched to the EPI template provided within SPM8. Data were then spatially normalized to standard Montreal Neurological Institute (MNI) brain space and spatially smoothed using a three-dimensional Gaussian kernel of 8 mm full-width at half-maximum, resulting in a resampled in-plane resolution of 2 × 2 × 2 mm^3 voxels. The functional data were then passed through a 1/128 Hz high-pass filter to remove low-frequency artifacts (e.g., respiratory artifact). In addition, at any time point for which estimates of head motion exceed 2 mm in length in any *x*, *y*, *z* dimension, these specific images were censored from the model by inclusion of a separate regressor that accounted for the variance related to that image only using the Art Detection Tool within MATLAB (http://web.mit.edu/swg/art/art.pdf). If over one-third of the images had to be censored due to movement, that participant was excluded from the analyses. For all analyses, a voxel-wise threshold of $P < 0.05$ (corrected) was used using an uncorrected threshold of $P < 0.005$ and a cluster volume larger than 200 voxels. Monte Carlo simulations conducted in analysis of functional neuroImages (AFNI) were used to select these threshold criteria and reject smaller clusters of activation that may be false positives [Forman et al., 1995; Saad et al., 2006; see Supporting Information for more specifics about the task and analyses used].

Functional Connectivity Analyses

Functional connectivity (the synchronization of brain activation between regions) was computed separately for each participant as a correlation between the average time-course of all the activated voxels in each member of a pair of regions of interest (ROIs) for the task. Anatomical ROIs were defined to encompass the main clusters of activation in the group activation map for each group in both the high-imagery versus fixation and the low-imagery versus fixation contrasts. ROIs were defined using templates from the WFU Pickatlas toolbox within SPM8 using the AAL or Talairach Daemon atlases [Lancaster et al., 2000; Maidjian et al., 2004]. The 11 ROIs included were: anterior cingulate cortex (ACC), lingual gyrus (LG), left middle occipital gyrus (LMOG), LIFG (including Broca's area), left inferior parietal lobule (including Wernicke's area, BA39/BA40), left middle frontal gyrus (LMFG), left medial prefrontal cortex, left middle temporal gyrus (LMTG), left parahippocampal gyrus (LPHG), left precuneus (LPrC), and left fusiform gyrus (LFG; including the visual word form area (VWFA)). The activation time-course was extracted for each participant over the activated voxels within each ROI originated from the normalized and smoothed images. The time-courses from these ROIs were extracted at a *t*-threshold of 4.5 which loosely corresponds to a familywise error corrected *P*-value of 0.05. To control for multiple comparisons, these ROIs were further grouped into larger regions/networks based on location (frontal, parietal, temporal, occipital), with middle temporal gyrus (MTG) being its own node representing the main language region in the temporal lobe.

Results

Behavioral Results

The ASD-EXP group showed significantly greater improvement in reading comprehension (from preintervention to postintervention), as measured by the GORT-4 Comprehension subtest, (paired *t*-test, $t(12) = 3.79$, $P = 0.002$). Conversely, the ASD-WLC group did not have a significant change in reading comprehension from the first to second imaging session (paired *t*-test, $t(12) = 1.12$, $P = 0.247$). The ASD-EXP group significantly improved their reading comprehension scores, compared with the ASD-WLC group (ASD-WLC mean: 3.9%, ASD-EXP mean: 13.9%, $t(24) = 2.05$, $P = 0.050$). The TD group had significantly higher GORT-4 comprehension scores than the children with ASD at the first session (ASD-EXP + ASD-WLC groups versus TD; $t(43) = 4.92$, $P < 0.0001$). After completing the intervention, the ASD-EXP group continued to have significantly lower GORT-4 comprehension scores than the TD group ($t(30) = 4.61$, $P < 0.0001$).

The behavioral results from the fMRI task demonstrated similar performance between the ASD groups and the TD group at the first imaging session. A 3 Group (ASD-EXP, ASD-WLC, TD) × 2 Sentence Type (high-imagery, low-imagery) ANOVA indicated no significant group difference either in reaction time (RT) or in performance accuracy; nor were there any significant interactions between group and sentence type for RT or accuracy. The high-imagery sentences had reliably longer RT across groups [mean low-imagery = 4590 msec, mean high-imagery 5170 msec, $t(43) = 3.26$, $P = 0.002$]. There were no differences in accuracy between sentence types. The ASD-EXP group showed significant improvements in accuracy in both high-imagery and low-imagery sentences from preintervention to postintervention (high-imagery: paired *t*-test, $t(12) = 2.99$, $P = 0.011$; low-imagery: paired *t*-test, $t(12) = 2.35$, $P = 0.035$). There were no differences preintervention to postintervention in RT for the ASD-EXP group; nor were there any differences in RT or accuracy for the ASD-WLC group between imaging sessions.

Brain Activation Results

Results: Preintervention neuroimaging. As there were no differences between the ASD-EXP and ASD-WLC groups at the first imaging session for either high-imagery or low-imagery conditions contrasted with fixation, within-group results of the first imaging session reported here include all children with ASD. The ASD group (ASD-WLC + ASD-EXP groups) and the TD group showed strong activation in visual and language regions while comprehending high-imagery sentences (Table 2). In particular, the children with ASD revealed activation in visual areas, including LMOG, LLG and right cuneus, and LH language regions, including LIFG, LMTG, and posterior superior temporal gyrus (STG). The TD group showed additional activation in the left VWFA, LPHG, and LPrCG (Table 2). In response to high-imagery sentences, both children with ASD and TD children activated additional RH visual regions, such as right lingual gyrus (RLG) and right cuneus, as well as, RH frontal-temporal areas (RIFG, right middle frontal gyrus (RMFG), right superior frontal gyrus (RSFG), and right superior temporal gyrus (RSTG)). In the low-imagery condition, the ASD groups showed primarily LH activation in the LMOG, LIFG, as well as, the Supplementary Motor Area (Table 3). The TD group also showed activation in the LMOG and LIFG, but also showed recruitment of a number of RH regions, such as RLG, RMFG, thalamus, and bilateral medial prefrontal cortex (MPFC) (Table 3).

Between-group comparison results (ASD-EXP + ASD-WLC groups versus TD group) in both the high-imagery and low-imagery conditions revealed that the ASD groups had less activation than the TD group in posterior brain regions, including the LMOG/LG, LFG, and right cuneus (Tables 2 and 3). For both conditions, there were no brain regions that showed less activation in the TD group compared with the ASD groups.

Results: Postintervention neuroimaging (intervention-related changes in fMRI activation). Preintervention to postintervention changes in activation in the ASD-EXP group were examined specific to this group of children with ASD who participated in the intervention between imaging sessions. Of particular interest was assessing changes in activation related to high-imagery sentences, as building visual imagery was the focus of the intervention. For the ASD-EXP group, greater activation was seen at the postintervention session, compared with the preintervention session, in the high-imagery condition in the left cuneus, LMOG, bilateral postcentral gyrus (PoCG), and right precentral gyrus (RPrCG) (see Fig. 1). For the low-imagery condition, the ASD-EXP group showed significantly greater activation at the postintervention session, compared with the preintervention session, in the bilateral cuneus, LMTG, left posterior cingulate cortex (LPCC), right postcentral gyrus (RPoCG), as well as subcortical structures, including the left thalamus and left putamen (see Fig. 1; Supporting Information Fig. 1). No region showed greater activation at preintervention compared with the postintervention session. Within the ASD-WLC group, there were no significant differences in activation between the first and second imaging session for either the high-imagery or low-imagery conditions.

To determine whether the activation related changes in the ASD-EXP group were specific to the intervention, between-group comparisons were conducted targeting differences in postintervention activation between the ASD-EXP group and the ASD-WLC group. In the high-imagery condition, between-group comparison revealed significantly greater activation in the ASD-EXP group compared with the ASD-WLC group, at the second imaging session (while covarying activation at the first imaging session), in the LPrC, left dorsolateral prefrontal cortex (LdlPFC), LMFG, as well as, a number of RH

Table 2. **Brain Regions of Activation for the High-Imagery Sentence Condition Both Within-Group and Between-Group Differences in the ASD Group (ASD-EXP + ASD-WLC Groups; $n = 26$) at the First Imaging Session and the TD Group ($n = 19$; $P < 0.005$, 200 voxels)**

Location of peak activation	High imagery condition			MNI coordinates		
ASD group	Brodmann's area	Cluster size	*t*	*x*	*y*	*z*
L Dorsolateral prefrontal cortex	9	4408[a]	6.65	−46	2	34
L Inferior frontal gyrus	44	4408[a]	4.47	−58	12	14
R Inferior frontal—opercular		436	3.58	46	10	34
L Middle frontal gyrus	46	4408[a]	4.88	−24	−94	−2
R Middle frontal gyrus		215	3.76	34	−4	66
L Superior frontal gyrus	8	1361[b]	4.72	−6	16	50
L Middle temporal gyrus	22	571	4.50	−54	−42	−2
L Inferior parietal lobule		1375[c]	4.33	−30	−50	44
L Superior parietal lobule		1375[c]	4.23	−28	−58	46
R Superior parietal lobule		321	4.42	32	−58	46
L Supplementary motor area	6	1361[b]	4.77	−2	8	58
L Middle occipital gyrus	18	3728[d]	10.29	−24	−102	4
L Lingual gyrus	18	3728[d]	8.77	−24	−94	−6
R Cuneus	17	3728[d]	7.90	12	−94	−2
TD group	Brodmann's area	Cluster size	*t*	*x*	*y*	*z*
L Inferior frontal gyrus	45	3554[e]	5.43	−50	22	20
L Middle frontal gyrus	9	3554[e]	6.18	−44	8	34
R Middle frontal gyrus	9	1698[f]	6.13	44	32	30
R Superior frontal gyrus		1698[f]	4.64	30	10	56
R Superior temporal gyrus		539	5.05	48	−32	2
L Supramarginal gyrus	40	302[g]	3.63	−40	−40	34
L Precuneus	7	302[g]	3.87	−24	−62	38
R Precuneus	19	355	4.68	30	−72	30
R Supplementary motor area	6	1831	5.06	2	18	58
L Thalamus		795	3.17	−2	−32	2
L Visual word form area	37	232	3.49	−48	−56	−6
L Parahippocampal gyrus	35	795	5.86	− −18	−30	−8
R Lingual gyrus	18	8730[h]	11.56	22	−92	−8
L Inferior occipital gyrus	18	8730[h]	8.71	−26	−92	−12
TD > ASD	Brodmann's area	Cluster size	*t*	*x*	*y*	*z*
L Fusiform gyrus		2612[i]	3.51	−30	−64	−10
L Lingual/middle occipital gyrus	17	2612[i]	4.43	−26	−92	10
R Cuneus/superior occipital	18	1128	3.40	24	−81	32

Note. L: left-hemisphere, R: right-hemisphere.
Superscripts (a–i) indicate regions of activation encompassed within the same cluster.

regions, including right middle temporal gyrus (RMTG), right inferior parietal lobule (RIPL), right superior parietal lobule (RSPL), and RIFG (Fig. 2; Supporting Information Fig. 2). In the low-imagery condition, the ASD-EXP group had greater activation than the ASD-WLC group, at second imaging session, in the LPCC and RSPL (Fig. 2). The ASD-WLC group showed no areas of more activation than the ASD-EXP group at second imaging session either in the high-imagery or in the low-imagery conditions.

Relationship between fMRI activation and improvement in reading comprehension scores. Multiple regression analysis was performed to determine whether behavioral improvement on reading comprehension, as measured by the GORT-4 Comprehension subtest, was related to brain activation in the ASD-EXP group, while controlling for verbal Intelligence Quotient (VIQ). Brain activation at the postintervention session for the high-imagery sentences revealed a significant positive correlation between percent change in GORT-4 scores and activation in visual processing regions [LLG, Lcuneus, LMOG], regions involved in language comprehension [LIFG (BA47), LMFG, and LdlPFC] as well as right medial prefrontal cortex (RMPFC) and RIFG (BA47; Fig. 3; Table 4). There was also a significant positive correlation between percent change in GORT-4 scores and activation in the right cingulate cortex ($x = 18$, $y = -10$, $z = 38$) and right insula ($x = 36$, $y = 20$, $z = 10$). Thus, greater improvement in reading comprehension was associated with greater activation in these brain regions postintervention.

Results: Intervention-Related Changes in Functional Connectivity. A series of univariate ANOVAs were conducted to compare the mean connectivities

Table 3. Brain Regions of Activation for the Low-Imagery Sentence Condition Both Within-Group and Between-Group Differences in the ASD Group (ASD-EXP + ASD-WLC Groups; $n = 26$) at the First Imaging Session and the TD Group ($n = 19$; $P < 0.005$, 200 voxels)

Location of peak activation	Low-imagery condition			MNI coordinates		
ASD group	Brodmann's area	Cluster size	*t*	*x*	*y*	*z*
L Dorsolateral prefrontal cortex	9	1817[a]	4.45	−50	6	34
L Superior frontal gyrus	8	576[b]	4.08	−4	14	54
L Insula	13	1817[a]	4.00	−54	10	4
L Supplementary motor area	6	576[b]	3.49	−8	20	68
L Middle occipital gyrus	18	3233[c]	8.61	−22	−102	2
R Middle occipital gyrus	18	3233[c]	6.52	20	−102	6
R Cuneus	17	3233[c]	7.93	12	−98	−2
TD group	Brodmann's area	Cluster size	*t*	*x*	*y*	*z*
L Medial prefrontal cortex		1744[d]	5.01	−6	22	50
R Medial prefrontal cortex		1744[d]	5.19	6	24	52
L Inferior frontal gyrus	45	2784[e]	5.31	−52	22	18
R Middle frontal gyrus		391	4.09	44	32	30
L Superior frontal gyrus	6	1744	4.74	−4	14	58
L Insula	13	2784[e]	4.02	−32	22	−4
R Middle temporal gyrus	39	787[f]	4.40	34	−58	36
R Thalamus		787[f]	5.44	24	−30	2
L Inferior/middle occipital gyrus	18	9991[g]	11.54	−22	−92	−8
R Lingual/middle occipital gyrus	17	9991[g]	11.31	22	−92	−2
TD > ASD	Brodmann's area	Cluster size	*t*	*x*	*y*	*z*
L Middle occipital gyrus	18,19	1279	4.35	−26	−94	8
R Middle occipital gyrus/Precuneus	19,31	610	3.20	30	−72	30
L Fusiform gyrus	19	506[h]	3.31	−30	−64	−10
L Cerebellum		506[h]	3.22	−8	−70	−10

Note. L: left-hemisphere, R: right-hemisphere.
Superscripts (a–h) indicate regions of activation encompassed within the same cluster.

between the ASD-EXP and ASD-WLC groups postintervention using interlobe groupings of ROIs across six network pairs (frontal–parietal, frontal–LMTG, frontal–occipital, LMTG–parietal, LMTG–occipital and parietal–occipital) while controlling for connectivity strength at the first imaging session. There was significantly stronger functional connectivity for high-imagery sentences in the ASD-EXP group postintervention in the LMTG-frontal network ($F(1,25) = 4.530$, $P < 0.05$; Fig. 4). This network also showed a trend toward greater connectivity in the ASD-EXP group for low-imagery sentences ($P = 0.033$), but this result was no longer significant after controlling for connectivity strength at the first imaging session ($P = 0.170$). Given that the only significant network pair was LMTG-frontal for the high-imagery sentences, we further assessed differences in connectivity strength between the ASD-EXP and ASD-WLC postintervention specific to each of the four frontal ROIs (LMTG-medial prefrontal cortex (MPFC), LMTG-inferior frontal gyrus (IFG), and LMTG-middle frontal gyrus (MFG), LMTG-ACC). Greater connectivity postintervention (controlling for preintervention connectivity) in the ASD-EXP group was specific to the LMTG–LIFG pair [$F(1,25) = 4.49$, $P < 0.05$].

Multiple regression analysis was performed to determine whether improvement in reading comprehension was related to functional connectivity in any of our six network pairs in the ASD-EXP group, while controlling for VIQ. A significant positive correlation was found in the ASD-EXP group between change in connectivity strength from preintervention to postintervention in only the LMTG-frontal network and percent change in GORT-4 comprehension scores for both high-imagery ($r(11) = 0.751$, $P = 0.003$) and low-imagery ($r(11) = 0.764$, $P = 0.003$) sentences. The correlations of GORT-4 scores to each of the four frontal ROIs paired with LMTG showed significant positive correlations between change in connectivity strength and percent change in GORT-4 scores in the LMTG–LIFG pair (high-imagery: $r(11) = 0.775$, $P = 0.002$; low-imagery: $r(11) = 0.835$, $P < 0.001$) and LMTG-LMFG pair (high-imagery: $r(11) = 0.833$, $P < 0.001$; low-imagery: $r(11) = 0.788$, $P = 0.002$). No differences were found in connectivity patterns between the TD group and ASD groups at the first imaging session.

Discussion

The results of this training-based neuroimaging study revealed greater postintervention activation in visual brain regions and relatively posterior language regions,

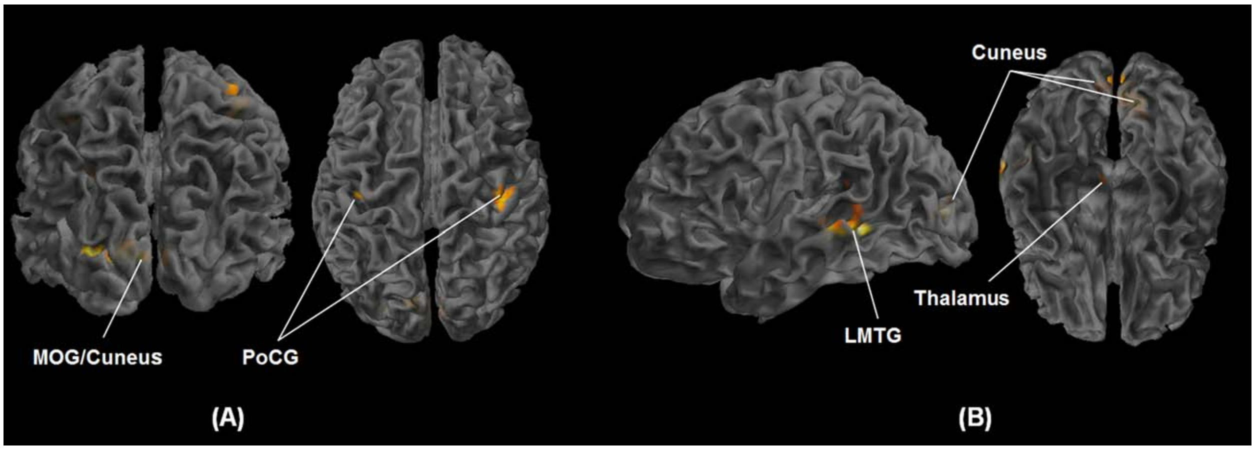

Figure 1. Areas of greater activation postintervention than preintervention in the ASD-EXP group for both the high imagery and low-imagery conditions ($P < 0.01$, 200 voxel extent threshold). MNI coordinates of peak activation: (A) High Imagery: L Cuneus: $x = -14$, $y = -88$, $z = 8$; L MOG: $x = -28$, $y = -84$, $z = 8$; bilateral PoCG: $x = -36$, $y = -34$, $z = 32$ and $x = 40$, $y = -24$, $z = 52$; **R PrCG: $x = 40$, $y = -20$, $z = 66$; (B) Low-Imagery: bilateral Cuneus: $x = 12$, $y = -92$, $z = 8$ and $x = 12$, $y = -72$, $z = 4$; L MTG: $x = -48$, $y = -46$, $z = -2$; **L PCC: $x = -18$, $y = -40$, $z = 32$; **R PoCG: $x = 52$, $y = -14$, $z = 50$; **L Putamen: $x = -26$, $x = -20$, $x = -2$; L Thalamus: $x = -14$, $y = -34$, $z = 4$. **Note: not shown in figure.

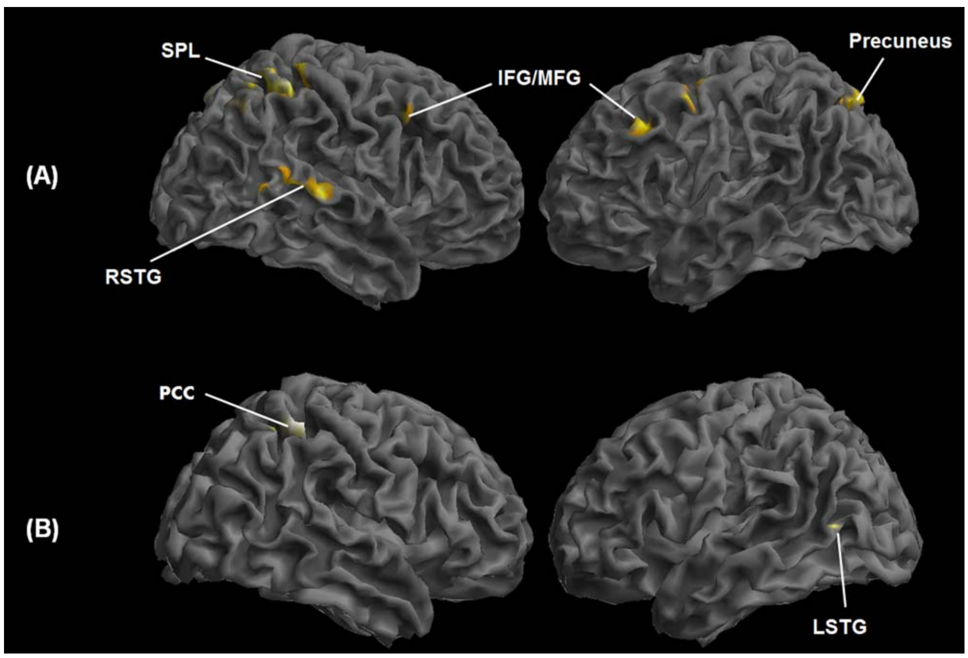

Figure 2. Areas of greater activation in the ASD-EXP group > ASD-WLC group at the second imaging session for both the high imagery and low-imagery conditions ($P < 0.01$, 200 voxel extent threshold). MNI coordinated of peak activation: (A) High Imagery: R STG: $x = 60$, $y = -32$, $z = 4$; **R IPL: $x = 42$, $y = -44$, $z = 56$; R SPL: $x = 34$, $y = -58$, $z = 56$; L Precuneus: $x = -18$, $y = -74$, $z = 50$; L IFG: $x = -48$, $y = 20$, $z = 40$; L MFG: $x = -34$, $y = 4$, $z = 62$; R IFG: $x = 46$, $y = 10$, $z = 40$. (B) Low-Imagery: **L PCC: $x = -18$, $y = -40$, $z = 32$; R IPL: $x = 42$, $y = -44$, $z = 56$. **Note: not shown in figure.

and this activation was correlated with more successful outcomes of the intervention. As would be predicted, increased postintervention activation for high-imagery sentences in visual and posterior language regions, bilateral insula (BA47, including orbital part of IFG), and right PoCG was accompanied by greater improvements in reading comprehension scores for the ASD-EXP group. The anterior insula/IFG has been shown to be activated with increasing processing demands of semantic information [Bookheimer, 2002; Friederici, 2002]. In addition, reading intervention studies have found increases in both left and right insula activation

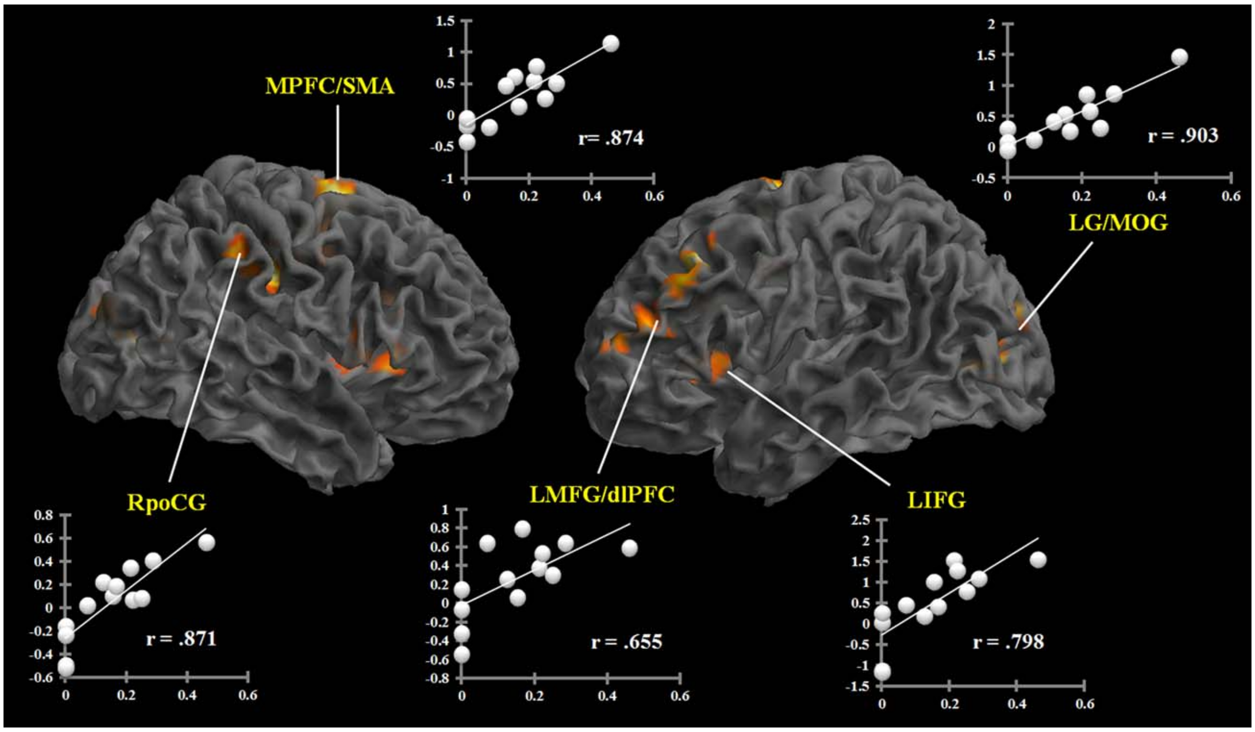

Figure 3. Brain areas showing significant positive correlations between percent change in reading comprehension scores (GORT-4) and activation postintervention to high imagery sentences in the ASD-EXP group ($P < 0.01$, 200 voxel extent threshold). For graphs, *x*-axis is region activation and *y*-axis is percent change in GORT-4 reading comprehension scores.

Table 4. Brain Regions at the Postintervention Session for the High Imagery Sentences With a Significant Positive Correlation Between Percent Change in GORT-4 Scores and Activation in the ASD-EXP Group ($n = 13$; $P < 0.01$, 200 Voxels Extent Threshold)

Location of peak activation EXP group postintervention	High imagery condition			MNI coordinates		
	Brodmann's area	Cluster size	*t*	*x*	*y*	*z*
L Dorsolateral prefrontal cortex	9	260[a]	6.00	−40	24	40
L Middle frontal gyrus		260[a]	4.47	−34	26	34
R Medial frontal gyrus	6	1584[b]	5.74	14	0	64
L Superior frontal gyurs	10	281[c]	3.76	−32	56	12
R Postcentral gyrus	2	1584[b]	5.59	40	−22	34
L Insula/inferior frontal-orbital	47	281[c]	3.84	−32	18	4
R Insula/inferior frontal-orbital	47	451	3.93	34	24	2
L Posterior cingulate cortex	30	220[d]	3.69	−22	−64	6
L Cuneus	18	251	4.44	−26	−82	10
L Lingual gyrus	19	220[d]	6.88	−22	−68	−2
L Middle occipital gyrus	18	220[d]	3.81	−34	−68	0

Note. L: left-hemisphere, R: right-hemisphere.
Superscripts (a–d) indicate regions of activation encompassed within the same cluster.

in children after intervention [Barquero et al., 2014], reflective of insula's role in increased coordination of relayed information [Menon & Uddin, 2010] to improve reading proficiency. Activation of parietal and occipital regions in children with ASD may suggest the use of visualization to aid in sentence comprehension. We also found that functional connectivity of the frontal-temporal language network was strengthened in the children with ASD who received V/V intervention. Furthermore, the performance of participants on the high-imagery sentences (e.g., *An H on top of an H on top of another H looks like a ladder)* was more predictive of behavioral success than that in the low-imagery sentences, which is intuitive given the emphasis on visualizing in V/V intervention to improve reading comprehension. Overall, these findings support the

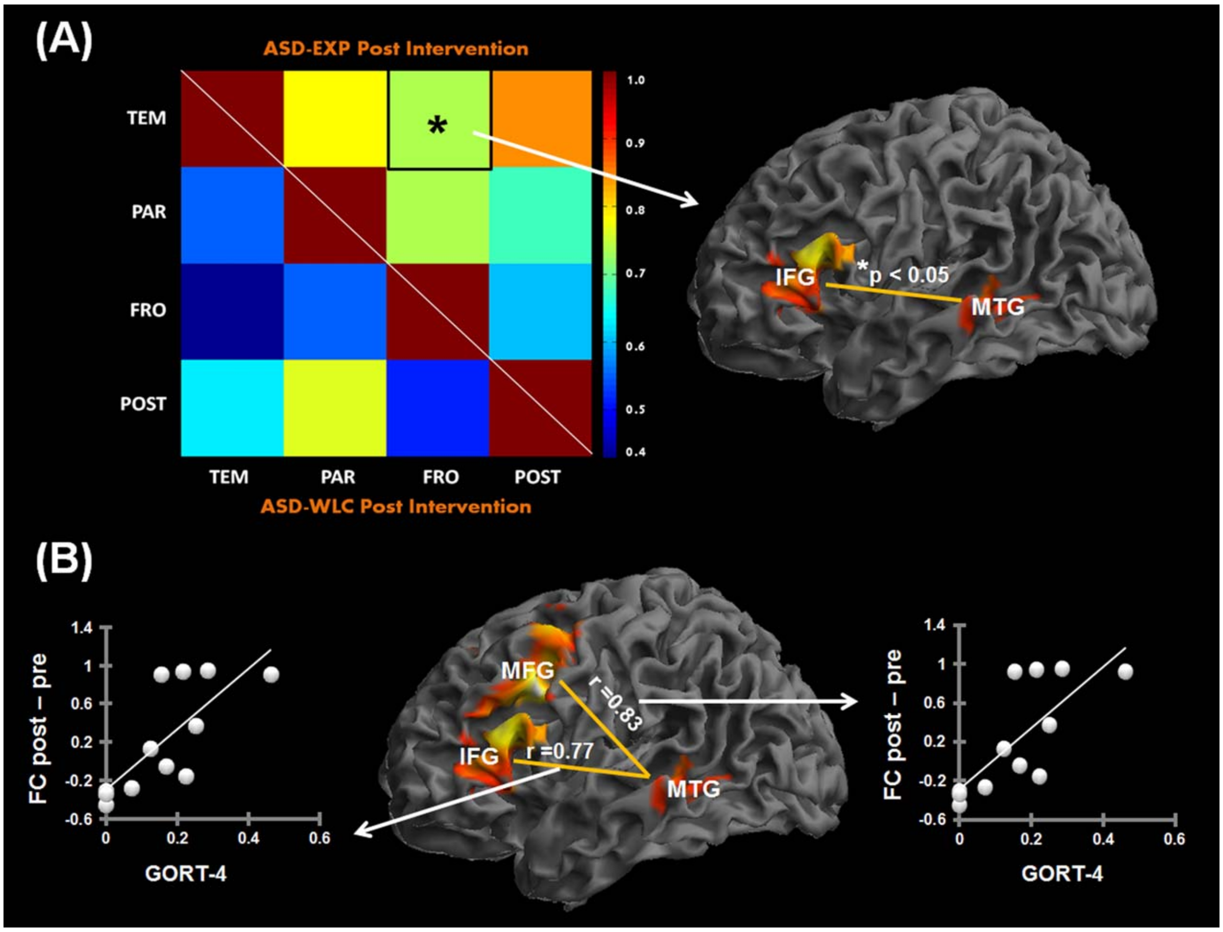

Figure 4. (A) Functional connectivities between intralobe networks by group (ASD-EXP and ASD-WLC), with the greater connectivity seen in the ASD-EXP group as compared with the ASD-WLC group in the MTG:Frontal network for high-imagery sentences. Significant group differences indicated by an asterisk. (B) Differences in functional connectivities between MTG and frontal regions (IFG and MFG) from preintervention to postintervention in the ASD-EXP group that showed significant positive correlation with improvement in reading comprehension scores (GORT-4) in high-imagery sentences. All rendered brain views are for illustrative purposes only.

principles of the DCT, which implies the equal status afforded to verbal and nonverbal modality-specific in apparent systems in thinking [Paivio, 2007]. According to DCT, all mental representations involve two separate codes or systems, a verbal code (specialized for processing language) and a nonverbal code [specialized for processing nonlinguistic information; Paivio, 2010; Sadoski, McTigue, & Paivio, 2012]. The V/V intervention used in the current study likely played a crucial role in teaching children with ASD to integrate visual and verbal information to successfully facilitate sentence comprehension. This is consistent with behavioral studies that have used V/V intervention, such as a multischool augmentative intervention that used V/V, finding significant improvement in reading performance [Sadoski & Wilson, 2006]. The results of the present neuroimaging study point to a few important aspects of neural changes as a result of intervention in children with ASD. First, a richer level of sentence processing involving more mental imagery, and visual and motor representation was found, evidenced by greater postintervention activation to high-imagery sentences in ASD-EXP children specific to left visual regions and bilateral PrCG (BA 4) and PoCG (BA 3). A number of studies have found the PrCG and PoCG to play an active role in comprehending action verbs or embodied motor simulation in language [e.g., Papeo, Acqua, & Rumiati, 2011; Pulvermuller, 2005; Pulvermuller, Harle, & Hummel, 2001], in processing abstract sentences [Sakreida et al., 2013] and in mental rotation and mental imagery [Kosslyn et al., 2001; Tomasino & Rumiati, 2013]. It is likely that as overall comprehension improved from preintervention to postintervention, evidenced by an increase in task accuracy postintervention specific to the ASD-EXP group, so did their mentalization of the high-imagery sentences (which included the ability to mentally rotate letters, numbers, and shapes to comprehend the sentences). Additionally, Koyama et al. [2001] found that greater connectivity between Broca's and Wernicke's areas and PrCG and

PoCG were correlated with increased reading competence in TD children, suggestive of automatized articulation.

Second, the changes observed in activation postintervention for the ASD-EXP group is also suggestive of compensatory mechanisms for comprehending language, specifically the recruitment of RH regions and subcortical regions. While LIFG is involved in phonological processing, cognitive control, and semantic integration [Rogalsky & Hickok, 2011], and LpSTS in phonological processing [Graves et al., 2014], the ASD-EXP group showed increased postintervention activation in the RH analogous regions, RIFG and RpSTS. This pattern was also seen in the low-imagery condition, with increased RpSTS activation in ASD-EXP group when compared with the ASD-WLC group postintervention. This suggests the use of RH language-analogous regions to assist reading. Additionally, the ASD-EXP group showed increased postintervention activation in the left putamen and the left thalamus. Mapping the reading network, Koyama et al. [2011] found an increased reliance on the thalamus that is unique to children. While the thalamus has been considered integral in relaying sensory information to cortical regions [Jones, 1985], it also has a role in language and verbal memory [Hebb & Ojemann, 2012] and in visual attention [Fan et al., 2005; Grieve, Acuna, & Cudeiro, 2000] suggestive of serial visual scanning during the initial steps of reading [Koyama et al., 2011]. The role of thalamus in reading is further emphasized by a meta-analysis of reading interventions for children with reading disorders that found consistent increase in activity in left thalamus after intervention [Barquero et al., 2014]. This may be a good predictor of a compensatory mechanism to aid in comprehension via alternative pathways. The left putamen has also been implicated in reading and language comprehension, especially in sublexical and lexical processing [Oberhuber et al., 2013]. In addition, it has been found that reading increases functional connectivity of the occipito-temporal—PrCG pathway via the putamen in skilled readers [Seghier & Price, 2010]. Interestingly, Meyler et al. [2008] found that poor readers, when compared with good readers, showed increased activation of the putamen after intervention, and this activity was stable at one-year follow-up. Overall, the children with ASD in the present study seem to use compensatory mechanisms by increasing activation in posterior language and visual brain regions, RH homologous regions (RIFG and RIPL) and subcortical regions to aid in language comprehension.

Finally, the V/V intervention in our study has also contributed to an increase in functional connectivity in ASD-EXP children. Increased connectivity between LMTG and left frontal (LIFG and LMFG) regions in the ASD-EXP group was correlated with greater improvement in reading comprehension. The LMTG, a key region of the brain's reading network, has direct functional connections with LIFG and LMFG during language comprehension, and this connection is especially critical when processing demands increase [Turken & Dronkers, 2011]. Moreover, increased LMTG–LIFG functional connectivity has been found during more active (making judgment about sentences) as opposed to passively listening or reading sentences where no response is required [Yue et al., 2013]. The functional role of this pathway is also evident from a recent study by Buchweitz et al. [2012] that showed an increase in LMTG–LIFG connectivity in typical individuals when they processed a dual task (listening to two people speak at the same time) compared with a single task. These findings suggest the modulation of LMTG-Frontal functional connectivity as task demands in processing language increase. The ASD-EXP children in the current study improved the connectivity of this pathway after intervention, which perhaps also facilitated their improved task performance.

In summary, the current study found that the application of a reading intervention aimed at using a relatively intact skill, visuospatial abilities, to address a relative deficit, problems in language comprehension, was successful in improving reading comprehension by modulating brain function in children with ASD. Participation in the intervention facilitated increased activation in brain regions underlying language and visuospatial processing, along with compensatory recruitment of RH and subcortical regions. Additionally, increased brain activation and functional connectivity of core language areas, LMTG and LIFG was predictive of greater success in the intervention as measured by increased reading comprehension proficiency. Overall, our study lends support of specialized intervention for children with ASD to increase higher-order learning skills, and support the growing literature of the plasticity of the young brain in ASD.

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Supporting Information

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Figure S1: Change in brain activation for ASD-EXP participants from preintervention-to-postintervention in key ROIs plotted for each participant for different experimental conditions. In each graph, the *X* axis represents the participants and the *Y* axis represents the parameter estimate of the BOLD signal. (A) High imagery condition and (B) Low-imagery condition.

Figure S2: Postintervention brain activation for ASD-EXP participants compared with ASD-WLC participants in high imagery condition in in key ROIs. In each graph, the *X* axis represents the participants and the *Y* axis represents the parameter estimate of the BOLD signal.