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*Biol Psychiatry Cogn Neurosci Neuroimaging*. 2016 March 1; 1(2): 169–177. doi:10.1016/j.bpsc.2015.11.001.**Shared neuroanatomical substrates of impaired phonological working memory across reading disability and autism****Chunming Lu<sup>1,2,3,#</sup>, Zhenghan Qi<sup>3,#,\*</sup>, Adrienne Harris<sup>4</sup>, Lisa Wisman Weil<sup>4</sup>, Michelle Han<sup>3</sup>, Kelly Halverson<sup>3</sup>, Tyler K. Perrachione<sup>5,6</sup>, Margaret Kjelgaard<sup>6,7</sup>, Kenneth Wexler<sup>6</sup>, Helen Tager-Flusberg<sup>4</sup>, and John D. E. Gabrieli<sup>3,6</sup>**<sup>1</sup>State Key Laboratory of Cognitive Neuroscience and Learning and IDG/McGovern Institute for Brain Research, Beijing Normal University, Beijing 100875, China<sup>2</sup>Center for Collaboration and Innovation in Brain and Learning Sciences, Beijing Normal University, Beijing 100875, China<sup>3</sup>McGovern Institute for Brain Research, Massachusetts Institute of Technology, Cambridge, MA 02139, USA<sup>4</sup>Department of Psychological & Brain Sciences, Boston University, Boston, MA 02215, USA<sup>5</sup>Department of Speech, Language & Hearing Sciences, Boston University, Boston, MA 02215, USA<sup>6</sup>Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology, Cambridge, MA 02139, USA<sup>7</sup>MGH Institute of Health Professions, Boston, MA 02129, USA**Abstract**

**Background**—Individuals with reading disability or individuals with autism spectrum disorder (ASD) are characterized, respectively, by their difficulties in reading or social communication, but both groups often have impaired phonological working memory (PWM). It is not known whether the impaired PWM reflects distinct or shared neuroanatomical abnormalities in these two diagnostic groups.

**Methods**—White-matter structural connectivity via diffusion weighted imaging was examined in sixty-four children, ages 5-17 years, with reading disability, ASD, or typical development (TD), who were matched in age, gender, intelligence, and diffusion data quality.

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#Equal contribution

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**Results**—Children with reading disability and children with ASD exhibited reduced PWM compared to children with TD. The two diagnostic groups showed altered white-matter microstructure in the temporo-parietal portion of the left arcuate fasciculus (AF) and in the temporo-occipital portion of the right inferior longitudinal fasciculus (ILF), as indexed by reduced fractional anisotropy and increased radial diffusivity. Moreover, the structural integrity of the right ILF was positively correlated with PWM ability in the two diagnostic groups, but not in the TD group.

**Conclusions**—These findings suggest that impaired PWM is transdiagnostically associated with shared neuroanatomical abnormalities in ASD and reading disability. Microstructural characteristics in left AF and right ILF may play important roles in the development of PWM. The right ILF may support a compensatory mechanism for children with impaired PWM.

### Keywords

transdiagnostic; reading disability; autism spectrum disorder; phonological working memory; diffusion tensor imaging; white matter

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### Introduction

Reading disability and autism spectrum disorder (ASD) are two neurodevelopmental disorders that affect millions of children's language and/or social communication abilities (1, 2). Although reading disability and ASD are typically considered as two fundamentally different disorders, children with either diagnosis often exhibit impaired phonological working memory (PWM) (3-11). PWM is measured by auditory tests of phonological awareness and verbal short-term memory that require children to briefly maintain and manipulate auditory verbal or phonological information in words, nonwords, or digits (5, 6). Such phenotypic similarity may reflect a shared neurobiological dimension as broadly conceptualized by the Research Domain Criteria (RDoC) approach to psychiatry (12). Here we asked whether there is a shared, transdiagnostic neuroanatomical correlate for impaired PWM across the diagnoses of reading disability and ASD, or alternatively, whether impaired PWM reflects different neuroanatomical correlates in these two different diagnostic disorders.

Deficits in PWM are closely associated with difficulty in learning to map the phonology of spoken language onto the orthography of print (13, 14). Poor readers have shown impaired PWM reflected by impaired phonological awareness and verbal short-term memory (15). Children with ASD, particularly those with broader language impairments, have also shown impaired phonological awareness and verbal short-term memory (8-11). Moreover, atypical verbal short-term memory was found among unaffected first-degree relatives, which indicates that impaired PWM is a prominent feature of the broader autism phenotype (16).

PWM deficits have been associated with neuroanatomical differences in poor readers relative to typically developing children (17). One of the most consistent differences is observed in or near the left arcuate fasciculus (AF), which connects inferior frontal and posterior temporal regions crucial for PWM. For example, poor readers exhibited decreased fractional anisotropy (FA) as measured by diffusion tensor imaging (DTI) (18). Although

the precise location of the difference varied across studies, in most studies poor readers exhibited decreased FA in or near the left AF (18-23). Atypical WM microstructure in poor readers has also been observed in the inferior longitudinal fasciculus (ILF), which connects anterior temporal cortex with occipital cortex, constituting a ventral pathway for visual and auditory processing (24, 25).

Many studies report WM differences in ASD as measured by DTI, but specific findings vary widely (26, 27). Some reported increased radial diffusivity (RD) in the left AF, accompanied with decreased left-lateralized mean diffusivity (MD) and FA in children with ASD (28, 29), but others have reported more widespread WM changes (30). Abnormalities in the left AF have also been found in children with ASD (28-30, see review 31), and altered left AF measures (streamline length and mean diffusivity) correlated with expressive language ability (32). In one study, when head movements were carefully controlled, the only difference in ASD was decreased FA in the right ILF (33). No study has examined the specific relation of WM microstructure to PWM or reading ability in ASD despite the multiple reports of impaired PWM in ASD.

Here, we asked whether a common weakness in PWM reflects shared or disparate WM microstructural anomalies in reading disability and ASD. If common WM microstructural anomalies are found in relation to impaired PWM in reading disability and ASD, the PWM deficits can be interpreted transdiagnostically at the behavioral and the neuroanatomical level. We hypothesized that common WM microstructural anomalies might occur in the left AF and right ILF. On the other hand, if distinct WM microstructural anomalies are found in reading disability and ASD, then the PWM deficits more likely reflect shared behavioral manifestations of two distinct pathophysiological mechanisms.

## Methods and Materials

### Participants

There were 29 children with reading disability (Poor Readers), 41 children with ASD, and 75 typically developing (TD) children recruited from the Boston area of the United States. After screening for data quality (see Image-data acquisition and analysis below) and matching for demographic characteristics, 64 children (19 Poor Readers, 25 children with ASD, and 20 TD children) ages 5-17 years were included in this study (Table 1). All children were native speakers of American English, right-handed, born at 32 or more weeks gestational age, had normal hearing and non-verbal cognitive ability, and no history of head injury or co-morbid psychiatric or neurological conditions, nor any genetic disorders associated with autism (e.g., fragile X syndrome). The three groups of children did not differ significantly on age ( $F_{(2,61)} = 0.91, P = 0.41$ ), nonverbal IQ (Kaufman Brief Intelligence Test -2,  $F_{(2,61)} = 1.86, P = 0.16$ ) (34), or gender ratio ( $K-W$  test,  $X^2 = 0.20, df = 2, P = 0.90$ ). This study was approved by the Committee on the Use of Humans as Experimental Subjects (COUHES) at the Massachusetts Institute of Technology.

## Participant Groups

The three groups of children were defined by exclusionary and inclusionary criteria. (1) Children in the Poor Reader group had standard scores below 90 (below 25<sup>th</sup> percentile) on at least two of the four subtests: Word Identification and Word Attack in the Woodcock Reading Mastery Test – Revised Normative Update (WRMT<sup>TM</sup>- R/NU) (35), Sight Word Efficiency and Phonemic Decoding Efficiency in the Test of Word Reading Efficiency (TOWRE) (36). A composite reading score was derived by averaging the standard scores of the four subtests in order to provide an overall estimate of reading ability. In addition, sentence-level reading ability was assessed by administering the reading fluency subtest in Woodcock-Johnson 3 Test of Achievement (37). (2) Children were included in the ASD group if they had a community-based clinical diagnosis of ASD that was confirmed by trained research staff using the Autism Diagnostic Observation Schedule (ADOS/ADOS-2) Module 3/4. To quantify the severity of the autism symptomatology, we converted participants' ADOS scores to autism severity scores by using the calibrated severity metrics (38, 39). (3) Participants in the TD group scored within normal limits on the above standardized assessments of reading and ADOS, and had no first-degree relatives with reading disabilities or ASD (details in Supplement 1).

## PWM measures

Four subtests (elision, blending words, memory for digits, and nonword repetition) from the Comprehensive Test of Phonological Processing (CTOPP) (40) and the Children's Test of Non-word Repetition (CNRep) (41) were used to measure participants' PWM (task details in Supplement 1). An intra-class correlation (ICC) analysis showed high-level consistency among the five subtests (ICC = 0.694,  $P < 0.001$ , Table S1). Thus, a composite score was calculated for each participant by averaging the  $z$ -transformed scores of the five tests to provide a more reliable measure of PWM ability than any individual test.

## Image-data acquisition

Participants were trained to lie still in a mock scanner 30 minutes before imaging. A person with expertise in image-data analysis oversaw the scan sessions and inspected the raw DWI data for visible motion immediately after scanning. In cases of excessive motion (4.1% of the initial sample), the scan was repeated either in the same or a different session. This process ensured that all raw DW-images were free of visible motion (details in Supplement 1).

**Anatomical imaging**—A whole-head, high-resolution T1-weighted multi-echo MP-RAGE anatomical volume was acquired. TR = 2530 ms, TE = 1640 ms, TI = 1400 ms, flip angle = 7°, FOV = 220×220, interleaved slice number = 176 slices, slice thickness = 1 mm, in-plane resolution = 1.0 mm<sup>2</sup>.

**Diffusion tensor imaging (DTI)**—TR = 9300 ms, TE = 84 ms, TI = 2500 ms, flip angle = 90°, FOV = 256×256, in-plane resolution = 2.0 mm<sup>2</sup>, slice thickness = 2 mm, 10 baseline volumes (b=0) and 30 diffusion-weighted volumes (b = 700 s/mm<sup>2</sup>) with 74 slices per volume.

## Image-data analysis

Individual data quality was screened by DTIprep, a quality-control software that allows automatic evaluation of the quality of diffusion images, b-values and gradient directions (42). Poor data quality resulted in removal of 14.5% of the initial sample from further analysis. Then, TRActs Constrained by UnderLying Anatomy (TRACULA) (43) was used to quantitatively assess data quality by calculating two motion (frame-to-frame translation and rotation parameters) and two intensity (averaged signal dropout score and the percentage of slices with scores greater than 1) measures (44) (details in Supplement 1). The four measures captured global frame-to-frame motion and the frequency and severity of rapid slice-to-slice motion. The three groups did not show any significant differences on these data-quality measures (Translation:  $F_{(2,61)} = 0.242$ ,  $P = 0.786$ ; Rotation:  $F_{(2,61)} = 0.593$ ,  $P = 0.556$ ; Signal-dropout score:  $F_{(2,61)} = 0.665$ ,  $P = 0.518$ ; Percent of bad slices:  $F_{(2,61)} = 0.686$ ,  $P = 0.507$ ).

Standard data processing was conducted in TRACULA. TRACULA performs automated global probabilistic tractography that estimates the posterior probability of each of 18 WM tracts. Segmented anatomical images of the same participants were used to facilitate the estimation. The default procedures can calculate either the posterior mean or maximum of *a posteriori* pathways for each participant. Here, the posterior means were used. Fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD) were calculated both over the whole pathway and along each measurement point over the arc of the pathway (43) (details in Supplement 1).

Based on prior reports of altered WM in the left AF in poor readers and right ILF in ASD, we examined these two tracts bilaterally as *a priori* tracts of interest, and then also performed whole-brain analyses to examine whether any group differences were specific to these two tracts, or extended more widely across tracts. Specifically, for the bilateral AF and ILF, ANCOVA procedures were conducted point-by-point along each of the two tracts to examine the group differences (43). Age, IQ, and gender were included as potential covariates. Only age significantly contributed to the model, so IQ and gender were removed from the final models. Results were corrected for multiple comparisons (i.e., 4 measures  $\times$  all points  $\times$  4 tracts) at  $P < 0.05$  level by using a Monte Carlo simulation method (Height,  $P < 0.005$ ; Extent, cluster  $> 6$  points; 3dClustSim within AFNI, <http://afni.nimh.nih.gov/afni/>). In addition, the relations between the diffusion measures and PWM were also examined (see Supplement 1). In order to validate the point-to-point analysis method, we further compared groups on the diffusion measures averaged across the whole tract of interest, as reported in previous studies (33, 45).

## Results

### Shared PWM deficits in Poor Readers and ASD

Both the Poor Reader group ( $M = -0.26$ ,  $SD = 0.83$ ) and ASD group ( $M = -0.11$ ,  $SD = 0.66$ ) had lower composite PWM scores than the TD group ( $M = 0.44$ ,  $SD = 0.47$ ) ( $t(37) = -3.26$ ,  $P = 0.002$  for Poor Reader vs. TD;  $t(43) = -3.14$ ,  $P = 0.003$  for ASD vs. TD) (Fig. 1). The Poor Reader and ASD groups did not differ significantly from one another ( $t(42) = 0.43$ ,

$P = 0.51$ ). These results were confirmed in a linear regression model controlling for age and using group as an independent variable (Table 2). Standard scores for each subtest are presented in Table S1.

### Shared WM alterations in Poor Readers and ASD

Shared patterns of WM alterations were found in the left AF and right ILF for both the Poor Reader and ASD groups compared to the TD group (Fig. 2A, uncorrected  $P$ ). After correcting for multiple comparisons, the significant WM structural differences were found to share the same location for the Poor Reader and ASD groups (Fig. 2A). Specifically, in the left temporo-parietal portion of the AF (TP-AF; 6 points, peak position,  $x, y, z = -37, -45, 13$ ; Fig. 2A), the Poor Reader and ASD groups had significantly lower FA than the TD group (Fig. 2B). In the same location (TP-AF, Fig. 2A), the Poor Reader and ASD groups showed significantly higher RD than the TD group (Fig. 2A and 2C). In the right occipito-temporal portion of the inferior longitudinal fasciculus (OT-ILF) (7 points, peak position,  $x, y, z = 33, -59, 0$ ), the ASD group had significantly lower FA and higher RD (Fig. 2A) compared to the TD group. Table 2 summarizes significant group differences. The diffusion measures of the right ILF in the Poor Reader group were between those found for TD and ASD but did not differ significantly from either group (Fig. 2A, 2B, and 2C). Direct comparisons between the Poor Reader and ASD groups did not reveal any significant differences on any diffusion measure in either tract after multiple comparison correction. There were no differences between any pairs of group in MD or AD of either tract after correction. No group differences were found in any microstructural measures of either right AF or left ILF.

In order to validate the specificity of our *a priori* hypothesis, analyses of group differences across all 18 tracts were conducted on FA and RD. The left TP-AF and right OT-ILF were the only two areas that differentiated the disordered groups from the TD group ( $P$ 's  $< 0.05$ , corrected), with the clinical groups exhibiting decreased FA and increased RD relative to the TD group. We also compared groups on the tract-averages of FA and RD for the left AF and right ILF. Largely consistent with the point-by-point analysis, the Poor Reader and ASD groups exhibited significantly decreased FA and increased RD in the left AF. The ASD group showed significantly decreased FA and increased RD in the right ILF, with Poor Reader group falling in between the ASD and the TD groups (see Supplement 1).

### Association between structural connectivity and PWM

We examined the relation of PWM ability to the left AF and the right ILF first by combining all three groups in a linear regression. There was a significant positive relation between the PWM scores and FA (z-normed) in both the left TP-AF (6 points, peak position,  $x, y, z = -35, -45, 17$ ,  $\beta = 0.392$ ,  $R^2 = 0.154$ ,  $P = 0.001$ ) and right OT-ILF (15 points, peak position,  $x, y, z = 32, -61, 0$ ,  $\beta = 0.474$ ,  $R^2 = 0.225$ ,  $P < 0.001$ ) (Fig. 3A). The relation remained significant while controlling for the effects of age (Table 3). The FA in the left TP-AF and right OT-ILF together explained 34% of the variance in PWM scores ( $F_{(3,61)} = 10.467$ ,  $P < 0.001$ ). Patterns of association between PWM and FA were replicated in the analysis on RD (Supplement 1). No significant results or similar patterns were found in AD or MD, and no significant results were found in other parts of either the left AF or the right ILF.



The relations between PWM scores and WM diffusion measures were further examined with linear regression models within each participant group. PWM scores and FA in the right OT-ILF were significantly correlated in both the Poor Reader group ( $fJ = 0.509$ ,  $R^2$  change = 0.318,  $P = 0.007$ ) and the ASD group ( $fJ = 0.351$ ,  $R^2$  change = 0.253,  $P = 0.006$ ), but not in the TD group ( $fJ = 0.040$ ,  $R^2$  change = 0.048,  $P = 0.731$ , Figure 3B). The relation between PWM score and FA of the right OT-ILF for the Poor Reader and ASD groups remained significant after controlling for age (Table 3). No significant relationship was found between PWM scores and FA in the left TP-AF for any group (Poor Readers:  $\beta = 0.200$ ,  $R^2$  change = 0.0008,  $P = 0.335$ ; ASD:  $\beta = 0.191$ ,  $R^2$  change = 0.044,  $P = 0.16$ ; TD:  $\beta = 1.676$ ,  $R^2$  change = 0.067,  $P = 0.560$ ). We observed similar patterns using RD as the dependent variable (Supplement 1).

Because the right ILF was found previously to be specifically atypical in children with ASD (33), we examined the relations between FA of the right OT-ILF and autism severity defined by the standardized severity score on the ADOS (38, 39). There was no significant association within any group (Poor Readers:  $\beta = 0.005$ ,  $R^2$  change = 0.059,  $P = 0.813$ ; ASD:  $\beta = -0.013$ ,  $R^2$  change = 0.015,  $P = 0.258$ ; TD:  $\beta = 0.012$ ,  $R^2$  change = 0.059,  $P = 0.815$ ).

## Discussion

In this study, both children who were poor readers and children with ASD exhibited impaired PWM and shared WM microstructure anomalies in left AF and right ILF relative to TD children. For both tracts, the Poor Reader and ASD groups exhibited decreased FA and increased RD, consistent with the idea that these tracts were less developed relative to the TD group. RD may be especially sensitive to myelination differences as opposed to axon fibers (46, 47, but see 48). Further, increased FA and decreased RD in the right ILF correlated with better PWM among the Poor Reader and ASD groups, consistent with the hypothesis that the right-hemisphere plays a more prominent role in language processing in these groups of children than in typically developing children. The striking similarities of altered WM organization in both clinical groups provide strong evidence for a transdiagnostic neuroanatomical basis of reduced PWM.

### PWM in Poor Readers and ASD

In this study, PWM ability was measured with a composite score combining children's performance on tests of phonological awareness (elision and blending words) and verbal short-term memory (non-word repetition and memory for digits). Performance on all these tasks reflects the ability to maintain and manipulate auditory verbal or phonological information in short-term memory (e.g., 49). Such PWM deficits have been well documented in separate studies of children with reading disability (6, 50-52) or ASD (8, 11, 16). Our results show directly that a similar impairment of PWM is shared across poor readers and the age-, IQ-, and gender-matched children with ASD.

The present study included children with ASD with both intact and impaired language skills in order to avoid an arbitrarily categorical definition of language deficit. Thus, analyses were based on a continuous range of language performance within the ASD group. Although the Poor Reader and ASD groups were similarly impaired on PWM tasks, the ASD group

performed significantly better than the Poor Reader group on reading tasks. The reading scores of children with ASD were near the standardized mean of 100, but significantly lower than the scores of the TD group. The different relation between PWM scores and reading scores in the ASD and Poor Reader groups is consistent with previous reports that difficulties in PWM and reading are variable despite the prominent role of phonological abilities in reading acquisition (53, 54).

### **Atypical white matter of the left AF**

We found shared WM abnormalities in the left AF across the Poor Reader and ASD groups. This finding is consistent with prior studies examining either poor readers (55) or ASD (31) separately. The shared WM anomaly for the two groups was striking in that it occurred at the same location of the left TP-AF. Anatomically, for a large pathway like the AF, different subgroups of fibers join the pathway for part of its trajectory, merging on or off at different points along the AF (43, 46, 57-59). Compared to other portions of the left AF, these fibers arch around the TP region and line up temporarily in parallel before fanning out towards dorsal parietal and frontal areas. It is unknown as to whether this anatomical feature of the TP region is related to pathological susceptibility, and which subgroups of fibers are affected in poor readers and children with ASD.

The left AF connects critical nodes of the language and reading network including the posterior superior temporal gyrus and the inferior frontal gyrus by passing through the left TP region. The left AF constitutes a dorsal phonological stream involved in phonological processing and sound-to-word mapping (60, 61). In this pathway, the left TP region supports phonological processing and reading acquisition in typical readers (62, 63). The altered WM microstructure of the left TP-AF reported here could therefore be related to the PWM impairment exhibited by both the Poor Reader and ASD groups.

Despite evidence linking the left AF to PWM, we did not find a significant correlation between PWM and left AF properties within any single participant group. Thus, the significant correlation between PWM and FA of the left TP-AF across all groups was driven by group differences, and not related to variability within any group. The lack of such a relation may reflect the large age range of the present study (5-17 years). There is evidence that in children ages 7-11 years, lower FA in the left AF is associated with better phonological awareness (59), but that in older children and adults, the relationship reverses (64). Thus, our age range may have straddled this period of reversal. Other possibilities are that our sample is not powered adequately to observe the degree of association within each group or that the wide age range of participants obscured associations. Future studies may clarify this developmental variation by including a larger sample or using a longitudinal design.

### **Atypical white matter of the right ILF**

The ASD group exhibited reduced FA and elevated RD of the right ILF compared to the TD group, and the Poor Reader group had FA and RD that were intermediate between the ASD and TD groups (albeit not significantly different from either group). Because there is evidence that people with congenital face recognition deficits have reduced FA in the right



ILF (65), and ASD children show a selective deficit in face recognition (66), the reduced WM connectivity in the right ILF of ASD was interpreted in the context of impaired social communication skills, including face recognition (33). However, there is no reported relation between variation in right ILF microstructure and either ASD severity or face recognition ability among ASD participants.

In this study, the magnitude of FA and RD in the right ILF significantly correlated with PWM ability in both the Poor Reader and ASD groups. This is consistent with previous evidence that the right ILF, which carries information from right occipito-temporal cortex, is implicated in some aspects of language, including the perception of speech prosody (67) and atypical language development (23, 24). Moreover, in this study, the FA of the right ILF did not differ significantly between the ASD and Poor Reader groups, even though the Poor Readers did not have impaired social communication scores as assessed by the ADOS. The lack of correlation between autism severity and the WM coherence in the right ILF further suggests variation in the right ILF microstructure was not related to a broad measure of social communication like the ADOS. Future studies using more sensitive or specific measures of social communication in ASD may find a relation with microstructural properties of the right ILF.

In general, phonological processes are most associated with the left-hemisphere language network, so the relation between PWM and the right ILF observed within the Poor Reader and ASD groups (but not the TD group) may reflect atypical right-lateralization of language processes in these groups (68-74). For example, both children (75) and adults (69) with reading disability showed reduced left-lateralization of either brain function (75) or WM characteristics (69) around the TP region. Moreover, greater FA in the right superior longitudinal fasciculus/AF predicted greater reading improvement in children with dyslexia, but not in TD children (76).

Children with ASD have also shown greater right-hemispheric activation than controls in language tasks ranging from passive speech perception to semantic processing (71, 77). Interestingly, the increased rightward asymmetry has been associated with better language skills in both toddlers and school-age children with ASD (78, 79). Taken together, these findings suggest that the atypical right hemispheric involvement might contribute to a compensatory mechanism of phonological processing in children with reading disability or those with ASD.

These findings have important implications for understanding neurodevelopmental disorders. NIMH's Research Domain Criteria (RDoC) approach to psychiatry (12) has emphasized a dimensional approach to relating behaviors to neural circuits across traditional diagnostic disease categories, including neurodevelopmental disorders (e.g., 80). Deficits in PWM cut across several diagnostic categories, including dyslexia, specific language impairment, and ASD, although the idea that the neurocognitive underpinnings of this impairment may be shared across disorders has been debated (e.g., 9, 10). Here we showed, for the first time, that the dimension of impaired PWM is related to shared neuroanatomical abnormalities of WM microstructure in two different diagnostic groups, reading disability and autism spectrum disorder.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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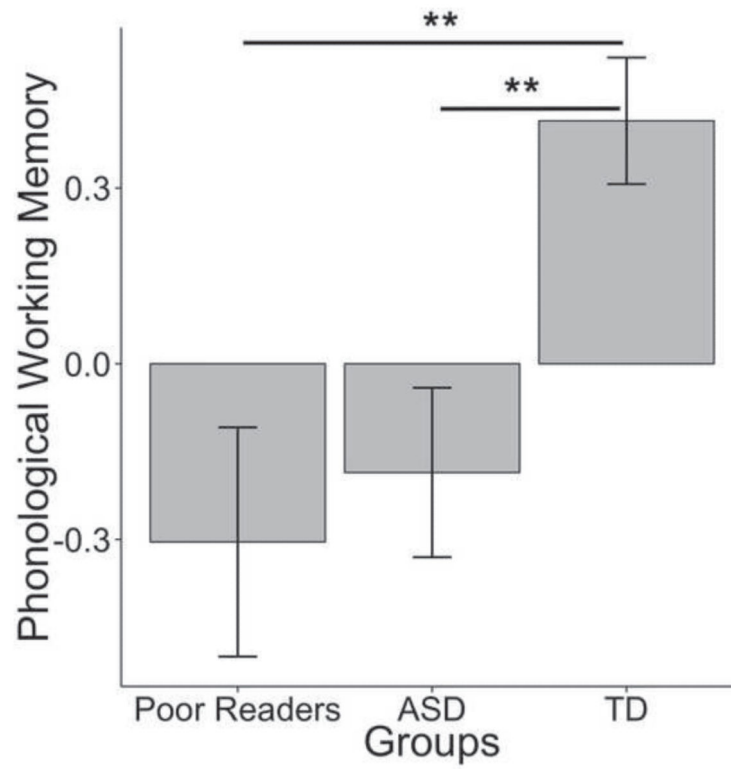
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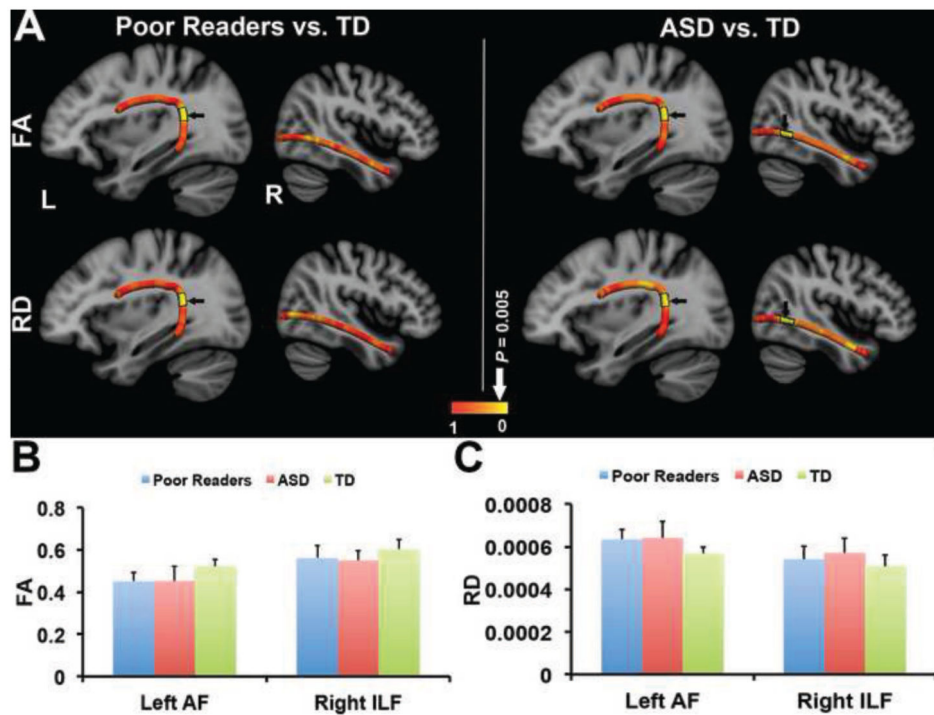
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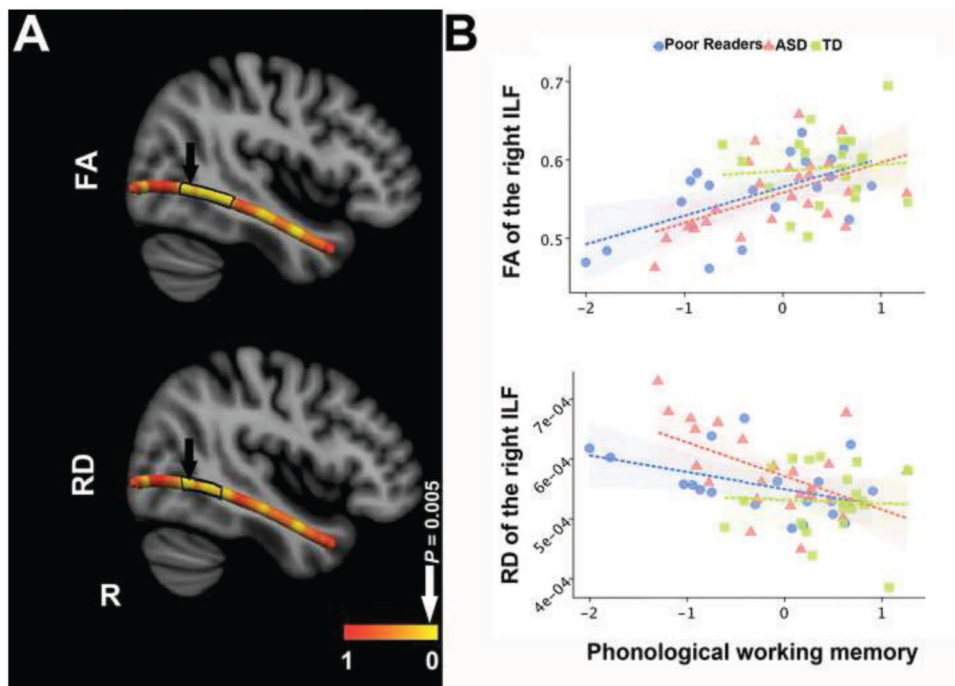




**Fig. 1.** Group means of phonological working memory performance in Poor Reader group, autism spectrum disorder (ASD) group, and age-, IQ-, and gender-matched typically developing (TD) group. Phonological working memory composite scores were averaged across the z-normed scores of five subtests. \*\*,  $P < 0.01$ .



**Fig. 2.** White-matter structural differences in Poor Reader group or autism spectrum disorder (ASD) group versus age-, IQ-, and gender-matched typically developing (TD) group. (A) The Poor Reader (left panel) and ASD (right panel) groups exhibited decreased fractional anisotropy (FA) (top row) and increased radial diffusivity (RD) (bottom row) in the left arcuate fasciculus (left column in each panel) and in the right inferior longitudinal fasciculus (right column in each panel). For visualization purposes, the diameter of each measurement point was increased to form a continuous fiber tract in both Fig. 2 and Fig. 3. Coloration along the tracts represents the uncorrected continuous  $P$ , from higher  $P$  in red through lower  $P$  in yellow. Portions of each tract that were significantly different between groups after correction for multiple comparisons are outlined in black; a black arrow next to the black outline indicates the position of peak group difference. The white arrow above the color bar indicates the color range for height threshold ( $P < 0.005$ ). (B) Average FA and (C) RD extracted from the portion or tracts outlined in black in each group. Error bars represent standard deviation. The bar graphs were used to demonstrate the pattern of group difference, and no statistical tests were conducted.



**Fig. 3.** Correlations between diffusion measures of the right ILF and phonological working memory. (A) Coloration along the tracts represents uncorrected continuous  $P$  in the correlation. This is used to demonstrate the overall pattern of the relation between structural connectivity and phonological working memory. Note that significant results were only found in the left AF and right ILF at  $P < 0.05$  level (corrected). The portions of tract that were significantly correlated with phonological working memory after correction for multiple comparisons are outlined in black; a black arrow next to the black outline indicates the position of peak correlation. The white arrow above the color bar indicates the color range for height threshold ( $P < 0.005$ ). (B) Relations between FA (upper) and RD (lower) extracted from significant clusters in right ILF and phonological working memory within each individual group. The colors and shapes of the dots indicate group membership. The straight lines represent the linear correlation within each group.

**Table 1**

## Group Characteristics

	Poor Readers	ASD	TD
Number	19	25	20
Age	11.8 (3.27)	11.3 (3.48)	10.3 (3.57)
Non-verbal IQ	101.8 (13.99)	108.9 (15.28)	110.1(14.27)
Gender ratio (F: M)	0.36	0.32	0.43
Autism severity	1.78 (1.52)	6.08 (2.48) ***	1.33 (0.69)
Word Reading	83.45 (9.90) ***	99.33 (13.16) **	112.48 (10.25)
Sentence Reading	79.65 (11.54) ***	100.04 (15.82) ***	115.68 (9.67)
Language	92.47 (21.07) ***	94.21 (18.87) ***	113.15 (11.39)

Note: Numbers outside and inside the bracket indicate mean and standard deviation, respectively. Statistical significance compared with TD:

Non-verbal IQ was measured by Kaufman Brief Intelligence Test Matrix subtest (34). Autism severity was measured with the standardized calibrated severity score, which ranges from 1 to 10 (38, 39). Word reading was measured with the average of the standard scores across four reading tests: word identification, word attack, sight word efficiency, and phonemic decoding proficiency. Sentence reading was measured with the standard score of the sentence reading fluency subtest of the *Wookcock-Johnson 3 Test of Achievement* (37). Language was measured with the core language score from CELF-4 (81) based on the sum of the scale scores of age-appropriate subtests, including concepts and following directions, recalling sentences, formulating sentences, word structure, word classes and word definitions.

\*\*  $P < 0.01$ ,

\*\*\*  $P < 0.001$ .

**Table 2**

## Group Comparison Statistics on PWM and White-matter Structure

	Poor Reader vs. TD	ASD vs. TD	ASD vs. Poor Reader
PWM	$F_{(1,34)} = 6.25, P = 0.017$	$F_{(1,40)} = 10.73, P = 0.002$	$F_{(1,41)} = 0.55, P = 0.463$
Left TP-AF (FA)	$F_{(1,36)} = 13.03, P < 0.001$	$F_{(1,42)} = 12.87, P < 0.001$	<i>n.s.</i>
Left TP-AF (RD)	$F_{(1,36)} = 26.85, P < 0.001$	$F_{(1,42)} = 12.15, P = 0.001$	<i>n.s.</i>
Right OT-ILF (FA)	<i>n.s.</i>	$F_{(1,42)} = 10.53, P = 0.002$	<i>n.s.</i>
Right OT-ILF (RD)	<i>n.s.</i>	$F_{(1,42)} = 15.86, P < 0.001$	<i>n.s.</i>

Note: Age was included as a covariate in all ANCOVA. *n.s.* not significant.

**Table 3**

Correlation between PWM and White-matter Structure

	Poor Reader	ASD	TD	ALL
Left TP-AF (FA)	$\beta = 0.194$ $R^2$ change = 0.053 $P = 0.353$	$\beta = 0.113$ $R^2$ change = 0.026 $P = 0.414$	$\beta = 0.028$ $R^2$ change = 0.003 $P = 0.801$	$\beta = 0.413$ $R^2$ change = 0.171 $P = 0.001^{**}$
Left TP-AF (RD)	$\beta = -0.209$ $R^2$ change = 0.063 $P = 0.310$	$\beta = -0.073$ $R^2$ change = 0.009 $P = 0.625$	$\beta = -0.002$ $R^2$ change = $2 \times 10^{-5}$ $P = 0.985$	$\beta = -0.356$ $R^2$ change = 0.127 $P = 0.005^{**}$
Right OT-ILF (FA)	$\beta = 0.499$ $R^2$ change = 0.361 $P = 0.008^{**}$	$\beta = 0.303$ $R^2$ change = 0.198 $P = 0.016^*$	$\beta = 0.157$ $R^2$ change = 0.086 $P = 0.192$	$\beta = 0.511$ $R^2$ change = 0.262 $P < 0.001^{***}$
Right OT-ILF (RD)	$\beta = -0.374$ $R^2$ change = 0.203 $P = 0.058^{\#}$	$\beta = -0.294$ $R^2$ change = 0.165 $P = 0.030^*$	$\beta = -0.200$ $R^2$ change = 0.113 $P = 0.130$	$\beta = -0.446$ $R^2$ change = 0.194 $P < 0.001^{***}$

Note: Age was controlled for in all correlation analyses.

 $^{\#} P < 0.06$ ; $^* P < 0.05$ ; $^{**} P < 0.01$ ; $^{***} P < 0.001$ .