Archival Report

Biological Psychiatry: CNNI

Shared Neuroanatomical Substrates of Impaired Phonological Working Memory Across Reading Disability and Autism

Chunming Lu, Zhenghan Qi, Adrianne Harris, Lisa Wisman Weil, Michelle Han, Kelly Halverson, Tyler K. Perrachione, Margaret Kjelgaard, Kenneth Wexler, Helen Tager-Flusberg, and John D.E. Gabrieli

ABSTRACT

BACKGROUND: Individuals with reading disability and individuals with autism spectrum disorder (ASD) are characterized, respectively, by their difficulties in reading and 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 64 children, age 5 to 17 years, with reading disability, ASD, or typical development, who were matched on age, gender, intelligence, and diffusion data quality.

RESULTS: Children with reading disability and children with ASD exhibited reduced PWM compared with children with typical development. The two diagnostic groups showed altered white matter microstructure in the temporoparietal portion of the left arcuate fasciculus and in the occipitotemporal 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 typically developing group.

CONCLUSIONS: These findings suggest that impaired PWM is transdiagnostically associated with shared neuroanatomical abnormalities in ASD and reading disability. Microstructural characteristics in left arcuate fasciculus 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: Autism spectrum disorder, Diffusion tensor imaging, Phonological working memory, Reading disability, Transdiagnostic, White matter

http://dx.doi.org/10.1016/j.bpsc.2015.11.001

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 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 (TD) 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 (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 white matter (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 diffusion tensor imaging, but specific findings vary widely (26,27). Some reported increased radial diffusivity (RD) in the left AF, accompanied by 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 with altered left AF measures (streamline length and MD) 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 TD children recruited from the Boston area of the United States. After screening for data quality (see Image Data Acquisition and Image Data Analysis, below) and matching for demographic characteristics, 64 children (19 poor readers, 25 children with ASD, and 20 TD children) ages 5 to 17 years were included in this study (Table 1). All children were native speakers of American English, were right-handed, were born at 32 or more weeks gestational age, had normal hearing and nonverbal cognitive ability, and had no history of head injury or comorbid psychiatric or neurological conditions or any genetic disorders associated with autism (e.g., fragile X syndrome). The three groups of children did not differ significantly on age ($F_{2,61}$ = .91, p = .41), nonverbal IQ (Kaufman Brief Intelligence Test, Second Edition, $F_{2,61}$ = 1.86, p = .16) (34), or gender ratio (Kruskal–Wallis test, χ^2 = .20, df = 2, p = .90). This study was approved by the Committee on the Use of Humans as Experimental Subjects at the Massachusetts Institute of Technology.

Participant Groups

The three groups of children were defined by exclusionary and inclusionary criteria. Children in the poor reader group had standard scores below 90 (below 25th percentile) on at least two of the four subtests: word identification and word attack in the Woodcock Reading Mastery Test–Revised Normative Update (35) and sight word efficiency and phonemic decoding efficiency in the Test of Word Reading Efficiency (36). A composite reading score was derived by averaging the standard scores of the four subtests to provide an overall estimate of reading ability. In addition, sentence-level reading ability was assessed by administering the reading fluency subtest in the Woodcock-Johnson III Tests of Achievement (37). 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). 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 (40) and the Children's Test of Nonword Repetition (41) were used to measure participants' PWM (task details in Supplement 1). An intraclass correlation analysis showed high-level consistency among the five subtests (intraclass correlation = .694, $p < .001$, Table S1 in Supplement 1). Thus, a composite score was calculated for each participant by averaging the Z-transformed scores of the five tests to

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)
Nonverbal IQ	101.8 (13.99)	108.9 (15.28)	110.1 (14.27)
Gender Ratio (F:M)	.36	.32	.43
Autism Severity	1.78 (1.52)	6.08 (2.48)[a]	1.33 (.69)
Word Reading	83.45 (9.90)[a]	99.33 (13.16)[b]	112.48 (10.25)
Sentence Reading	79.65 (11.54)[a]	100.04 (15.82)[a]	115.68 (9.67)
Language	92.47 (21.07)[a]	94.21 (18.87)[a]	113.15 (11.39)

Numbers outside and inside the bracket indicate mean and standard deviation, respectively. Nonverbal 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 Woodcock-Johnson III Tests of Achievement (37). Language was measured with the core language score from Clinical Evaluation of Language Fundamentals, Fourth Edition (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.

ASD, autism spectrum disorder; F, female; M, male; TD, typically developing.

[a]Statistical significance compared with TD: $p < .001$.

[b]Statistical significance compared with TD: $p < .01$.