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Longitudinal processing speed impairments in males with autism and the effects of white matter microstructure

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ABSTRACT

The present study used an accelerated longitudinal design to examine group differences and age-related changes in processing speed in 81 individuals with autism spectrum disorder (ASD) compared to 56 age-matched individuals with typical development (ages 6–39 years). Processing speed was assessed using the Wechsler Intelligence Scale for Children-3rd edition (WISC-III) and the Wechsler Adult Intelligence Scale-3rd edition (WAIS-III). Follow-up analyses examined processing speed subtest performance and relations between processing speed and white matter microstructure (as measured with diffusion tensor imaging [DTI] in a subset of these participants). After controlling for full scale IQ, the present results show that processing speed index standard scores were on average 12 points lower in the group with ASD compared to the group with typical development. There were, however, no significant group differences in standard score age-related changes within this age range. For subtest raw scores, the group with ASD demonstrated robustly slower processing speeds in the adult versions of the IQ test (i.e., WAIS-III) but not in the child versions (WISC-III), even though age-related changes were similar in both the ASD and typically developing groups. This pattern of results may reflect difficulties that become increasingly evident in ASD on more complex measures of processing speed. Finally, DTI measures of whole-brain white matter microstructure suggested that fractional anisotropy (but not mean diffusivity, radial diffusivity, or axial diffusivity) made significant but small-sized contributions to processing speed standard scores across our entire sample. Taken together, the present findings suggest that robust decreases in processing speed may be present in ASD, more pronounced in adulthood, and partially attributable to white matter microstructural integrity.

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1. Introduction

The ability to process implicit social cues and filter essential signals from a complex array of stimuli requires fast-paced integration of a large number of sensory inputs. Therefore, processing speed, or the speed at which we are able to perceive and react to stimuli in the environment, is a fundamental cognitive ability. Clinically, individuals with autism spectrum disorder (ASD) often demonstrate the need for increased time to process information and perform tasks, which appears to contribute to functioning in daily life. Research studies also have found evidence of slower processing speeds across the lifespan in individuals with ASD. On standardized Wechsler tests of intelligence, lower processing speed index scores have been reported in children, (Mayes & Calhoun, 2003, 2008; Oliveras-Rentas, Kenworthy, Roberson, Martin, & Wallace, 2012; Wechsler, 2003) adolescents, and adults with ASD (Spek, Schatorjé, Scholte, & van Berckelaer-Onnes, 2009). These slower processing speeds were associated with more severe ASD communication

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symptoms in high-functioning children with ASD (Oliveras-Rentas et al., 2012) and were found to be predictive of educational achievements in math, reading, and writing (Assouline, Foley Nicpon, & Dockery, 2011). These observations and results suggest that slower processing speed may be a common difficulty experienced by individuals with ASD and may relate to core ASD features, as well as educational and occupational prospects.

Although processing speed difficulties have been consistently reported in persons with ASD, little is known regarding how processing speed develops and changes with age in this population. In individuals with typical development, cross-sectional and longitudinal studies suggest rapid increases in processing speed during the first year of life (Rose, Feldman, & Jankowski, 2002), followed by continued increases through childhood and adolescence (Kail, 2007; Kail & Ferrer, 2007). Although very little is known about typical processing speed changes in middle age, processing speed appears to decline and may be related to other age-related declines in cognitive functions in older-adult populations (Salthouse, 1996; Salthouse & Ferrer-Caja, 2003, Silwinski & Buschke, 1999; Sternäng, Wahlin, & Nilsson, 2008; Zimprich & Kurtz, 2013). In both typically developing and patient populations, age-appropriate development of processing speed may be a critical predictor of a number of important cognitive and outcome measures. For example, processing speed may be a key predictor of general intelligence in typically developing adolescents (Coyle, Pillow, Snyder, & Kochunov, 2011), and in individuals with schizophrenia, processing speed may predict vocational outcome and social function (Sánchez et al., 2009). Therefore, understanding the longitudinal development of processing speed in persons with ASD may be a key element to better understanding and accommodating the needs of persons with ASD throughout the lifespan.

A better understanding of processing speed development in ASD may also elucidate underlying neural substrates contributing to the etiology of ASD. DTI studies in individuals with typical development suggest that processing speed may be associated with the white matter microstructure of a number of white matter tracts across the brain, including the bilateral anterior corona radiata, bilateral superior fronto-occipital fasciculus, bilateral superior longitudinal fasciculus, bilateral internal capsule, bilateral posterior cingulum, right inferior fronto-occipital fasciculus, and bilateral posterior corona radiata (Bendlin et al., 2010). In individuals with traumatic brain injury, processing speed was related to white matter microstructure of the superior longitudinal fasciculus (Turken et al., 2008), ventral striatum (Shah et al., 2012), as well as the corpus callosum and centrum semiovale (Kourtidou et al., 2012). Further, decreases in white matter integrity of the corpus callosum were related to decreases in processing speed in children with multiple sclerosis (Bethune et al., 2011) and in children and adults with ASD (Alexander et al., 2007). These results provide converging evidence across distinct samples and methodologies that the white matter microstructure of a number of tracts is likely involved in processing speed.

Because of the number of tracts likely involved, it is possible that a metric of whole-brain white matter microstructure may predict processing speed more accurately than the white matter microstructure of any individual tract. Indeed, in older individuals with typical development, a measure of higher radial diffusivity (RD) across all lobes of the brain was found to be associated with executive function and processing speed measures (Jacobs et al., 2013). Furthermore, two studies have found that a composite white matter integrity factor (i.e., a combination of FA, RD, MD, and axial diffusivity (AD) across eight major tracts, or an aggregation of the white matter integrity of healthy looking white matter tracts) was more predictive of processing speed than when the individual tracts were treated as single predictors (Penke et al., 2010; Venkatraman et al., 2011). Given that white matter microstructure atypicalities have been commonly reported in ASD (see Travers et al., 2012 for a review), investigating white matter microstructure as a predictor of processing speed is essential to better understand the links between the behavioral and the neural manifestations of ASD.

To examine the intersection among possible processing speed differences in ASD, age-related development of processing speed, and white matter contributions to processing speed, the present study longitudinally examined age-related processing speed changes in 81 individuals with ASD and 56 age-matched individuals with typical development from childhood to mid-adulthood (6–39 years old). Additional analyses examined whether whole-brain white matter FA, MD, RD, and AD predicted processing speed in a subset of participants who underwent multiple DTI scans.

2. Materials and method

2.1. Design

As part of a 13-year longitudinal study, the current study employed an accelerated longitudinal design (i.e., cohort-sequential design) (Harezlak, Ryan, Giedd, & Lange, 2005; Nesselroade & Baltes, 1979), which simultaneously measured individual longitudinal changes in processing speed across multiple age cohorts. Data were collected at four separate time points: Pre-Time 1 (henceforth called Time 0), Time 1, Time 2, and Time 3. Processing speed data were collected at Time 0, Time 1, and Time 3. DTI scans were collected at Time 1, Time 2, and Time 3. Therefore, in the context of the broader longitudinal study, the current study analyzes processing speed data from Time 0, Time 1, and Time 3, and the DTI data are analyzed for Time 1 and Time 3. See Fig. 1 for a depiction of the accelerated longitudinal design.

2.2. Participants

Participants for this study included 81 males with ASD and 56 males with typical development between the ages of 6.3 and 39.8 years. These participants were selected from the broader longitudinal neuroimaging study (109 ASD and 80 typically developing controls [TDC]) based on processing speed data completeness and age matches (three processing speed assessments were excluded in participants with ASD over 40 years of age because there were no typically developing matched controls in that age range). In the broader longitudinal study, the retention rate (at least two scans and two assessments) was 85% for the group with ASD and 71% for the group with typical development. The participants with ASD were rigorously diagnosed based on Autism Diagnostic Interview-Revised (Lord, Rutter. & Le Couteur, 1994), Autism Diagnostic Observation Scale-General (Lord et al., 2000), Diagnostic Statistical Manual-IV (APA, 1994), and International Statistical Classification of Diseases and Related Health Problems (ICD-10) criteria. Participants with ASD met criteria for a lifetime diagnosis of autistic disorder, Asperger's syndrome, or pervasive developmental disorder not otherwise specified

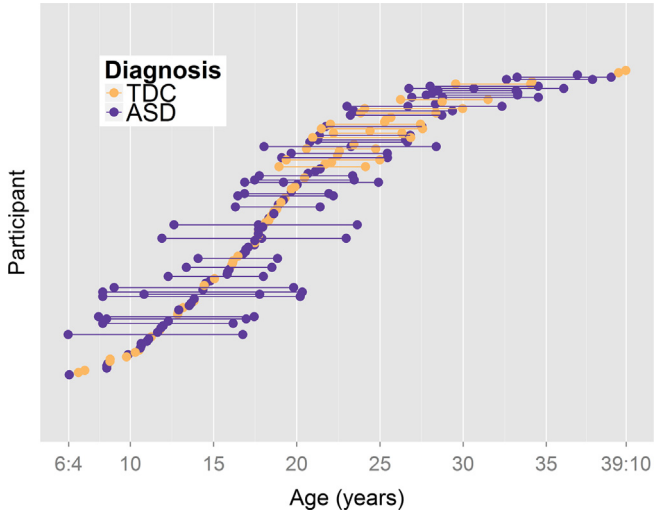

Fig. 1. Depiction of accelerated longitudinal design, including the age at each processing speed assessment and the number of processing speed assessments for each participant within each group (autism spectrum disorder [ASD] and typically developing controls [TDC]).

Table 1
(a) Demographic characteristics of the longitudinal study sample.

	ASD	TDC	Total
Number of participants	81	56	137
Age in years[a], *Mean* (*SD*)	18.5 (6.9)	19.8 (7.3)	19.0 (7.0)
Age range	6.3–38.9	6.9–39.8	6.3–39.8
Full Scale IQ[a] *Mean* (*SD*)	101.9 (16.4)	117.3 (14.2)	108.2 (17.3)
Full Scale IQ range	61–137	68–152	61–152
Verbal IQ[a] *Mean* (*SD*)	101.3 (23.5)	116.1 (14.2)	107.0 (21.5)
Verbal IQ range	58–138	84–140	58–140
Performance IQ[a] *Mean* (*SD*)	100.2 (16.8)	112.2 (17.8)	104.9 (18.1)
Performance IQ range	66–127	77–155	66–155
Processing speed assessments per participant, *Mean* (*SD*)	1.6 (0.7)	1.2 (0.4)	1.4 (0.6)
Participants with 1 Assessment	43	45	88
Participants with 2 Assessments	31	11	42
Participants with 3 Assessments	7	0	7
Inter-Assessment Interval[b] (years), *Mean* (SD)	6.0 (2.1)	5.1 (0.7)	5.9 (1.9)

(b) Demographic characteristics of the DTI longitudinal study subsample.

	ASD	TDC	Total
Number of participants	67	54	122
Age in years[a], *Mean* (*SD*)	20.4 (6.5)	20.2 (7.1)	20.3 (6.8)
Age range	10.6–36.9	6.9–39.8	6.9–39.8
Full scale IQ[a] *Mean* (*SD*)	103.2 (15.8)	117.6 (14.4)	109.6 (16.8)
Full scale IQ range	61–137	78–152	61–152
Verbal IQ[a] *Mean* (*SD*)	104.9 (21.4)	113.2 (15.1)	109.8 (18.2)
Verbal IQ range	58–138	84–140	58–140
Performance IQ[a] *Mean* (*SD*)	107.7 (15.5)	113.7 (18.6)	111.2 (17.5)
Performance IQ range	73–127	77–155	73–155
DTI scans per participant, *Mean* (*SD*)	1.5 (0.5)	1.3 (0.5)	1.4 (0.5)
Participants with 1 Scan	44	43	86
Participants with 2 Scans	23	11	36
Inter-Scan Interval[c] (years), *Mean* (SD)	5.4 (0.7)	5.0 (0.8)	5.2 (0.7)

[a] Defined as mean for each individual then averaged across each group.
[b] Interval between Time 0, Time 1, and Time 3.
[c] Interval between Time 1 and Time 3.

(89% met full criteria for autistic disorder). Participants with ASD were excluded from the present study if they had a known medical cause of ASD (determined by patient history, physical exam, fragile-X testing, and karyotype), or if they had a history of severe head injury, hypoxia–ischemia, seizure disorder, or other neurological disorders. TDC participants were confirmed as having typical development through history, ADOS-G testing, IQ testing, neuropsychological assessment, and standardized psychiatric assessment. All participants were verbal at the time of testing and had English as their first language. Participant groups were matched on age (grand mean across the multiple time points) in the processing speed total sample, $t(1\,3\,5)=1.08$, $p=.28$, and in the DTI subsample, $t(1\,1\,9)=-0.12$, $p=.90$. However, compared to the typically developing group, the ASD group had significantly decreased full-scale IQ in the processing speed total sample, $t(1\,3\,5)=5.72$, $p<.001$, and in the DTI subsample, $t(1\,1\,9)=5.19$, $p<.001$. See Table 1 for more detailed participant information.

2.3. Assessments

2.3.1. Processing speed index (PSI)

Processing speed was assessed using the processing speed subtests of the Wechsler Intelligence Scale for Children-3rd edition (WISC-III; Wechsler, 1991) or the Wechsler Adult Intelligence Scale-3rd edition (WAIS-III; Wechsler, 1997) at three separate points during longitudinal data collection. The WISC-III or WAIS-III subtests were administered depending on age of the participant. The overall processing speed index was a standardized score that was based on the Coding and Symbol Search subtests of the WISC-III and the Digit-Symbol Coding (henceforth called "Coding") and Symbol Search subtests of the WAIS-III. WISC-III and WAIS-III testing for this project began prior to the emergence of the fourth editions of each of these tests. For longitudinal consistency, all participants received the third editions of the WISC and WAIS for all time points.

2.3.2. IQ

At Times 0 and 1, IQ was assessed in all participants using standard scores in verbal, nonverbal, and overall ability using the WISC-III (Wechsler, 1991) or WAIS-III (Wechsler, 1997) (depending on age). At Time 3, participants completed the two-subtest version of the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999) to obtain an estimate of full scale IQ.

2.4. Imaging protocol

At Times 1 and 3, participants received magnetic resonance and DTI scans at the University of Utah (44 participants with ASD provided one scan, 23 provided two scans; 43 TDC participants provided one scan, 11 provided two scans). Time 2 DTI data were also collected, but the corresponding Time 2 processing speed data were not collected. Therefore, the Time 2 DTI data were not included in the analyses. Magnetic resonance images were acquired on a Siemens Trio 3.0 T Scanner at the University of Utah. At both time points, the DTI acquisition used a product single-shot, spin-echo, echo planar imaging (EPI) pulse sequence with diffusion weighting, performed with bipolar gradients with dual-echo refocusing to reduce eddy currents (Reese, Heid, Weisskoff, & Wedeen, 2003). Parallel imaging with a geometric reduction factor of two was used to reduce image distortions from magnetic field inhomogeneities. For each slice, we obtained twelve diffusion weighted images with non-collinear diffusion encodings with a $b=1000\ \mathrm{s/mm^2}$ and a single b0 image. Sixty contiguous axial slices 2.5 mm thick were acquired over the cerebrum and cerebellum (matrix$=128\times128$, FOV$=256$ mm, resolution$=2\times2\times2.5$ mm, averages$=4$, TR$=7000$ ms, TE$=84$ ms at Time 1 and TE$=91$ ms at Time 2, pixel bandwidth$=1346$ Hz). Between the Time 1 and Time 3 scans, the scanner hardware (e.g., head coil: 8-channel at Time 1, 12-channel at Time 3) and software were upgraded.

2.5. DTI image analysis

Image processing and analyses were conducted at the University of Wisconsin-Madison. Diffusion weighted images were corrected for distortion, translation, and rotation from bulk head motion and eddy currents using an affine registration tool provided by the fMRIB FSL software library (Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012). The gradient orientation was corrected for rotation (Leemans & Jones, 2009). Brain images were skull stripped. Then, the tensors were fit using a robust estimation algorithm (RESTORE; Chang, Jones, & Pierpaoli, 2005) performed in Camino (Cook et al., 2006). The eigenvalue maps (λ_1, λ_2, λ_3) were computed from the estimated diffusion tensors. Maps of FA (the normalized standard deviation of the eigenvalues reflecting the relative degree of diffusion anisotropy), MD (average of the eigenvalues), RD (average λ_3), and AD (average λ_1) were calculated. The units for MD, RD, and AD were $\mathrm{mm^2/s}$, scaled 10^{-3}. Quality

control checks were manually performed on the DTI images, looking for instances of slice intensity banding, motion-induced FA hyperintensities, frontal lobe distortions, or blurring that could affect the analyses. Additionally, the white matter masks were checked to make sure that they were adequately covering the white matter in each brain scan. After quality control checks on the data, 98% of the scans met the quality control standards, rendering a total of 155 scans that corresponded with a processing speed assessment (90 ASD scans and 65 TDC scans). Therefore, the majority of the participants included in the processing speed analyses also had corresponding DTI data.

A population-specific template was estimated iteratively, aligning all the subjects using affine and diffeomorphic diffusion tensor registration implemented in DTI-TK (Zhang, Yushkevich, Alexander, & Gee, 2006). To segment the major white matter tracts, the JHU ICBM-DTI-81 template FA (Mori, Wakana, Nagae-Poetscher, & Van Zijl, 2005) was registered to our population FA template using a diffeomorphic spatial normalization tool, ANTS (Avants & Gee, 2004), and the 48 tract labels from this template were transferred to our template using nearest neighbor interpolation. These regions of interest were combined to create a unitary whole brain mask of the deep white matter tracts. Using a method similar to that described by Faria et al. (2011), this mask was then transferred to the native space of each participant using the inverse of the corresponding spatial transformations estimated during the population normalization. The mean FA, mean MD, mean RD, and mean AD were calculated across the whole brain white matter mask.

2.6. Statistical analyses

To examine longitudinal, age-related changes in processing speed index (PSI) scores, we fit linear mixed-effects models, accounting for the repeated measurements (Venables & Ripley, 2002). The model examined PSI as function of age and diagnostic group, while controlling for full scale IQ and random effects (PSI = intercept + age + group + age × group + full scale IQ + random effects). Similar linear mixed-effects models were performed for the WAIS-III (adult) Symbol Search and Coding subtest raw scores (WAIS-III Coding/Symbol Search = intercept + age + group + age × group + full scale IQ + random effects). However, because there were no repeated measurements in the WISC-III (childhood) subtests, the WISC-III models were examined using standard linear regression (WISC-III Coding/Symbol Search = intercept + age + group + age × group + full scale IQ). Furthermore, because there was a different range of raw scores for children younger than 8, the WISC-III analyses did not include two ASD and two TDC data points of children under the age of 8 years. In all models, age and full scale IQ were included as mean-centered variables to reduce the potential of multicollinearity. Additionally, all linear models were tested against a quadratic age model (intercept + age + age^2 + group + age × group + age^2 × group + full scale IQ), and the linear models were shown to have better fits determined by lower AICs (Akaike, 1974). All models were found to meet the assumptions of the general linear model. One-sample *t*-tests were employed to examine the ASD group's and the typically developing group's PSI performance compared to the standardized test's norms ($M = 100$).

To examine the relation between whole-brain DTI and PSI measures, linear mixed-effects analyses were conducted. Because there were significant group differences in both PSI scores and the DTI measures and because age is likely to affect these relations, the linear mixed-effects model controlled for group status, age, and random effects (PSI ~ intercept + whole brain FA + group + whole brain FA × group + age + random effets). Because of the head coil change between Time 1 and Time 3 data collection, we also conducted standard regression models separately for Time 1 (Time 1 PSI ~ Time 1whole brain FA + group + Time 1 whole brain FA × group + Time 1 age) and for Time 3 (Time 3 PSI ~ Time 3 whole brain FA + group + Time 3 whole brain FA × group + Time 3 age) to make sure that the results were similar. This replication approach was selected as a way to validate findings across both head coils. These analyses were repeated for whole-brain MD, whole-brain RD, and whole-brain AD.

3. Results

3.1. Longitudinal group differences in processing speed index (PSI)

We tested for group differences in PSI scores and their longitudinal trajectories. PSI scores for each participant are presented in Fig. 2. A linear mixed-effects model analysis controlling for full scale IQ suggested slower processing speed in individuals with ASD, such that the group with ASD averaged 12 points lower on PSI scores than typically developing peers (see Table 2). These significant group differences were not accompanied by significant age-related changes in PSI from six to 39 years of age, which is consistent with the fact that these scores are age-normed. However, there was a marginally significant interaction between group and age ($p = .09$), suggesting that the effect of group on PSI may vary slightly with age. When not controlling for full scale IQ, the same pattern of results remained; however, the group with ASD averaged 18.8 points lower on PSI scores, suggesting that controlling for full scale IQ conveys a more conservative estimate of PSI group differences. The average PSI scores in our typically developing group was 107.1 ($SD = 13.9$). A one-sample *t*-test indicated that this was a significantly higher PSI score compared to the typically developing individuals with whom these tests were normed ($M = 100$, $SD = 15$), $t(55) = 4.10$, $p < .001$. However, a one-sample *t*-test in the ASD group demonstrated that PSI scores in ASD were significantly lower than the standard score ($M = 100$), $t(80) = -7.49$, $p < .001$, suggesting that our ASD group demonstrated significantly lower PSI scores in comparison to our typically developing control group and in comparison to the standard score.

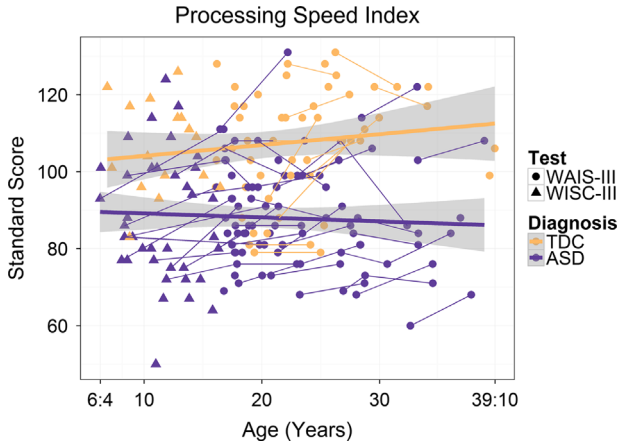

Fig. 2. Processing speed standard scores plotted as a function of age and group (autism spectrum disorder [ASD] and typically developing controls [TDC]).

3.2. Longitudinal group differences in the processing speed WAIS-III and WISC-III subtests

Because WISC-III and WAIS-III standardized norms are based on what might be expected at particular ages in children with typical development, we also wanted to examine the raw (not age-normed) scores of the subtests that make up the processing speed index score. Therefore, we tested for group differences and age-related changes in the WISC-III and WAIS-III Symbol Search and Coding subtest raw scores. Subtest scores for each participant can be viewed in Fig. 3. The linear mixed-effects results suggested robust group differences in both the WAIS-III Symbol Search and Coding subtests (see Table 2). However, linear regression results suggested no group differences in the WISC-III Symbol Search subtest raw scores, and only a marginally significant group difference in the WISC-III Coding subtest raw scores ($p = .07$). There were no significant age effects for WAIS-III Symbol Search or Coding subtests, but significant age effects were present for the WISC-III Symbol Search and Coding subtests, suggesting age-related increases in processing speed performance in the childhood version but not adult version of these tests. There were no significant interactions between group and age.

3.3. Processing speed and whole brain white matter correlates

Prior to examining if PSI was related to whole brain white matter microstructure, initial analyses examined if the groups differed in overall FA, MD, RD, and AD metrics. Significant group differences were found in average whole brain FA, $t(119) = 2.10$, $p = .04$, MD, $t(119) = -3.14$, $p = .002$, RD $t(119) = -3.08$, $p = .003$, and AD, $t(119) = -2.7$, $p = .009$. Because group differences existed in both the DTI metrics and PSI scores, the DTI-PSI correlations were conducted while controlling for group status.

Table 2
IQ Test, regression type, beta coefficients, and corresponding *p*-values for each regression model examining processing speed as a function of diagnostic group and age, after controlling for full scale IQ (FSIQ). Regression type was determined by whether or not the particular analysis contained participants with longitudinal data.

	IQ test	Regression type	Intercept	*p*-Value	Group	*p*-Value	Age	*p*-Value	Group × Age	*p*-Value	FSIQ	*p*-Value
PSI	WISC-III & WAIS-III	Linear mixed-effects	102.85	< .001	−12.31	< .001	0.20	.32	−0.41	.09	0.46	< .001
Coding raw	WISC-III	Linear	44.74	< .001	−6.06	.07	4.01	.001	−1.26	.31	0.27	.001
Coding raw	WAIS-III	Linear mixed-effects	79.92	< .001	−18.11	< .001	0.33	.28	−0.57	.13	5.79	< .001
Symbol search raw	WISC-III	Linear	24.02	< .001	−1.01	.63	2.54	< .001	−1.04	.18	0.24	< .001
Symbol search raw	WAIS-III	Linear mixed-effects	37.14	< .001	−5.48	< .001	0.02	.90	−0.23	.30	0.24	< .001

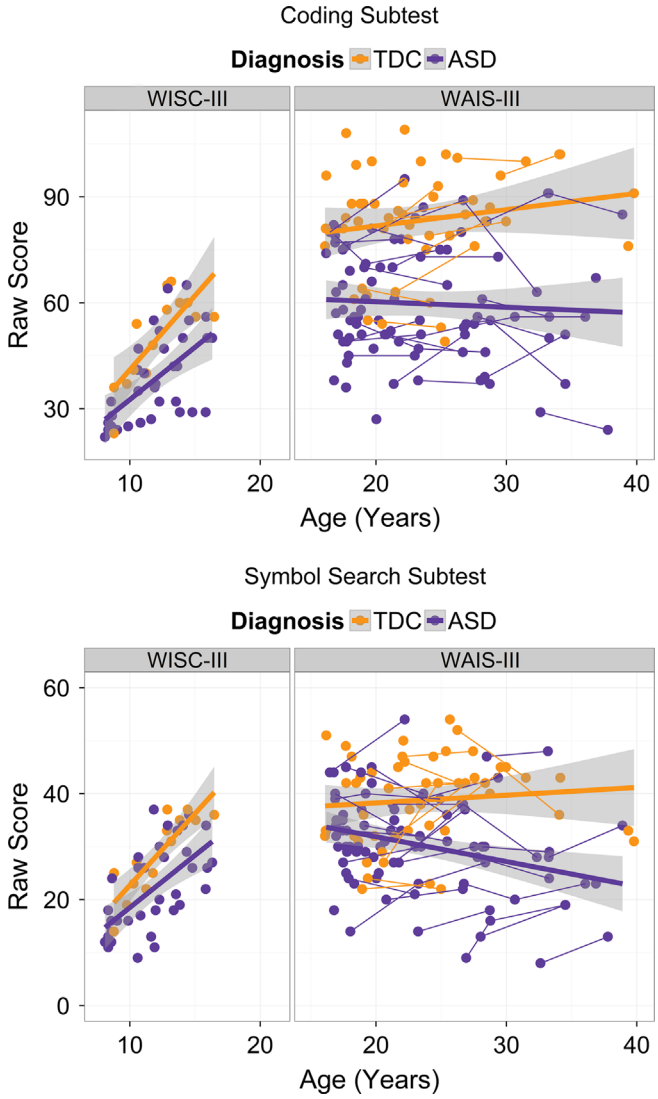

Fig. 3. WISC-III and WAIS-III Coding and Symbol Search subtest raw scores plotted as a function of age and group (autism spectrum disorder [ASD] and typically developing controls [TDC]). Note that the WAIS-III Digit-Symbol Coding subtest is labeled as "Coding." Because there is a different range of raw scores for children younger than 8 years of age, the WISC-III analyses (and these plots) do not include two ASD and two TDC data points of children who were 6–7 years old at the time of testing.

Scatterplots of PSI and white matter FA, MD, RD, and AD can be seen in Fig. 4. As can be seen in Table 3, longitudinal linear mixed-effects models suggested that whole brain FA significantly predicted PSI scores (p=.04) across Times 1 and 3 combined. However, this effect was quite small. Therefore, it is likely that there are other, possibly stronger, predictors of PSI in ASD and typically developing participants than whole-brain white matter FA. When Time 1 and Time 3 data were analyzed separately, the effects of FA on PSI were in the same direction and similarly sized, but they did not reach statistical significance (p=.36, and p=.09, respectively). The lack of statistical significance may have been due to decreased power to detect smaller effects when splitting the data across Time. PSI was not significantly predicted by whole brain MD, RD, or AD across both Times combined nor within each Time independently (all p's > .11). There were no significant group-by-whole brain DTI interactions, suggesting that there were similar relations between DTI metrics and PSI scores across both groups.

4. Discussion

Using an accelerated longitudinal design, the present study examined group differences and age-related changes in processing speed in individuals with ASD compared to individuals with typical development from childhood into adulthood. The results yielded three important findings: (1) A significant processing speed standard score deficit in ASD that tends to be sustained from childhood to adulthood, (2) a significant and robust processing speed raw score deficit in the ASD group in the adult but not childhood versions of the Coding and Symbol Search subtests (likely due to the differential complexity of the tests), and (3) PSI being modestly predicted by whole-brain FA across Time 1 and Time 3. Each of these findings is discussed in more detail below.

4.1. Group differences in processing speed index (PSI) standard scores

Across a wide age range (6–39 years), individuals with ASD exhibited PSI scores that were approximately 12-points lower than PSI scores of individuals with typical development. This finding from our longitudinal investigation is consistent with previous cross-sectional studies, suggesting decreased PSI in children, adolescents, and adults with ASD (i.e., Mayes & Calhoun, 2003, 2008; Oliveras-Rentas et al., 2012; Spek et al., 2009; Wechsler, 2003). However, our longitudinal study extends the findings of past cross-sectional studies by showing that processing speed deficits in individuals with ASD tend to be sustained. The present study's 12-point decrease in PSI in ASD is clinically noteworthy, suggesting that the ASD group was on average almost one standard deviation below the typically developing group in processing speed performance, even after controlling for differences in full scale IQ. This finding indicates that processing speed may be a particular difficulty for many individuals with ASD, regardless of age or overall intellectual functioning. Therefore, educational or vocational accommodations that allow individuals with ASD to have more time to process information would likely enable them to perform better in a variety of domains. Common processing-speed-directed educational accommodations for children and adolescents with ASD include extended time for assignments or tests, slowing down the rate of speech during instruction, and allowing time for the student to think through an answer to a question. More generally, it is interesting to think how beneficial these types of accommodations might be outside of the classroom and throughout adulthood, whereby

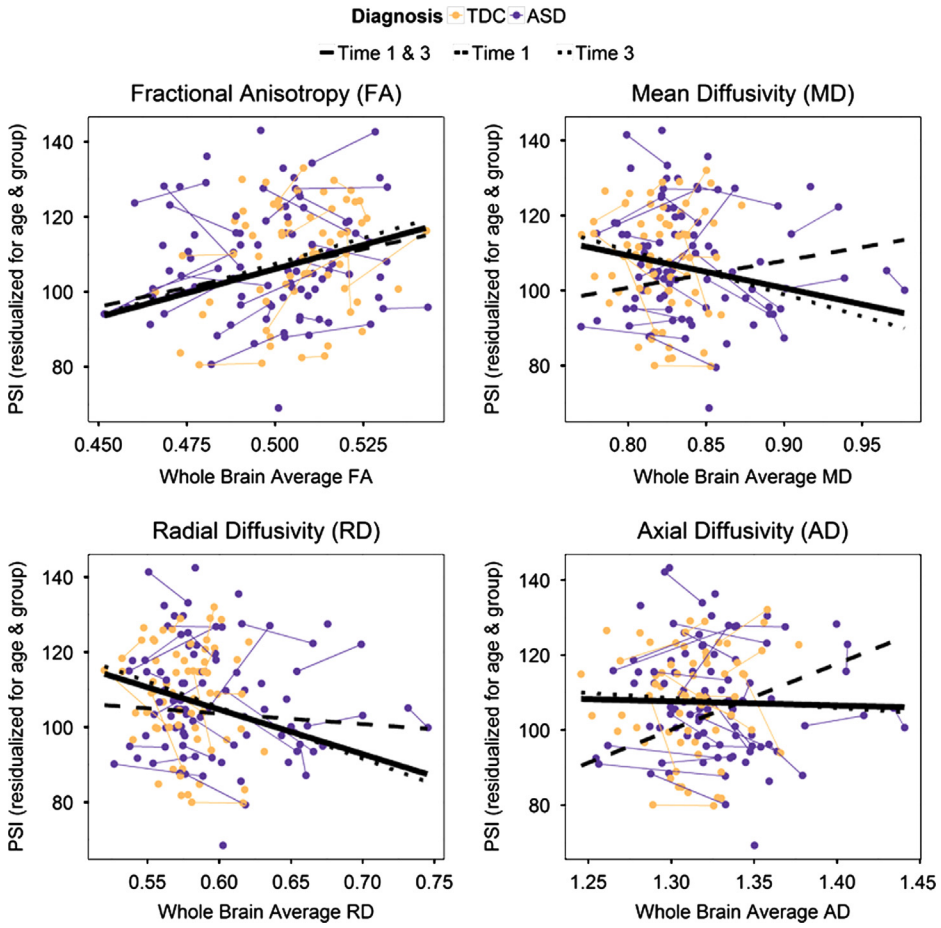

Fig. 4. Processing speed index (PSI) standard scores as a function of whole-brain mean fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD) at Time 1 and Time 3. The unit of measurement for MD, RD, and AD was mm^2/s, scaled 10^{-3}.

Table 3
Regression type, beta coefficients, and corresponding *p*-values for each model examining Processing Speed Index (PSI) as a function of whole brain fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD), after controlling for age and group status. Because of head coil changes in the DTI data collection, Time 1 and Time 3 were examined together (using a longitudinal linear mixed-effects model) and then separately (using separate linear regressions).

	Regression type	Intercept	*p*-Value	Whole brain FA	*p*-Value	Group	*p*-Value	Age	*p*-Value	Whole brain FA × Group	*p*-Value
PSI ~ intercept + whole brain FA + group + age + whole brain FA × group											
Time 1 & Time 3	Linear mixed-effects	−22.25	.71	256.69	.04	87.67	.19	−0.04	.82	−210.05	.12
Time 1	Linear	3.77	.97	205.00	.36	1.95	.99	0.09	.83	−41.74	.88
Time 3	Linear	−29.59	.71	274.17	.09	139.88	.15	−0.15	.42	−310.03	.10
PSI ~ intercept + whole brain MD + group + age + whole brain MD × group											
Time 1 & Time 3	Linear mixed-effects	178.88	< .001	−86.91	.24	−70.22	.29	0.03	.87	63.12	.43
Time 1	Linear	43.10	.80	72.07	.71	127.45	.48	0.24	.57	−174.48	.41
Time 3	Linear	204.67	.02	−117.43	.27	−118.47	.22	−0.11	.56	123.51	.29
PSI ~ intercept + whole brain RD + group + age + whole brain RD × group											
Time 1 & Time 3	Linear mixed-effects	176.02	< .001	−118.84	.11	−73.44	.11	0.01	.95	95.54	.23
Time 1	Linear	120.48	.25	−28.06	.87	18.90	.86	0.21	.63	−63.01	.74
Time 3	Linear	187.43	< .001	−136.88	.16	−99.43	.11	−0.12	.50	143.03	.19
PSI ~ intercept + whole brain AD + group + age + whole brain AD × group											
Time 1 & Time 3	Linear mixed-effects	122.33	.12	−11.28	.85	−9.43	.92	0.06	.71	−6.99	.92
Time 1	Linear	−128.65	.52	175.96	.25	327.94	.18	0.15	.71	−261.33	.15
Time 3	Linear	143.17	.23	−26.62	.77	−58.09	.68	−0.08	.66	30.86	.77

slowing down rate of speech and providing ample time for responses may facilitate social engagement in individuals with ASD. Furthermore, processing speed may not be a static entity in this population. Specifically, after an average of 30 months of supported employment, processing speed increased in adults with ASD compared to their baselines and compared to a non-employed, waitlist ASD comparison group (García-Villamisar & Hughes, 2007). Therefore, it is possible that vocational or educational enrichment in adults with ASD may improve processing speed. However, future investigations are needed to confirm and expand upon the

mechanisms of processing speed improvement in ASD as a function of employment.

In the present analyses, we additionally examined group differences in age-related changes in processing speed. There was only a statistical trend for more disparate group performance in adulthood compared to childhood, suggesting that age-related changes in processing speed in ASD and typical development are similar. Because the oldest individuals in these analyses were under 40 years of age, it will be critical to extend these analyses in older individuals in order to determine if age-related changes in processing speed during older adulthood occurs similarly in ASD and typical development. These future investigations would importantly inform us of what cognitive aging in ASD may entail. Overall, these results suggest that processing speed difficulties may be a persistent and clinically significant impairment in ASD from childhood into adulthood.

4.2. Robust group differences in adult but not childhood subtest raw scores

Group differences in subtest raw scores were significant and robust in the adult versions of the test but not in the childhood versions of these tests. These results suggest that processing speed impairments in ASD may be more pronounced in adult IQ tests, even though the rate of age-related processing speed changes were similar across groups for the WISC-III and the WAIS-III. The child and adult versions of the tests are similar in that participants have 120 s to complete as many items as possible. However, the child and adult versions of the tests differ in the complexity of the to-be-drawn coding symbols and in the number of task items that are available for completion within the 120-s timeframe. These differing task demands may elicit different approaches from children and adults with typical development. A key avenue for future investigations will be to see whether or not individuals with ASD similarly adapt differing approaches to child versus adult processing speed tasks. Nevertheless, the fact that individuals with ASD perform more similarly to individuals with typical development on the less-complex, child processing speed subtests but perform more disparately on the more-complex adult subtests is similar to prior findings of individuals with ASD demonstrating difficulty with tasks that entail higher-order or more complex information processing (Minshew, Goldstein, & Siegel, 1997; Minshew, Sweeney, & Luna, 2002; Williams, Goldstein, & Minshew, 2006).

Although not as robust as the group differences in the adult subtests, the children with ASD demonstrated trend-level lower raw scores on the Coding subtest (but not the Symbol Search subtest). The Coding subtest may have slightly stronger motor demands than the Symbol Search subtest (drawing the symbol on the Coding subtest rather than crossing out “yes” or “no” on the Symbol Search subtest). Speculatively, this greater reliance on motor ability may have differentially impacted the children with ASD, as children with ASD are often reported to have motor difficulties (see Fournier, Hass, Naik, Lodha, & Cauraugh, 2010] for a meta-analysis). Future research will be needed to investigate this possibility. Another possible explanation is that the children with ASD may have utilized greater attention to detail when drawing the coding symbols, which may have affected their speed in the Coding subtest more so than their speed on the Symbol Search subtest. Theories of “weak central coherence” (Happé & Frith, 2006) or “enhanced perceptual functioning” (Mottron, Dawson, Soulières, Hubert, & Burack, 2006) of ASD both propose that individuals with ASD have a tendency to focus on details rather than the global whole, which may have impacted symbol-drawing speed in the children with ASD in the present study.

4.3. White matter microstructure and PSI standard scores

Measures of whole-brain white matter microstructure suggested that higher FA was associated with higher processing speed index standard scores across Times 1 and 3. However, these effects were quite small, with approximately a .01 increase in DTI FA (11% of the entire range of DTI FA values) being associated with a 2.5 point increase in processing speed standard scores. These effects were similarly sized but not statistically significant when examining Time 1 and Time 3 data separately, possibly due to the reduction of power when splitting the sample across Time. Furthermore, these effects were not seen when examining PSI as a function of other metrics of white matter microstructure (i.e., MD, RD, and AD). Indeed, the effect sizes of the models using DTI metrics and age to predict PSI were lower than expected, but these small-sized effects are consistent with previous studies in older adults with typical development. Specifically, Penke et al. (2010) found a.24 correlation between their FA integrity factor and their processing speed factor (R^2=.06) and a .16 correlation between MD integrity factor and their processing speed factor (R^2=.03), after accounting for gender and age. The fact that MD had only half of the explanatory power to predict processing speed compared to FA is consistent with our current results, finding trends but not significant relations between MD and processing speed standard scores. In older-adult men, Venkatraman et al. (2011) found a .21 correlation between their FA integrity factor and a measure of processing speed (R^2=.04). The consistency of the magnitude of the present results with prior findings in other populations suggests that white matter microstructure might partially underlie processing speed ability. The small effect sizes of FA-processing-speed relations, however, suggest that there are likely other factors contributing to PSI scores that if included would make for stronger predictive models of PSI. These may include more specific regions of white matter microstructure (i.e., the corpus callosum) or other factors such as cortical volume, cortical thickness, or functional connectivity. Therefore, the present results likely indicate that decreased white matter microstructural integrity often reported in ASD (see Travers et al., 2012 for a review) might partially underlie the processing speed difficulties observed in ASD. However, there are likely other contributing variables to PSI in ASD that will need to be explored in order to create better predictions of which individuals with ASD are more or less likely to show processing speed difficulties.

4.4. Limitations

There are several potential limitations associated with this present study. First, although these assessments were part of a larger longitudinal study, 64% of participants had only one time point represented for the processing speed measures. Therefore, the overall group trajectories derived from this longitudinal analysis likely reflect cross-sectional influences in addition to the longitudinal trajectories. This high number of participants with only one processing speed score was not due to attrition in the longitudinal sample, as retention was 85% for the group with ASD and 71% for the group with typical development. Instead, it appears to be due to the fact that a number of the participants entered the original longitudinal study when they were younger than six years of age, and they were therefore too young to receive an initial WISC-III measure of processing speed. This effect was compounded by not collecting processing speed data at Time 2. As more longitudinal data continue to be collected from participants, we will be better able to examine longitudinal changes in these measures. Second, the group with ASD had significantly more longitudinal measures of processing speed than the group with typical development (ASD M=1.6 processing speed measures, TDC M=1.2), which may have led to more practice effects in the ASD group. However, we examined overall PSI scores as

a function of the number of times the participant had completed the processing speed tests (in both groups and in each group separately), and there were no differences (and any trend suggested that those with more testing longitudinal measures had overall lower scores). Therefore, we do not believe that increased practice on these measures in ASD accounts for the present findings. However, because the ASD group had more longitudinal data points than the typically developing group, it is possible that the longitudinal age-related changes may be more reliably modeled in the ASD group than in the typically developing group in this study. A third limitation is that our typically developing group appeared to have higher PSI scores than the typically developing sample on which the test was normed. However, to make sure that this was not driving the results, we tested and found that the ASD group's PSI scores were significantly lower than the normed PSI scores. A fourth limitation is that even though processing speed is a basic and fundamental cognitive process, the processing speed subtests of the WISC-III and WAIS-III may be measuring multiple cognitive domains, including visual perception/analysis, visual scanning speed, visual-motor coordination, motor speed, mental speed, and visual working memory. It is possible that if we had had a more precise measure "mental speed," we may have had stronger correlations to white matter microstructure. Fourth, analyses examining longitudinal changes in processing speed controlled for full scale IQ, which at Times 0 and 1 was partially calculated from PSI. This may have been an overly conservative approach, and it may not even be appropriate to control for full scale IQ when examining between-group analyses in ASD compared to typical development (Dennis et al., 2009). Therefore, we reported the group results with and without the full scale IQ covariate. Finally, differences in the present study between raw scores of tests (WISC-III versus WAIS-III) and differences in DTI head coil changes (Time 1 versus Time 3) made it complicated to test these measures in a single (likely more powerful) model. Therefore, both the full models and Time-separated models were reported.

4.5. Conclusions

The present study examined longitudinal group differences and age-related changes in processing speed in individuals with ASD compared to individuals with typical development (ages 6–39 years). The results suggest lower PSI standard scores in ASD but similar age-related changes in both groups. The PSI scores in ASD were almost one standard deviation lower than in the typically developing controls after controlling for full scale IQ, likely representing a clinically significant difference. In examining non-standardized subtest raw scores, adults with ASD demonstrated robustly slower processing speed on subtests of the WAIS-III that were not evident in children with ASD, even though age-related changes were similar in both the ASD and typically developing groups. This pattern of results may reflect difficulties becoming increasingly evident in ASD on more complex measures of processing speed or more difficulty with processing speed in ASD in adulthood compared to childhood. Finally, DTI measures of whole-brain white matter microstructure suggested that FA (but not MD, RD, or AD) made significant but modest contributions to PSI across our entire sample. Taken together, the present findings suggest that robust decreases in PSI standard scores may be commonly present in ASD, more pronounced on adult versions of IQ tests, and partially attributable to whole-brain white matter microstructural integrity in individuals with ASD and individuals with typical development.

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