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Maturation differences in thalamocortical white matter microstructure and auditory evoked response latencies in autism spectrum disorders

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Abstract

White matter diffusion anisotropy in the acoustic radiations was characterized as a function of development in autistic and typically developing children. Auditory-evoked neuromagnetic fields were also recorded from the same individuals and the latency of the left and right middle latency superior temporal gyrus auditory ~50ms response (M50)¹ was measured. Group differences in structural and functional auditory measures were examined, as were group differences in associations between white matter pathways, M50 latency, and age. Acoustic radiation white matter fractional anisotropy did not differ between groups. Individuals with autism displayed a significant M50 latency delay. Only in typically developing controls, white matter fractional anisotropy increased with age and increased white matter anisotropy was associated with earlier M50 responses. M50 latency, however, decreased with age in both groups. Present findings thus indicate that although there is loss of a relationship between white matter structure and auditory cortex function in autism spectrum disorders, and although there are delayed auditory responses in individuals with autism than compared with age-matched controls, M50 latency nevertheless decreases as a function of age in autism, parallel to the observation in typically developing controls (although with an overall latency delay). To understand auditory latency delays in autism and changes in auditory responses as a function of age in controls and autism, studies examining white matter as well as other factors that influence auditory latency, such as synaptic transmission, are of interest.

Keywords

Magnetoencephalography; Autism spectrum disorder; Auditory evoked response; Fractional anisotropy; White matter; M50

¹M50: superior temporal gyrus auditory 50 ms response; FA: fractional anisotropy; WM: white matter; MEG: magnetoencephalography; DTI: diffusion tensor imaging; ASD: autism spectrum disorder; TD: typically developing.

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1. Introduction

During typical development, myelination of white matter (WM) confers electrical insulation to allow more efficient axonal signal conduction. This myelination is a critical determinant in processing basic sensory information as well as increasing processing speed during more complex cognitive tasks (Dockstader et al., 2012; Kandel et al., 1991; Stufflebeam et al., 2008). Due to the importance of myelination during development, an investigation of white matter maturation and its consequences in individuals with developmental disorders is of interest. Diffusion tensor imaging (DTI) allows indirect measurement of white matter maturation and of the microstructural properties of WM through fractional anisotropy (FA), a measure of the organization of water diffusion (Beaulieu, 2002; Harsan et al., 2006).

Whereas DTI provides measures of brain structure, magnetoencephalography (MEG) permits recording of neural activity with high temporal resolution. Thus MEG's functional complement to DTI's microstructural data offers insight into the relationship between brain anatomy and function (Dockstader et al., 2012; Roberts et al., 2009, 2010; Stufflebeam et al., 2008). DTI studies have found an increase in FA with age throughout childhood (Ashtari et al., 2007; Hasan et al., 2007; Schmithorst et al., 2002), and other studies have shown an inverse relationship between age and the latency of evoked responses in children (Paetau et al., 1995; Roberts et al., 2009, 2010). The maturational relationship of FA and latency with development has prompted examination of an association between these measures (Dockstader et al., 2012; Roberts et al., 2009; Stufflebeam et al., 2008), with studies indicating a link between increasing FA and decreasing latency as a biophysical feature of developmental change (Roberts et al., 2009).

Previous studies have demonstrated atypical white matter FA and delayed auditory responses in children with ASD versus typically developing (TD) children (Lange et al., 2010; Lee et al., 2007; Gage et al., 2003a, 2003b; Oram Cardy et al., 2008; Roberts et al., 2008, 2010). Furthermore, a previous study observed associations between FA of the acoustic radiations (a critical WM pathway extending from the medial geniculate nucleus of the thalamus to the primary auditory cortex in the superior temporal lobe) and the latency of the 100 ms auditory response (M100) in TD children, with both FA and M100 latency showing age-dependent developmental changes (Roberts et al., 2009).

The present study builds on previous studies, (Reite et al., 1988), examining the earlier “middle latency” cortical 50 ms auditory response (M50) and M50 latency associations with age and FA of the thalamocortical projections (see Fig. 1). Some ($N = 24$) of the TD individuals reported by Roberts et al. (2009) are included in the present cohort (although the MEG paradigm and auditory response of interest differ between the studies). It was hypothesized that group differences would be observed in the rate of maturation of the M50 latency and WM thalamocortical projections, as well as group differences in associations between these measures, with the ASD population demonstrating a weaker relationship between M50 latency and FA.

2. Results

Seven subjects were excluded from final analyses because they were unable to complete the MRI exam (2 ASD) or because of excessive metal artifact in the MEG data (2 TD, 3 ASD). Useable data was obtained from 39 TD children/adolescents (mean age = 11.02, SD = 2.68) and 53 children/adolescents with ASD (age = 10.42, SD = 2.43). In this slightly reduced sample, groups did not differ in age ($p = 0.23$).

Repeated-measure ANOVA indicated no main effect of hemisphere for FA ($F = 1.34$, $p = 0.24$), with no significant group or group $\times$ hemisphere interactions. As such, subsequent analyses collapsed across hemisphere, averaging left and right DTI or MEG. For M50, in cases where bilateral responses were not observed (no left M50 in 8 subjects (3 TD and 5 ASD) and no right M50 in 15 subjects (4 TD and 11 ASD)), only the discernible response was used. No group or hemispheric difference in the presence of M50 was observed (Fisher Exact Test, $p > 0.05$). In addition, subjects with or without an M50 response did not differ in age or FA. For further analyses, hierarchical regressions examining FA and M50 latency were performed, entering age first, diagnosis second, and the interaction term third.

For age-corrected marginal mean FA, there was no difference between the TD (mean 0.37 ± 0.049) and ASD (mean 0.36 ± 0.047) groups, $F = 0.07$, $p = 0.79$. For age-corrected marginal mean M50 latency, there was a significant difference between the TD (mean 67.67 ± 14.94) and ASD (mean 73.49 ± 14.27) groups, $F = 4.31$, $p = 0.04$, with a latency prolongation ($\sim 10\%$) in ASD consistent with the M100 latency findings reported by Roberts et al. (2010).

M50 latency and age: As shown in Fig. 2, M50 latency decreased with age in TD ($r = 0.43$, $p < 0.01$, slope = -2.4 ms/yr) and ASD ($r = 0.44$, $p < 0.01$, slope = -2.6 ms/yr). The group difference between slopes was not significant ($p = 0.43$).

FA and age: As shown in Fig. 3, FA increased with age in TD ($r = 0.50$, $p < 0.01$, slope = 0.009 /yr) but not in ASD ($r = 0.11$, $p = 0.44$, slope = 0.002 /yr). The group difference between slopes was significant ($p = 0.03$).

M50 latency and FA: As shown in Fig. 4, M50 latency decreased with increasing FA in TD ($r = 0.42$, $p < 0.01$, slope = -127.13) but not in ASD ($r = 0.028$, $p = 0.85$, slope = 8.37). The group difference between slopes was significant ($p = 0.03$).

Considering the TD group only, after regressing out effects of age on FA ($p < 0.01$), a residual association with CELF-4 CLI was marginally significant ($p = 0.054$), with a positive slope of 0.001 FA units per point increase in CELF-4 CLI. This positive association was apparently lost in the ASD group (reminiscent of the loss of FA versus M50 relationship), with ASD CELF-4 accounting for only 1% R^2 change in FA ($p = 0.46$). In neither ASD nor TD was an association with non-verbal IQ (PRI of the WISC-IV) identified ($p > 0.05$). For M50 latency, similar to the M100 findings by Roberts et al. (2010) and Roberts et al. (2012) (in SLI), no association was found with CELF-4 CLI for TD or ASD ($p > 0.05$).

Despite the lack of main effects of hemisphere, to allow comparisons with other studies, hemispheric results are shown in Tables 1–3.

To understand the biological underpinning of the reduced age-dependence of fractional anisotropy (FA) in ASD versus TD, the related diffusion parameters mean, axial and radial diffusivity (MD, AD, RD) were analyzed. Results are presented in Tables 4–6. Individuals with ASD had increased axial diffusivity versus TD (Table 4). Individuals with ASD showed a maturational decrease of radial diffusivity but at a slower rate than that observed in TD. Also, individuals with ASD showed a non-significant tendency towards an axial diffusivity decrease with age, whereas the TD group showed a lack of age-dependence on axial diffusivity.

3. Discussion

As hypothesized, FA of the acoustic radiations was positively associated with age (although only in TD children), and M50 latency was negatively associated with age (for both TD and

ASD). Examining between-group differences, the ASD group showed a delayed M50 response, a finding predicted from previous studies examining the M100 response (Roberts et al., 2010). Of interest, although the ASD group had a delayed M50 response, the slope of the M50 latency versus age relationship did not differ between groups; rather, the intercept did. In addition, although there was no group difference in mean acoustic radiation FA between groups (correcting for age), FA increased with age in the TD but not in the ASD group. In fact, a major finding of this study is the apparent absence, or at least considerable slowing, of developmental change in the acoustic radiation FA in children with ASD.

In the TD group, FA of the acoustic radiations was related to age and M50 latency, suggesting a role of WM development in the maturation of the auditory cortex electrophysiologic response. In the ASD group, although M50 latency showed a significant maturational age dependence, it was not significantly associated with acoustic radiation FA, indicating an uncoupling between the structure–function relationship of auditory cortex electrophysiology and thalamocortical white matter in ASD. Thus factors other than white matter conduction velocity impact the maturation of the auditory evoked response and at least some of these factors do not exhibit an atypical developmental rate in ASD. Studies of these factors, such as synaptic transmission, are of interest. As an example, Edgar et al. (2013) showed that pre-stimulus power predicts M100 response latencies, with increased pre-stimulus power (i.e., more noise) predicting longer M100 response latencies.

In contrast to FA, mean diffusivity of the acoustic radiations decreased with age in ASD in a similar fashion to TD. However, examination of underlying axial and radial diffusivity changes suggests that the mechanisms underlying the mean diffusivity finding differ between groups. In particular, radial diffusivity tended to decrease at a slower rate in ASD than in TD, whereas axial diffusivity tended to decrease in ASD while being asymptotic in TD. The combination of these trends accounts for the significant difference in age-slopes between ASD and TD observed for FA, and the lack of group difference in age-slopes of MD. Considering the M50 developmental trajectory in ASD, which did not differ in slope from that observed in TD, a shift of 5–6 ms persisted in the ASD compared to the TD group at each age, perhaps attributable to the atypical WM maturation in the ASD group. Despite the age-related changes in axial diffusivity and radial diffusivity in the ASD group, the lack of association of these changes (and indeed the composite measure, mean diffusivity) with the maturing M50 latency suggests that the WM maturation processes indexed by these DTI parameters are indeed atypical in ASD. Of note, these DTI parameters alone may be insufficient to fully and specifically characterize the relevant biophysics, such as conduction velocity, which might be more directly associated with latency findings.

A limitation of this developmental study is its cross-sectional design: as ASD is clearly a developmental disorder, examinations of relationships between age, indices of WM maturation, and auditory cortex response latencies for individual subjects over time would be of benefit, examining not only group differences but tracking and comparing the intra-individual differences within and between groups with age. Furthermore, as M50 latency decreases through childhood and early adolescence, with both groups following similar (although shifted) developmental trajectories, a study of auditory latencies in late adolescence and adult subjects is needed to determine whether evoked responses in the ASD population eventually “catch up” to the TD population, perhaps hitting the latency plateau a few years later, and thus achieving more typical auditory latencies in adulthood.

4. Experimental procedures

Participants were 41 TD children/adolescents (mean age = 10.88, SD = 2.70) and 58 children/adolescents with ASD (age = 10.41, SD = 2.51). Groups did not differ in age ($p =$

0.37). ASD diagnosis was previously made based on expert clinician judgment of DSM-IV criteria and confirmed during study participation by empirically established cut-offs on the Autism Diagnostic Observation Schedule (ADOS) as well as parent-completed questionnaires, including the Social Communication Questionnaire (SCQ) and the Social Responsiveness Scale (SRS) (for additional details on subject recruitment as well as exclusion and inclusion criteria, see Roberts et al., 2010). Scores on Clinical Evaluation of Language Fundamentals (CELF-4) Core Language Index and Wechsler Intelligence Scale for Children (WISC-IV) Full Scale IQ, Perceptual Reasoning Index (PRI), and Verbal Comprehension Index (VCI) were also obtained.

4.1. Structural measures

DTI consisted of whole-brain $2 \times 2 \times 2 \text{ mm}^3$ isotropic acquisitions in the axial plane with 30 directions and b -value of 1000 s/mm^2 at 3 T (Siemens Verio™, Siemens Medical Solutions, Erlangen, Germany) using a modified monopolar Stejskal–Tanner sequence with TE of 70 ms, TR of 11 s, spin-echo echoplanar sequence, a 32-channel head coil, maximal gradient strength of 45 mT/m, and a parallel acquisition factor of 2 with generalized autocalibrating partially parallel acquisition. Post-processing involved calculation of tensor eigenvalues, FA, and fiber tracking. Analyses were performed in DTIStudio using the Fiber Assignment by Continuous Tracking (FACT) algorithm with an FA threshold of 0.25 and an angle cutoff of 70° (Mori et al., 1999; Paetau et al., 1995). Image quality of each case was visually inspected for any indication of artifact due to metal and/or motion. Cases where such artifact was observed were excluded from analysis (Roberts et al., 2010).

DTI analyses examined left and right acoustic radiations, the thalamocortical projections connecting the medial geniculate nucleus to the primary auditory cortex of the superior temporal lobe. Regions of interest (ROIs) were drawn on axial directionally color-coded FA maps (see Fig. 1) and interrogated directly for FA. Fiber tracking by placing seeds within the left and right ROIs also allowed reconstruction of the fiber tracts of the left and right acoustic radiations and was used to confirm ROI placement. To further explore details of the microstructure of the thalamocortical pathways, mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD) measures were also computed. These parameters are related by the three eigenvalues of the diffusion tensor: axial diffusivity is equal to the value of the principal eigenvalue (λ_1) and radial diffusivity is the arithmetic mean of the second and third eigenvalues ($(\lambda_2 + \lambda_3)/2$). Mean diffusivity is computed as the arithmetic mean of all three eigenvalues (and can thus be considered as a 2:1 weighted average of RD and AD). FA can be considered as the standard deviation of the three eigenvalues.

4.2. Functional measures

Prior to data acquisition, 1000 Hz tones of 300 ms duration and 10 ms rise time were presented binaurally and incrementally until reaching auditory threshold for each ear. Tones during the task were presented at 45 dB sensation level (above threshold). Task stimuli consisted of 1000 Hz and 2000 Hz tones presented using Eprime v1.1. Tones were presented via a sound pressure transducer and sound conduction tubing to the subject's peripheral auditory canal via ear-tip inserts (ER3A, Etymotic Research, Illinois). Each stimulus trial consisted of a 50 ms tone (randomly presented 1000 Hz and 2000 Hz tones) and a 2350 ms (± 100 ms) intertrial interval. Artifact-contaminated epochs were rejected, non-artifact epochs averaged, and a 1 Hz (6 dB/octave, forward) to 40 Hz (48 dB/octave, zero-phase) bandpass filter applied.

MEG analyses focused on the latency of the M50 response. Applying methods outlined by Roberts et al. (2009), using all 275 channels of MEG data, determination of the peak latency of M50 sources was accomplished by applying to each participant a standard source model

that included left and right STG sources in order to transform each participant's raw MEG surface activity into brain space (Scherg and Von Cramon, 1985). Bilateral STG sources were oriented for each subject at M50 peak amplitude. M50 peaks were picked using methods similar to those described by Roberts et al. (2009), with the M50 peak being the first peak with appropriate sensor-level topography immediately preceding M100 and in a scoring window of 30–130 ms post-stimulus onset. M50 latency responses were scored using in-house MATLAB software correcting for baseline. The extended latency range of the M50 scoring window accommodated the longer M50 latencies observed in young children and ASD (Roberts et al., 2010).

Repeated-measure ANOVA assessed main effects of group and hemisphere as well as group $\times$ hemisphere interactions. Since hemisphere effects were not significant for acoustic radiation FA, further analyses were conducted collapsing across hemisphere. Group differences in marginal mean FA and M50 latency were assessed with an age-covaried general linear model. Group differences in the association between FA and M50 latency with age were examined using hierarchical linear regression with age entered first, group second, and the interaction term (i.e., group $\times$ M50 latency) third. Group differences in associations between FA and M50 were similarly examined using hierarchical linear regression.

5. Conclusion

WM diffusion anisotropy and electrophysiological auditory cortex responses mature across development, with greater fractional anisotropy and earlier auditory latencies in older individuals. Individuals with ASD showed aberrant WM development as well as delays in the M50 response. A strong correlation between diffusion fractional anisotropy and M50 latency was observed only in the TD group, suggesting that WM maturation facilitates the conduction of electrical impulses to achieve more efficient and rapid electrophysiological activity. Although a loss of a WM structure and auditory cortex function relationship was observed in individuals with ASD, M50 latency did decrease as a function of age in ASD, although systematically delayed compared to age-matched typically-developing controls. Thus, factors other than white matter conduction velocity impact the auditory evoked response, and at least some of these factors do not exhibit an atypical developmental trajectory in ASD. To further understand auditory latency delays in ASD and changes in auditory responses as a function of age in controls and ASD, studies examining white matter as well as other factors that influence auditory latency, such as synaptic transmission, are of interest.

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Fig. 1.
Auditory radiation: An example of a ROI drawn around the auditory radiation (in this case, the left) on a participant's MRI.

Fig. 2.

M50 latency and age: The TD group is represented by squares and solid line, and the ASD group by circles and dotted line. M50 latency decreased with age in TD ($r = 0.43$, $p < 0.01$, slope = -2.4 ms/yr) and in ASD ($r = 0.44$, $p < 0.01$, slope = -2.6 ms/yr). The group difference between slopes was not significant ($p = 0.43$).

Fig. 3.

FA and age: The TD group is represented by squares and solid line, and the ASD group by circles and dotted line. FA increased with age in TD ($r = 0.50$, $p < 0.01$, slope = 0.009/yr) but not in ASD ($r = 0.11$, $p = 0.44$, slope = 0.002/yr). The group difference between slopes was significant ($p = 0.03$).

Fig. 4.

M50 latency and FA: The TD group is represented by squares and solid line, and the ASD group by circles and dotted line. M50 latency decreased with increasing FA in TD ($r = 0.42$, $p < 0.01$, slope = -127.13) but not in ASD ($r = 0.028$, $p = 0.85$, slope = 8.37). The group difference between these slopes was significant ($p = 0.03$).

Table 1

Age corrected marginal means.

	TD	ASD
Left M50	70.00 ± 15.00 ms	74.43 ± 15.24 ms
Right M50	66.00 ± 14.58 ms	71.33 ± 14.92 ms
Mean M50 *	67.67 ± 14.94 ms	73.49 ± 14.27 ms
Left FA	0.37 ± 0.054	0.37 ± 0.060
Right FA	0.36 ± 0.054	0.35 ± 0.055
Mean FA	0.37 ± 0.047	0.36 ± 0.047

M50 and FA marginal mean values. While individual hemisphere M50 latency value differences between groups did not reach statistical significance, collapsing across hemispheres revealed a statistically significant ($p < 0.05$) delay in M50 latency in ASD compared to that in TD. There were no between group differences in marginal mean FA, for either hemisphere, or for values collapsed across hemispheres.

* Difference between groups $p < 0.05$.

Table 2

Regressions with age.

	TD	ASD
Left M50 latency	$p < 0.05$, slope = -2.2 ms/yr	$p < 0.05$, slope = -2.9 ms/yr
Right M50 latency	$p < 0.05$, slope = -2.8 ms/yr	$p = 0.11$, slope = -1.6 ms/yr
Mean M50 latency	$p < 0.01$, slope = -2.4 ms/yr	$p < 0.01$, slope = -2.6 ms/yr
Left FA	$p < 0.05$, slope = 0.007 /yr	$p = 0.55$, slope = 0.002 /yr
Right FA *	$p < 0.05$, slope = 0.011 /yr	$p = 0.54$, slope = 0.002 /yr
Mean FA *	$p < 0.01$, slope = 0.009 /yr	$p = 0.44$, slope = 0.002 /yr

M50 latency and age: M50 latency decreased with age in TD in the left hemisphere ($r = 0.34$, $p < 0.05$, slope = -2.2 ms/yr) and right hemisphere ($r = 0.53$, $p < 0.05$, slope = -2.8 ms/yr). There was no significant within-group difference between hemispheres ($p = 0.63$). M50 latency decreased with age in ASD in the left hemisphere ($r = 0.45$, $p < 0.05$, slope = -2.9 ms/yr) and the right hemisphere ($r = 0.25$, $p = 0.11$, slope = -1.6 ms/yr). The group difference between slopes was not significant for either hemisphere ($p > 0.36$). Collapsed across hemispheres there was a significant age-dependent shortening of M50 latency in both groups, that did not differ significantly in slope, although a significant difference in intercept reveals persistent M50 latency delay in ASD compared to that in TD. FA and age: FA increased with age in TD in the left hemisphere ($r = 0.33$, $p < 0.05$, slope = 0.007 /yr) and right hemisphere ($r = 0.50$, $p < 0.05$, slope = 0.011 /yr). FA did not change with age in ASD in the left hemisphere ($r = 0.08$, $p = 0.55$, slope = 0.002 /yr) or right hemisphere ($r = 0.09$, $p = 0.54$, slope = 0.002 /yr). The group difference between slopes was not significant for the left ($p = 0.19$) but was significant for the right hemisphere ($p < 0.05$). Collapsing across hemisphere revealed significant group differences in the slope (TD = 0.002 units/yr; ASD = 0.009 units/yr, $p < 0.05$).

* Difference between groups $p < 0.05$.

Table 3

Relationship between FA and M50 latency.

	TD	ASD
Left *	$p < 0.05$, slope = -102.16	$p = 0.24$, slope = 44.22
Right	$p < 0.05$, slope = -87.19	$p = 0.39$, slope = -40.46
Mean *	$p < 0.01$, slope = -127.13	$p = 0.85$, slope = 8.37

M50 latency and FA: M50 latency decreased with increasing FA in TD in the left ($r = 0$, $p < 0.05$, slope = -102.16) and right hemisphere ($r = 0$, $p < 0.05$, slope = -87.19). M50 latency did not change with FA in ASD in the left ($r = 0$, $p = 0.24$, slope = 44.22) or the right hemisphere ($r = 0$, $p = 0.39$, slope = -40.46). The group difference between slopes was significant in the left ($p < 0.05$) but not in the right hemisphere ($p = 0.44$).

* Difference between groups $p < 0.05$.

Table 4

Component diffusion metrics: marginal means.

Age corrected marginal means	TD	ASD
Mean MD	$8.10 \pm 0.44 \times 10^{-4} \text{ mm}^2/\text{s}$	8.27 ± 0.47
Mean AD *	11.40 ± 0.88	11.79 ± 0.91
Mean RD	6.50 ± 0.47	6.49 ± 0.47

Whereas no group differences in mean diffusivity (MD) or radial diffusivity (RD) were observed, there was elevated axial diffusivity (AD) in the ASD group ($p < 0.05$).

* Difference between groups $p < 0.05$.

Table 5

Component diffusion metrics: regression with age.

Regressions versus age	TD	ASD
Mean MD	$p < 0.05$, slope = -0.067	$p < 0.01$, slope = -0.064
Mean AD	$p = 0.89$, slope = 0.008	$p = 0.18$, slope = -0.066
Mean RD	$p < 0.01$, slope = -0.090	$p < 0.05$, slope = -0.055

Mean diffusivity decreased with age in both groups, driven in part by a decrease in radial diffusivity. Interestingly, although the RD slope appears less in ASD versus TD, there is also a decrease (non-significant) in AD in the ASD group. The combination of these effects results in a significant decrease in MD.

Table 6

Component diffusion metrics: regression with M50.

Regressions versus M50	TD	ASD
Mean MD	$p < 0.05$, slope = 0.014	$p = 0.21$, slope = 0.005
Mean AD	$p = 0.48$, slope = 0.007	$p = 0.92$, slope = 0.001
Mean RD	$p < 0.01$, slope = 0.017	$p = 0.30$, slope = 0.005

Mean diffusivity and radial diffusivity (but not axial diffusivity) are both significantly associated with M50 latency in the TD group, paralleling age-related maturational changes. No such associations are seen in the ASD group (analogous to the reported lack of association between FA and M50 latency in ASD).