NeuroImage: Clinical 19 (2018) 840–847

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Diffusion-weighted imaging evidence of altered white matter development from late childhood to early adulthood in Autism Spectrum Disorder

Fikret Işık Karahanoğlu[a,b,*,1], Bengi Baran[a,b,1], Quynh Trang Huong Nguyen[a,b], Djalel-Eddine Meskaldji[c], Anastasia Yendiki[b,d], Mark Vangel[e], Susan L. Santangelo[a,f,g], Dara S. Manoach[a,b]

[a] Department of Psychiatry, Massachusetts General Hospital, Harvard Medical School, Boston, MA, United States
[b] Athinoula A. Martinos Center for Biomedical Imaging, Charlestown, MA, United States
[c] Institute of Bioengineering, Ecole Polytechnique Fédérale de Lausanne (EPFL), Lausanne, Switzerland
[d] Department of Radiology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, United States
[e] Department of Biostatistics, Massachusetts General Hospital, Harvard Medical School, Boston, MA, United States
[f] Maine Medical Center Research Institute, Scarborough, ME, United States
[g] Tufts University School of Medicine, Department of Psychiatry, Boston, MA, United States

ARTICLE INFO

Keywords:
Autism Spectrum Disorder
Development
White matter
Diffusion-weighted imaging
Fractional anisotropy

ABSTRACT

Autism Spectrum Disorder (ASD) is thought to reflect disrupted development of brain connectivity characterized by white matter abnormalities and dyscoordination of activity across brain regions that give rise to core features. But there is little consensus about the nature, timing and location of white matter abnormalities as quantified with diffusion-weighted MRI. Inconsistent findings likely reflect small sample sizes, motion confounds and sample heterogeneity, particularly different age ranges across studies. We examined the microstructural integrity of major white matter tracts in relation to age in 38 high functioning ASD and 35 typically developing (TD) participants, aged 8–25, whose diffusion-weighted scans met strict data-quality criteria and survived group matching for motion. While there were no overall group differences in diffusion measures, the groups showed different relations with age. Only the TD group showed the expected positive correlations of fractional anisotropy with age. In parallel, axial diffusivity was unrelated to age in TD, but showed inverse correlations with age in ASD. Younger participants with ASD tended to have higher fractional anisotropy and axial diffusivity than their TD peers, while the opposite was true for older participants. Most of the affected tracts – cingulum bundle, inferior and superior longitudinal fasciculi – are association bundles related to cognitive, social and emotional functions that are abnormal in ASD. The manifestations of abnormal white matter development in ASD as measured by diffusion-weighted MRI depend on age and this may contribute to inconsistent findings across studies. We conclude that ASD is characterized by altered white matter development from childhood to early adulthood that may underlie abnormal brain function and contribute to core features.

1. Introduction

Autism Spectrum Disorder (ASD) manifests as early as infancy and is characterized by impaired communication, social deficits and restricted, repetitive behaviors. Converging lines of evidence support the view that ASD reflects disruptions in the development of brain connectivity in which white matter abnormalities and reduced coordination of activity across brain regions give rise to core features (Agam et al., 2010; Geschwind and Levitt, 2007; Just et al., 2007, 2004; Kenet et al., 2012; Khan et al., 2013; Kitzbichler et al., 2015; Minshew and Williams, 2007). The developmental course and nature of these disruptions are not well-understood and could span from gestation, during which pathogenic events may interfere with the establishment of connectivity, through childhood and adulthood. The present study investigated whether the trajectory of white matter development, from late childhood through early adulthood, is altered in high functioning individuals with ASD compared with typically developing (TD) peers. This age range is characterized by accelerated synaptic proliferation and pruning and the myelination of white matter tracts, which continues into the twenties and beyond, and supports the development of

* Corresponding author at: Massachusetts General Hospital, Charlestown Navy Yard, 149 13th Street, Charlestown, MA 02129, United States.
E-mail address: fkarahanoglu@mgh.harvard.edu (F.I. Karahanoğlu).
[1] Equal contribution.

https://doi.org/10.1016/j.nicl.2018.06.002
Received 11 December 2017; Received in revised form 18 May 2018; Accepted 3 June 2018
Available online 07 June 2018

highly evolved cognitive and emotional capacities (Benes et al., 1994; Huttenlocher, 1979; Petanjek et al., 2011).

We used diffusion-weighted MRI (DW-MRI) to measure white matter microstructural integrity. DW-MRI measures the amount, rate and direction of water diffusion, which reflects the structural organization of axons. Despite the many DW-MRI studies of ASD, there is little consensus about the presence, location, nature and timing of white matter abnormalities (Rane et al., 2015; Travers et al., 2012). While most DW-MRI studies report decreased fractional anisotropy (orientation specificity of diffusion) (Ikuta et al., 2014; Jou et al., 2011; Keller et al., 2007; Lee et al., 2007; Shukla et al., 2011b; Walker et al., 2012) and increased mean diffusivity (speed of diffusion) either globally or in multiple fiber tracts in ASD compared with TD (Barnea-Goraly et al., 2005; Fletcher et al., 2010; Groen et al., 2011; Shukla et al., 2011b), others report increased fractional anisotropy (Ben Bashat et al., 2007; Billeci et al., 2012; Bode et al., 2011; Roine et al., 2015; Weinstein et al., 2011) or no group differences (Hong et al., 2011; Joseph et al., 2014). Artifacts caused by head motion may contribute to these inconsistencies. During MRI studies, ASD participants tend to move more than their TD peers and head motion can artifactually give rise to findings of reduced fractional anisotropy (Yendiki et al., 2014). For example, Koldewyn et al. (2014) reported reduced fractional anisotropy in multiple white matter tracts in ASD compared with TD, but only one tract difference remained significant after matching groups on motion parameters. This suggests that some prior DW-MRI findings in ASD are confounded by motion artifact and future studies must overcome this problem to be valid. Several studies of ASD have addressed potential motion confounds using techniques that include sedation or rewards for remaining still during scanning, the exclusion of scans corrupted by motion (e.g., “scrubbing”) and statistical controls such as using motion as a regressor (Jou et al., 2011; Koolschijn et al., 2017; Nordahl et al., 2016; Ouyang et al., 2016; Peeva et al., 2013; Shukla et al., 2010; Solso et al., 2016; Walker et al., 2012). In the present study, we minimized the potentially confounding effects of head motion by using a pre-scan training regimen to minimize subject movement and rigorous data quality criteria to both exclude scans corrupted by motion and to match groups on motion parameters.

Another potential culprit in inconsistent findings in DW-MRI studies is the differing age ranges of the samples. During typical development, white matter maturation is most dramatic during the first few years of life, but myelination continues throughout adulthood (Benes et al., 1994). In parallel, fractional anisotropy increases from childhood through adulthood (Barnea-Goraly et al., 2005; Dennis and Thompson, 2013; Hagmann et al., 2010; Kochunov et al., 2012; Lebel et al., 2008) and the rate of increase varies across tracts (Lebel et al., 2008). While higher fractional anisotropy tends to reflect more mature, strongly myelinated tracts and is regarded as a developmental biomarker (Bonekamp et al., 2007; Dennis and Thompson, 2013), its significance in ASD may depend on age. Findings of increased fractional anisotropy in young children with ASD have been hypothesized to reflect excess neurons and axons (Solso et al., 2016) consistent with postmortem studies finding excessive neurons in children with ASD (Courchesne et al., 2011), while reduced fractional anisotropy in older children and adults may reflect decreased myelination, reduced directional coherence of axons and/or fewer or thinner axons (Ikuta et al., 2014; Keller et al., 2007; Shukla et al., 2010, 2011b). Although not tested in longitudinal studies, findings of increased fractional anisotropy in young children with ASD and decreased fractional anisotropy in older children and adults support the hypothesis that ASD is characterized by an early excess of axons, ‘hyperconnectivity’, and a later consequent failure to form and maintain effective long range axonal connections (Courchesne et al., 2007; Courchesne and Pierce, 2005).

In the present cross-sectional study, we examined the correlations of age with diffusion measures in ASD and TD participants from 8 to 25 years. We expected that age would correlate positively with fractional anisotropy in TD participants, that the slope of this relation would be shallower in ASD (Ikuta et al., 2014; Shukla et al., 2011b; Solso et al., 2016) and that reduced fractional anisotropy in ASD would primarily be seen in older participants. While fractional anisotropy was our primary measure of white matter microstructural integrity, we also analyzed mean diffusivity, axial diffusivity (diffusivity in the main diffusion direction) and radial diffusivity (mean of diffusivity perpendicular to the main diffusion direction), which provide complementary information.

Table 1
Participant characteristics.

All participants	TD (n = 36)	ASD (n = 51)	t(85)	p
Age	14.4 ± 4.6	13.9 ± 3.8	0.65	.52
Sex (F/M)	6/30	7/44	$\chi^2 = 0.17$	.76
Education (years)	7.9 ± 4.6	7.7 ± 4.1	0.2	.81
Estimated FSIQ	116 ± 16	114 ± 15	0.8	.42
Handedness[a]	57 ± 55	42 ± 52	1.3	.20
Mean parental education	16.2 ± 2.8	15.9 ± 2.2	0.3	.74
Mean parental SES[b]	1.8 ± 1.1	1.8 ± 0.8	0.2	.86
Translation (mm)	0.58 ± 0.22	0.68 ± 0.31	−1.70	.09
Rotation (degrees)	0.29 ± 0.12	0.34 ± 0.23	−2.16	.03*
Benner score	1.0 ± 0.06	1.0 ± 0.05	−0.01	.92
% Gradients removed	3.5 ± 8.2	7.6 ± 10.9	−1.89	.06

Motion matched sample	TD (n = 35)	ASD (n = 38)	t(71)	p
Age	14.6 ± 4.5	14.3 ± 4.0	0.3	.76
Sex (F/M)	6/29	7/31	$\chi^2 = 0.02$	.89
Education (years)	8.1 ± 4.6	8.2 ± 4.1	0.04	.97
Estimated FSIQ	116 ± 17	116 ± 15	0.2	.87
Handedness[a]	57 ± 55	45 ± 50	1.0	.32
Mean parental education	16.1 ± 2.9	16.2 ± 2.3	−0.2	.86
Mean parental SES[b]	1.8 ± 1.0	1.7 ± 0.8	0.8	.45
Translation (mm)	0.56 ± 0.14	0.58 ± 0.14	−0.72	.48
Rotation (degrees)	0.29 ± 0.12	0.29 ± 0.06	−1.58	.12
Benner score	1.0 ± 0.02	1.0 ± 0	1.04	.30
% Gradients removed	2.5 ± 5.3	3.8 ± 6.1	−0.96	.34

FSIQ: Full Scale Intelligence Quotient based on the Wechsler Abbreviated Scale of Intelligence (49).

* Significant at $p \leq .05$.

[a] Based on the modified Edinburgh Handedness Inventory (76, 77) Laterality scores of −100 and +100 denote exclusive use of left or right hand, respectively.

[b] Socio-Economic Status based on the Hollingshead Index (78). A lower score denotes higher status.

2. Methods

2.1. Participants

51 individuals with ASD without intellectual disability and 36 TD controls, aged 8–25, participated. After data quality exclusions and matching the groups for motion (see description below) 38 ASD and 35 TD participants were retained for analysis. ASD and TD groups were matched for age, sex, education, estimated full scale IQ, handedness, mean parental education and parental socioeconomic status. (Table 1 provides participant characteristics and data quality measures for both the entire sample and the motion-matched sample).

ASD participants were recruited from the Autism Consortium database (http://www.autismconsortium.org). Diagnoses were made by experienced clinicians on the basis of current presentation and developmental history using the Autism Diagnostic Interview-Revised (ADI-R; Rutter et al., 2003) and the Autism Diagnostic Observation Schedule (ADOS; Lord et al., 1999). Individuals with known genetic syndromes (e.g., tuberous sclerosis, fragile X, RETT syndrome, neurofibromatosis) were not enrolled. TD participants were recruited from the community