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ORIGINAL ARTICLE

Differential effects on white-matter systems in high-functioning autism and Asperger's syndrome

G. M. McAlonan[1,2]*, C. Cheung[2], V. Cheung[2], N. Wong[2], J. Suckling[3] and S. E. Chua[1,2]

[1] *State Key Laboratory for Brain and Cognitive Sciences, University of Hong Kong, Pokfulam, Hong Kong SAR China*
[2] *Department of Psychiatry, University of Hong Kong, Pokfulam, Hong Kong SAR China*
[3] *Cambridge Brain Mapping Unit, Department of Psychiatry, University of Cambridge, Cambridge, UK*

Background. Whether autism spectrum maps onto a spectrum of brain abnormalities and whether Asperger's syndrome (ASP) is distinct from high-functioning autism (HFA) are debated. White-matter maldevelopment is associated with autism and disconnectivity theories of autism are compelling. However, it is unknown whether children with ASP and HFA have distinct white-matter abnormalities.

Method. Voxel-based morphometry mapped white-matter volumes across the whole brain in 91 children. Thirty-six had autism spectrum disorder. A history of delay in phrase speech defined half with HFA; those without delay formed the ASP group. The rest were typically developing children, balanced for age, IQ, gender, maternal language and ethnicity. White-matter volumes in HFA and ASP were compared and each contrasted with controls.

Results. White-matter volumes around the basal ganglia were higher in the HFA group than ASP and higher in both autism groups than controls. Compared with controls, children with HFA had less frontal and corpus callosal white matter in the left hemisphere; those with ASP had less frontal and corpus callosal white matter in the right hemisphere with more white matter in the left parietal lobe.

Conclusions. HFA involved mainly left hemisphere white-matter systems; ASP affected predominantly right hemisphere white-matter systems. The impact of HFA on basal ganglia white matter was greater than ASP. This implies that aetiological factors and management options for autism spectrum disorders may be distinct. History of language acquisition is a potentially valuable marker to refine our search for causes and treatments in autism spectrum.

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Introduction

People with an autism spectrum disorder (ASD) have difficulties in three core areas, namely social reciprocity, communication and repetitive behaviours or intense preoccupations. Within the spectrum, those affected have a large range of intellectual abilities. People with a normal intelligence quotient (IQ) can be further classified as having Asperger's syndrome (ASP) or high-functioning autism (HFA). Children who have a delay in acquisition of phrase speech have HFA, while those who use phrases before 36 months may have ASP (Gilchrist *et al*. 2001; Howlin, 2003). However, there is considerable debate over whether ASP is distinct from HFA (Rinehart *et al*. 2002*b*; Klin & Volkmar, 2003).

* Address for correspondence: G. M. McAlonan, Ph.D., M.B., B.S., Department of Psychiatry, University of Hong Kong, Pokfulam, Hong Kong SAR China.
(Email: mcalonan@hkucc.hku.hk)

Using a history of phrase speech acquisition as a marker to distinguish HFA and ASP, we recently reported that distinct patterns of grey-matter abnormalities characterized these subgroups. The HFA and ASP groups had similar impairment in the three core symptom domains mentioned above, but compared with controls, children with HFA had greater left-sided frontal lobe grey-matter deficits than children with ASP; children with ASP had less grey matter in the caudate and thalamus (McAlonan *et al*. 2008). This finding suggested that maldevelopment of different components of cortico-striatal loop systems may give rise to features of ASP and HFA.

Evidence that autism may involve disruption at a brain-systems level is compelling. We have shown that distributed grey-matter volume abnormalities are associated with a disruption in volumetric correlations across fronto-limbic-striatal and cerebellar systems (McAlonan *et al*. 2005). Numerous functional imaging studies show that regional brain activity is

desynchronized in autism (Horwitz *et al*. 1988; Just *et al*. 2004, 2007; Koshino *et al*. 2005) and these observations are consistent with convincing evidence for anomalous postnatal white-matter development in autism (Herbert *et al*. 2004; Herbert, 2005, Ben Bashat *et al*. 2007). Following dramatic brain expansion in very young children with autism (Courchesne, 2002, 2004; Courchesne *et al*. 2003), we and others have shown that white-matter volume and diffusion tensor imaging indices are significantly lower in older children and adults with autism compared with typically developing controls (McAlonan *et al*. 2002, 2005; Barnea-Goraly *et al*. 2004; Waiter *et al*. 2005; Keller *et al*. 2007; Sundaram *et al*. 2008; Cheung *et al*. in press) but whether HFA and ASP affect white matter differently has not been examined.

Therefore we planned a voxel-based study of white-matter volume in ASP and HFA. Based on our previous study of grey-matter abnormalities in ASP and HFA (McAlonan *et al*. 2008) we hypothesized that similar discrete patterns of abnormalities in white matter would distinguish in children with ASP from those with HFA. Specifically we predicted left-sided frontal abnormalities would predominantly affect the HFA group.

Method

Participants

Ninety-one, right-handed children aged 6–16 years with an IQ > 70 (estimated using the vocabulary subset of the Wechsler Intelligence Scale for Children) participated in the study. Grey-matter volumetric analysis of data from 88 of these children has already been reported (McAlonan *et al*. 2008). Exclusion criteria were co-morbid psychiatric (e.g. mood disorder or attention deficit hyperactivity disorder) or medical conditions (e.g. epilepsy) requiring intervention, history of head injury, or genetic disorder associated with autism (e.g. tuberous sclerosis or fragile X syndrome). Thirty-six were non-medicated children with an independent clinical diagnosis of ASD. Following the same definition as previous neuroimaging studies (Kwon *et al*. 2004; Lotspeich *et al*. 2004; McAlonan *et al*. 2008), 18 children (three females) with phrase speech before the age of 36 months comprised the ASP group. Eighteen (three females) with a history of delayed phrase speech formed the HFA group. As shown in Table 1 the children did not differ in diagnostic algorithm scores of the Autism Diagnostic Interview, Revised (ADI-R; Western Psychological Services, Los Angeles, CA, USA). Fifty-five typically developing control children (eight females) were recruited from local schools and screened for major psychiatric illness using the Diagnostic Interview Schedule for Children for DSM-IV. They did not differ in mean age or verbal IQ (see Table 1), maternal language or ethnicity from the autism spectrum group. Every child's parent gave informed consent for the protocol approved by the University of Hong Kong Faculty of Medicine Research Ethics Committee, and each child gave their assent.

Table 1. *Group characteristics*

	Contrast	Mean	(S.D.)	Test statistics
ADIA	ASP	19.1	(2.96)	$t = 0.41$
	HFA	18.5	(4.92)	$p = 0.68$
ADIB	ASP	14.9	(4.27)	$t = 1.10$
	HFA	13.5	(3.28)	$p = 0.28$
ADIC	ASP	5.2	(5.17)	$t = 0.15$
	HFA	5.1	(5.06)	$p = 0.88$
Age, months	ASP	134.4 11.2 yr	(30.26)	$t = 0.33$
	HFA	138.6 11.5 yr	(35.43)	$p = 0.74$
Age, months	Control	128.0 10.7 yr	(32.9)	$t = -1.21$
	ASD	136.5 11.4 yr	(32.5)	$p = 0.23$
VIQ	ASP	109.8	(16.2)	$t = 1.34$
	HFA	114.8	(19.1)	$p = 0.19$
VIQ	Control	117.1	(18.1)	$t = 1.23$
	ASD	112.3	(17.7)	$p = 0.22$

S.D., Standard deviation; ADIA, social interaction subscale of the Autism Diagnostic Interview, Revised (ADI-R; Western Psychological Services, Los Angeles, CA, USA); ASP, Asperger's syndrome ($n = 18$); HFA, high-functioning autism ($n = 18$); ADIB, communication subscale of the ADI-R; ADIC, repetitive behaviours subscale of the ADI-R; ASD, autism spectrum disorder, combined group ($n = 36$); VIQ, pro-rated verbal intelligence quotient.

Magnetic resonance imaging and analysis

An interleaved dual-echo fast-spin echo (FSE) sequence [repetition time = 3000 ms, echo times, TE1 = 20 ms (proton density weighted images) and TE2 = 100 ms (T2-weighted images)] was used to collect whole-brain data on a GE Signa 1.5 T system (General Electric, Milwaukee, WI, USA). Images were aligned to the anterior commissure–posterior commissure (AC–PC) line, with contiguous slices 0.859 mm in-plane and 3 mm thick. Each scan was screened by a consultant radiologist to exclude clinically significant abnormalities. Extracerebral tissues were removed (Suckling *et al*. 1999*a*) and brain tissue segmented

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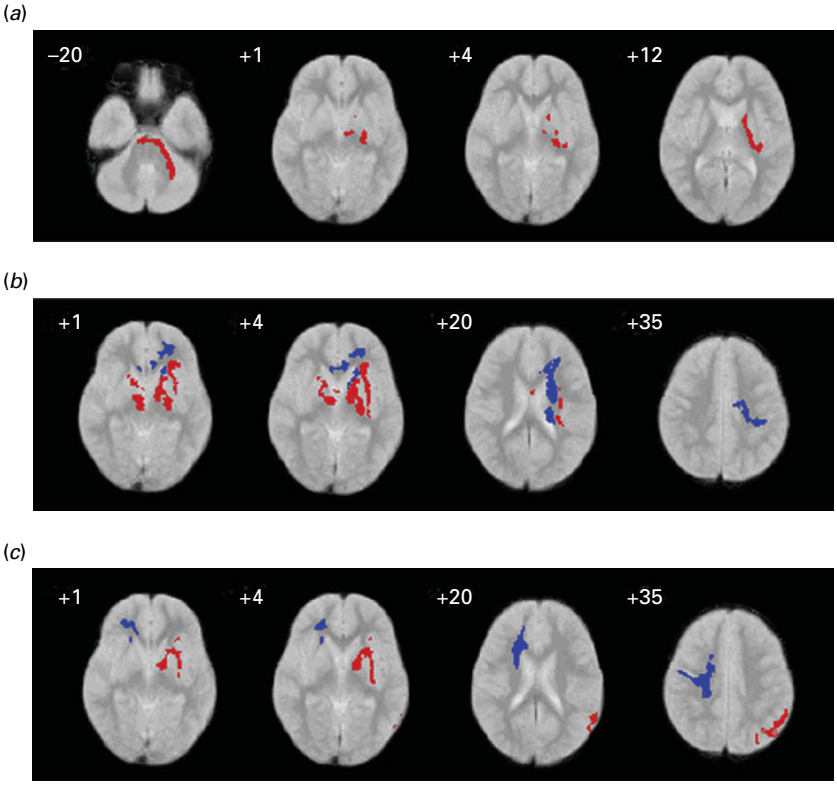

Fig. 1. White-matter volume in children with autism spectrum compared with controls: (*a*) high-functioning autism (HFA) relative to Asperger's syndrome (ASP); (*b*) HFA relative to controls; (*c*) ASP relative to controls. Red indicates relative volume excess; blue indicates relative volume deficit. The right side of the brain is shown on the left side of each panel. The z coordinate for each axial slice in standard space (Talairach & Tournoux, 1988) is given in mm.

into grey and white matter, cerebrospinal fluid and a fourth class including dura, vessels and other extraneous tissues (Suckling *et al*. 1999*b*). The current protocol yielded superior grey/white differentiation compared with high-resolution T1 scans, as demonstrated previously (see fig. 1*a* in Chua *et al*. 2007). The white-matter images were mapped into the standard space of Talairach & Tornoux (1988) by minimizing the sum-of-square intensity difference of each proton density image to a group-specific template image (McAlonan *et al*. 2005) and smoothed with a 4.4 mm kernel. The main effect of diagnostic group was estimated at each voxel by regression of a general linear model using BAMM software (Brain Analysis Morphological Mapping version 2.5; University of Cambridge, Cambridge, UK; http://www-bmu.psychiatry.cam.ac.uk/BAMM/index.html) on a SPARC workstation (Sun Microsystems Europe Inc., Camberley, Surrey, UK) as previously described (McAlonan *et al*. 2002, 2005, 2007; Chua *et al*. 2007). The between-group structural differences (spatial extent statistics) at each intracerebral voxel were assessed using non-parametric methods. This involved randomly reassigning group membership to generate 10 permutated white-matter maps, thereby sampling the null hypothesis that group differences occur by chance (Bullmore *et al*. 1999). The statistical thresholds were corrected for multiple comparisons by controlling the 'family-wise error rate' and results reported where the number of false-positive clusters (FPC) expected under the null-hypothesis <1.

There were three contrasts: (1) HFA and ASP; (2) HFA and controls; (3) ASP and controls.

Regional white-matter volumes in any of the autism spectrum groups were defined as greater or less, relative to the control group. White-matter volumes in HFA were described relative to ASP. The effect size of each contrast was examined using partial η^2 measures in SPSS (version 16.0; SPSS Inc., Chicago, IL, USA).

Global white-matter volumes were not different across groups: control 463.8 (S.D. = 19.8) ml; ASP 459.0 (S.D. = 28.6) ml; HFA 465.2 (S.D. = 19.7) ml.

Regional white-matter volumes

HFA compared with ASP

Compared with ASP, children with HFA had significantly greater white-matter volume around the left basal ganglia (internal and external capsules), thalamus and cerebellum (see Fig. 1 and Table 2).

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Table 2. *White-matter differences in autism spectrum*

	Centre of mass[a]	Voxel number	Mean volume, ml (S.D.) ASP	Mean volume, ml (S.D.) HFA	Partial η^2
HFA–ASP contrast					
Excess in HFA					
Internal capsule	−13.8, −16.7, −5.6	652	2.37 (0.30)	3.06 (0.43)	0.48
HFA–control contrast					
Deficit in HFA					
Left frontal lobe (FOF, genu left corpus callosum, dorsal basal ganglia)	−18.9, 11.1, 16.4	1102	5.88 (0.35)	5.06 (0.54)	0.44
Excess in HFA					
Left basal ganglia (internal capsule, anterior and posterior limbs and external capsule)	−23.2, 6.0, 4.8	1060	3.25 (0.69)	4.30 (0.52)	0.34
Right basal ganglia (internal capsule)	7.5, −3.1, 1.1	284	0.53 (0.13)	0.69 (0.16)	0.19
ASP–control contrast					
Deficit in ASP					
Right frontal lobe (FOF, genu right corpus callosum)	20.6, 16.4, 20.3	1108	7.00 (0.28)	6.24 (0.59)	0.43
Excess in ASP					
Left basal ganglia (internal capsule)	−23.2, 6.0, 2.4	495	1.04 (0.21)	1.37 (0.19)	0.34
Parietal lobe	−44.9, −53.5, 31.5	388	0.54 (0.08)	0.80 (0.15)	0.55

S.D., Standard deviation; ASP, Asperger's syndrome; HFA, high-functioning autism; FOF, fronto-orbital fasciculus.

[a] A sample Talaraich coordinate (x, y, z) is given for the approximate centre of each cluster. The three-dimensional clusters are not confined to these areas, nor are they all encompassing.

HFA compared with control

Children with HFA also had significantly more white matter than controls in bilateral subcortical circuits including the internal and external capsule. However, they had significantly less white matter in left frontal pathways corresponding to the orbitofrontal fasiculus and extending to the genu of the corpus callosum and basal ganglia. The lower the volume of white matter in the left frontal lobe, the older the age in months that the child with HFA acquired phrase speech, although this relationship did not reach significance (Spearman's $\rho = -0.34$, $p = 0.09$) (see Fig. 1 and Table 2).

ASP compared with control

Children with ASP had significantly more white matter in subcortical circuits and the parietal lobe of the left hemisphere when compared with controls. However, they had significantly less white matter in the right frontal lobe than controls especially around the orbitofrontal fasiculus and right genu of the corpus callosum (see Fig. 1 and Table 2).

Discussion

Our main finding was that intellectually able children with ASDs subgrouped on the basis of their history of language acquisition had distinct patterns of white-matter abnormalities. Children with ASP had predominantly right-sided white-matter deficits compared with controls. Children with HFA had greater white-matter deficits in the left hemisphere. Both groups had larger white-matter volumes in deep white-matter regions around the basal ganglia regions compared with controls. These white-matter volumes were significantly greater in HFA than ASP. These findings extend our previous study of grey matter in ASP and HFA (McAlonan *et al*. 2008) and carry the important implication that the autism spectrum maps onto a spectrum of brain abnormalities.

Total white-matter tissue volumes were not significantly different in the autism spectrum groups or controls. This may be initially surprising given that brain volumes are dramatically larger in autism in early life (Carper *et al*. 2002; Courchesne, 2002, 2004; Hazlett *et al*. 2005). Larger cerebral white-matter volumes in children with autism persist through age 7–11 years (Herbert *et al*. 2003), especially in radiate white matter (Herbert *et al*. 2004). With increasing age, these volume increases abate (Courchesne, 2004; Herbert, 2005). The participants in our study were aged up to 16 years and this older age group may explain why we detected only regional differences, not global volume differences in those with autism.

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Our findings implicate pathways corresponding to deeper white-matter tracts such as the fronto-occipital fasciculus and internal capsule in autism spectrum. These systems have recently been shown to continue to mature well into late adolescence and young adulthood (Lebel *et al*. 2008), and this slower maturation may make such tracts vulnerable to damage for a longer period. However, the distinctive involvement of the left and right hemisphere in HFA and ASP, respectively, indicates that the developmental pressures on white matter in subgroups of children in autism spectrum may not fully coincide.

White-matter deficits in the corpus callosum have previously been reported in autism. For example, young children with ASD have disproportionately smaller corpus callosum volumes than typically developing controls (Boger-Megiddo *et al*. 2006), although in older groups the deficits may be more posterior (Egaas *et al*. 1995; Waiter *et al*. 2005). Still others have reported that the size of the genu of the corpus callosum is highly correlated with the extent of frontoparietal asynchrony during executive function tasks (Just *et al*. 2007). In general, the literature is not completely clear (for a review, see Brambilla *et al*. 2003). The current study indicates that the corpus callosum findings depend upon the nature of the ASD samples examined, as we found that lower corpus callosum volumes were predominantly right-sided in HFA and left-sided in ASP.

In frontal regions also, children with ASP had mainly right-sided deficits; those with HFA had left-sided deficits. We found the same pattern when we examined grey-matter differences in many of these children in an earlier study; the HFA group had left-sided frontal grey-matter deficits relative to controls (McAlonan *et al*. 2008). In that study the extent of grey matter decrease in the HFA group was correlated with their delay in language acquisition. In the current study the correlation between age (in months) of phrase language acquisition in the HFA group and white-matter volume in the left frontal lobe was less striking, but consistent. This backs the possibility that brain structure in autism at least partly reflects the developmental language difference distinguishing subgroups.

Evidence from other sources echoes this relationship between language ability and brain lateralization in autism spectrum. Right-sided asymmetries in children with developmental language delay or autism have been recorded (Herbert *et al*. 2002, 2005) and children with autism who have severe language impairment have a significant decrease in serotonin synthesis in the left hemisphere relative to the right (Chandana *et al*. 2005). Similarly, in language-impaired children with autism the normal asymmetry in Broca's area (left inferior frontal lobe) is reversed – i.e. right frontal lobe volumes are greater than left (De Fosse *et al*. 2004). Additional support for distinct patterns of lateralization comes from a careful dissection of executive function performance in HFA and ASP, showing left-sided abnormalities in HFA (Rinehart *et al*. 2002*a*). In contrast, the social interaction and motor symptoms of ASP have been compared with 'non-verbal language disorder', which is thought to arise from right-hemisphere dysfunction (Gunter *et al*. 2002). In 1999, Ellis & Gunter hypothesized that this apparent right-hemispheric dysfunction seen in ASP could be a disorder of white-matter development (Ellis & Gunter, 1999). The results from the present study appear to agree with their prediction, but because we did not examine behavioural features outside the diagnostic triad, this interpretation of our results is tentative.

In our study of grey-matter differences in these children, we observed that both ASP and HFA groups had significant abnormalities in white matter associated with the basal ganglia and thalamus (McAlonan *et al*. 2008). Basal ganglia pathways carry afferent information from the entire cerebral cortex for integration and output to motor and thalamic targets (Utter & Basso, 2008). Of particular relevance to autism are limbic circuits through the basal ganglia and thalamus which interconnect social brain areas strongly associated with autism, including the amygdala and fusiform gyrus (Baron-Cohen *et al*. 2000; Schultz, 2005), superior temporal sulcus (Zilbovicius *et al*. 2006), together with the medial prefrontal lobe (Happe *et al*. 1996; Castelli *et al*. 2002). The concentration of white-matter abnormalities noted fits with a functional disturbance of basal ganglia–thalamo–cortical loop systems which coordinate social behaviours in autism. Moreover, since the basal ganglia are a major motor output structure, the incidence of neuromotor symptoms in ASD (Vilensky *et al*. 1981; Rinehart *et al*. 2006*b*; Freitag *et al*. 2007, Loh *et al*. 2007) also fits with theories of pathology in these circuits (Damasio & Maurer, 1978; Vilensky *et al*. 1981).

The extent of basal ganglia abnormalities was greatest in the HFA group. Children with HFA also had significantly more white matter than ASP in the left cerebellum. Given the key role of the basal ganglia as a limbic–motor interface (Alexander *et al*. 1990; Utter & Basso, 2008), and its connections with the cerebellum, we speculate that these anatomical differences may have something to do with the distinct motor output phenomena ascribed to each group. Clumsiness may be a feature of ASP, while children with autism may have postural abnormalities (Rinehart *et al*. 2006*a*, *c*). In a fractionation of movement planning and execution, Rinehart's group

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reported a quantitatively greater impairment in motor preparation in children with HFA compared with those with ASP. The authors suggested that the particular motor phenotypes in HFA and ASP could represent a downstream effect of this 'quantitative dissociation' in motor planning (Rinehart *et al*. 2006*a*).

In our study, children with ASP had greater white-matter volumes than controls around the inferior parietal lobule in the left hemisphere. Recently Nordahl *et al*. completed an elegant study of cortical folding abnormalities in autism spectrum (Nordahl *et al*. 2007). They reported that children with ASP had the greatest sulcal depth differences from typically developing controls in the left intraparietal sulcus of children (Nordahl *et al*. 2008). This convergence of morphometric abnormalities to the left parietal lobe in two distinct structural studies is striking. Moreover, in a functional magnetic resonance imaging study of working memory, Koshino *et al*. (2005) noted that individuals with autism showed greater activation in the left extrastriate cortex, near the cluster of higher white-matter volume observed here in the ASP group (Koshino *et al*. 2005). The authors interpreted this spurious posterior activation in ASD as due to a greater reliance on lower-order visual analysis (Koshino *et al*. 2005). Although the ASD sample in their study was described as high functioning, the language history of the participants was not explicitly determined. It is feasible that this complementary collection of data points to some compensatory reorganization of white matter in the left parietal lobe in ASP, but this idea needs much further investigation.

An important limitation of our study was that we did not directly examine how white-matter abnormalities relate to the behavioural features of individuals with HFA and ASP outside the diagnostic triad (e.g. motor symptoms, executive functioning, etc). However, a key feature of our study was that HFA and ASP groups had no difference in their diagnostic scores on the ADI-R. Thus, the differences in white matter that we observed, taking history of language acquisition as the only discriminative marker, are quite dramatic. We would emphasize that language was solely used as a discriminatory marker to define subgroups in our study. We do not believe that the history of language acquisition can fully explain the results. It is much more likely that the white-matter systems involved in HFA and ASP are associated with a constellation of features, including executive function, motor skills and language which potentially separate HFA from ASP.

Another limitation of our study was that subdividing the ASD sample lowered numbers and hence statistical power. However, we observed sizable effect sizes in each subgroup contrast, and take this to indicate that more homogeneous subject groupings may be key to a better understanding of the autism spectrum. In focusing on HFA and ASP we excluded the majority of children with autism who have learning disability. Therefore we cannot extrapolate our findings more generally. It will be important to consider to what extent the brain determinants of autistic children with low IQ are distinct from these intellectually able samples. In this investigation we included children and adolescents only. Of note, we conducted a study of adults with ASP some years ago (McAlonan *et al*. 2002). In that study we found white-matter excesses in the left basal ganglia similar to those reported here. This suggests that some of the abnormalities present in childhood are persistent and could therefore contribute to the pervasive nature of ASD. The plan is to follow-up the present cohort to determine whether there are longitudinal differences in ageing in ASP and HFA.

In conclusion, we used the history of language acquisition as a marker for HFA and ASP. We found that ASDs have heterogeneous effects on white-matter systems. This has important implications for the causal mechanisms underlying HFA and ASP. The present study, along with our previous assessment of grey-matter abnormalities in ASP and HFA, indicates that the autism spectrum cannot be described along a single dimension of severity. We believe our work should encourage further research into the heterogeneous nature of autism, focusing as much on individual differences as shared pathologies.

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Declaration of Interest

None.

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