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

G. M. McAlonan, C. Cheung, V. Cheung, N. Wong, J. Suckling and S. E. Chua

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 disconnection 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. 2002b; Klin & Volkmar, 2003).

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 children 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.

**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. 1999a) and brain tissue segmented

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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.
into grey and white matter, cerebrospinal fluid and a fourth class including dura, vessels and other extraneous tissues (Suckling et al. 1999b). The current protocol yielded superior grey/white differentiation compared with high-resolution T1 scans, as demonstrated previously (see fig. 1a in Chua et al. 2007). The white-matter images were mapped into the standard space of Talairach & Tournoux (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 permuted 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 \( \eta^2 \) 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).
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 fasciculus 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–control contrast

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<td>Voxel number</td>
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<td>Mean volume, ml (S.D.)</td>
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### ASP–control contrast

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<th>Excess in ASP</th>
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<td>Left basal ganglia (internal capsule)</td>
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<tr>
<td>Centre of mass</td>
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<tr>
<td>Voxel number</td>
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<tr>
<td>Mean volume, ml (S.D.)</td>
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<td>Partial $\eta^2$</td>
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| Parietal lobe |
| Centre of mass | 44.9, –53.5, 31.5 |
| Voxel number  | 388 |
| Mean volume, ml (S.D.) | 0.54 (0.08) | 0.80 (0.15) |
| Partial $\eta^2$ | 0.55 |

s.d., Standard deviation; ASP, Asperger’s syndrome; HFA, high-functioning autism; FOF, fronto-orbital fasciculus.

* 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.

### 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.
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. 2002a). 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-thalamocortical loop systems which coordinate social behaviours in autism. Moreover, since the basal ganglia are major motor output structure, the incidence of neuromotor symptoms in ASD (Vilensky et al. 1981; Rinehart et al. 2006b; 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. 2006a, c). In a fractionation of movement planning and execution, Rinehart’s group...
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. 2006a).

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 re-organization 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.

References


