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# Frontal anatomy and reaction time in Autism

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**Abstract**

Widespread frontal lobe abnormalities, encompassing anatomy and function, are known to be implicated in Autistic Spectrum Disorders (ASD). The correlation between neurobiology and behaviour, however, is poorly understood in ASD. The aim of this study was to investigate frontal lobe anatomy and cognitive function in individuals with ASD, compared to control subjects. Thus, we assessed whole brain and frontal lobe parenchymal volume, and grey and white matter density differences in ASD, compared to control subjects, using high resolution T1-weighted magnetic resonance imaging (MRI). Furthermore, all subjects underwent a computerized reaction time task (RTT) for cognitive assessment. No differences in total parenchymal brain volume were observed, however, autistic individuals showed significantly smaller frontal lobe parenchymal volume (FLPV) and decreased white matter density, compared to control subjects. Error rates did not differ significantly between groups during the RTT, but ASD individuals responded significantly slower to target stimuli. Furthermore, reduced FLPV correlated positively with increased reaction time in individual with ASD. Decreased FLPV could be an indicator for abnormal brain development resulting in reduced processing speed in ASD.


*Keywords:* Autistic Spectrum Disorder; Frontal lobe volume; Reaction time; Whole brain parenchymal volume; White matter integrity

Autistic Spectrum Disorder (ASD, including High-Functioning Autism (HFA) and Asperger's Syndrome (AS)) is an important and costly neurodevelopmental condition [9], characterised by obsessional stereotyped behaviours, and pervasive abnormalities, affecting social emotions [18,47]. ASD is a strongly genetic neurodevelopmental condition [2,4,7], possibly originating from abnormal brain maturation, metabolism and white matter connectivity, primarily affecting the frontal lobes and related brain areas [7,8,12,31]. Neurodevelopmental abnormalities are thought to be the underlying cause of cognitive-behavioural characteristics of the disorder [12,15] and frontal lobe anatomical abnormalities have increasingly been implicated in ASD [30,39,43,48]. Recently, reduced cognitive processing speed (slower reaction time (RT) to target stimuli) in ASD is hypothesized to be caused by disturbed brain synchronization, particularity affecting the frontal lobes by destroying their coherence of brain rhythm [45,46]. The link between frontal lobe brain abnormalities and autistic behaviour is, however, not clear.

Functional magnetic imaging (fMRI) studies in ASD identified frontal lobe activation abnormalities during several cognitive-behavioural investigations, such as (i) socio-emotional tasks (affecting fronto-striatal and cingulate brain regions [6,14,17]); (ii) language processing (inferior frontal and superior temporal cortex [20,22]); (iii) spatial working memory (dorsolateral-prefrontal and anterior cingulate cortex (and parietal regions) [27], and, (iv) executive functions (frontal cortex and insula) [41].

Structural MRI findings in ASD encompass global and regional anatomical abnormalities in frontal, limbic, basal ganglia, parietal and cerebellar brain regions [7,8,11,30,31,37]. Metabolic changes have also been reported for the frontal lobes [33,34] and hippocampal-amygdala regions [35].

There is an increasing understanding of brain function, structure and metabolism in individuals with ASD. However, to date, these separate streams of knowledge have not been combined and cognitive deficits in ASD have not directly been related to brain abnormalities. Cognitive deficits are, however, an indicator for the characteristic behavioural abnormalities of the disorder.

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Previous cognitive studies in ASD reported, amongst others, a generalized impairment in complex processing or "weak central coherence" [16,20,32]. These impairments have been explained by the pervasive nature of cognitive processing in ASD. Specific brain abnormalities responsible for these deficits have not yet been identified. The frontal lobe, however, could be the main player in determining the origin of cognitive (processing speed) deficits in ASD.

We hypothesize that individuals with ASD may suffer from abnormal frontal lobe anatomy, resulting in abnormal cognitive function. However, today there are no studies in ASD, comparing cognitive-behavioural variables, such as RT to brain anatomy. We therefore used a computerized experimental task, measuring RT to target stimuli, and acquired quantitative structural MRI in the same population, to investigate global and regional brain volume, white matter integrity and cognitive function.

We recruited 12 healthy control subjects locally by advertisement. Nine right handed adult male individuals of normal intelligence with ASD were recruited through the Maudsley-Hospital/Institute of Psychiatry. All participants of the study gave written informed consent as approved by the local research ethics committee (Institute of Psychiatry, South London and Maudsley Trust) and were between 20 and 52 years of age at time of inclusion. Subjects did not differ significantly in age or IQ (see Table 1). ASD was diagnosed by a consultant psychiatrist (D.M.), using ICD-10 criteria (World Health Organisation, 1992, 10th-revised version). In addition, where parental informants were available, the Autism Diagnostic Interview (ADI [26]) was carried out (this was possible in six out of nine individuals).

All subjects underwent a structured clinical examination (including eyesight and routine blood tests) to exclude co-morbid medical and psychiatric disorders, and biochemical, haematological or chromosomal abnormalities (including fragile-X-syndrome), possibly affecting brain. None of the participants had a history of major medical illnesses or psychiatric disorders other than ASD. IQ was measured using the Wechsler Adult Intelligence Scale-Revised (WAIS-R, short form [13]). None of the subjects were taking medication.

All participants were scanned at the Neuroimaging Unit of the Institute of Psychiatry (IOP), London, UK, using a 1.5 Tesla GE Signa System (*General-Electric*, Milwaukee, WI, USA).

High resolution structural T1-weighted volumetric images were acquired with full head coverage, 124 contiguous slices (1.5 mm thick, with 0.89 mm × 0.89 mm in-plane resolution), a 256 × 256 × 124 matrix and a repetition time/echo time (TR/TE) of 24/5 ms (flip angle 45″, FOV 24 cm). A (birdcage) head coil was used for radiofrequency transmission and reception. Consistent image quality was ensured by a semi-automated quality control procedure.

RT was measured, using a computerized continuous performance task of the MARS battery [40] (field version), automatically recording response-RT (in milliseconds (ms)) and response-errors to target stimuli. All participants received standardized instructions. Viewing a continuous string of 480 letters (of 1000 ms presentation time each, with a gap of 800 ms), subjects had to respond as quickly and accurately as possible, to two target stimuli, only; while neglecting all other letters. The target stimuli were the letter X and the letter O, but only, when following the letter A. Randomly alternating per subject, one of the target stimuli (X or O (preceded by an A)) would be linked to monetary reward, to enforce RT speed and accuracy. Individuals were asked to always respond to both target stimuli (X and O, preceded by the letter A), equally. The letters X and O were interspersed with at least three, and at the most five randomly selected non-target letters. All subjects viewed the tasks on a computer-monitor in the same, quiet examination room with the lights dimmed. Subject used the right button on a diamond shaped game pad for response. For all subjects, RT to target stimuli (ms), correct answer to target stimuli and incorrect or premature answers were recorded during the entire paradigm.

Neuroimaging data were analysed, using a volumetric tool implemented in SPM2 (http://www.fil.ion.ucl.ac.uk/spm/ext/) [3]. Total parenchymal brain volume was calculated for all

Table 1
Subject characteristics

| Patient | Age at scanning in years | IQ[a] (full) | Verbal | Performance | Autism Diagnostic Interview (ADI)[b,c] | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Diagnosis[d] | Social | Nonverbal communication | Restricted interests and repetitive behaviour[e] | Handedness[f] |
| All patients | | | | | | | | | Right |
| Mean | 38 | 105 | 99 | 108 | AS ($n = 7$) and HFA ($n = 2$) | 16 | 13 | 5 | |
| S.D. | 9 | 14 | 8 | 17 | | 8 | 4 | 7 | |
| All controls | | | | | – | – | – | – | Right |
| Mean | 39 | 106 | 104 | 108 | – | – | – | – | – |
| S.D. | 6 | 13 | 9 | 4 | – | – | – | – | – |

AS: Asperger Syndrome, ADI: Autism Diagnostic Interview, HFA: High-Functioning Autism, IQ: Intelligence Quotient.
[a] Wechsler Intelligence Scale.
[b] Social/nonverbal cut off for autism: 10/8.
[c] In seven out of 10 individuals.
[d] ICD-10 diagnosis.
[e] Cut off for autism.
[f] Based on neurological examination.