Neural Correlates of Executive Function in Autistic Spectrum Disorders

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Background: *Some clinical characteristics of high-functioning individuals with autistic spectrum disorder (ASD) such as repetitive stereotyped behaviors, perseveration, and obsessionality have been related to executive function (EF) deficits, more specifically to deficits in inhibitory control and set shifting and mediating frontostriatal neural pathways. However, to date, no functional imaging study on ASD has investigated inhibition and cognitive flexibility and no one has related EF brain activation to brain structure.*

Methods: *We compared brain activation (using functional magnetic resonance imaging) in 10 normal intelligence adults with ASD and 12 healthy control subjects during three different EF tasks: 1) motor-inhibition (GO/NO-GO); 2) cognitive interference-inhibition (spatial STROOP); and 3) set shifting (SWITCH). Using voxel-based morphometry, we investigated if cortical areas which were functionally different in people with ASD were also anatomically abnormal.*

Results: *Compared with control subjects, ASD individuals showed significantly increased brain activation in 1) left inferior and orbital frontal gyrus (motor-inhibition); 2) left insula (interference-inhibition); and 3) parietal lobes (set shifting). Moreover, in individuals with ASD, increased frontal gray matter density and increased functional activation shared the same anatomical location.*

Conclusions: *Our findings suggest an association between successful completion of EF tasks and increased brain activation in people with ASD, which partially may be explained by differences in brain anatomy.*

Key Words: Autistic spectrum disorder, executive function, frontal cortex, functional magnetic resonance imaging, fMRI, voxel based morphometry, VBM

Autistic spectrum disorder (ASD), comprising autism and Asperger Syndrome (AS), is a strongly genetic neurodevelopmental condition (Bailey et al 1995), affecting many more people than previously recognized (approximately 60 per 10,000 children under the age of 8 years) (Chakrabarti and Fombonne 2001). Autistic spectrum disorder is characterized by pervasive abnormalities in socioemotional communication and stereotyped and obsessional behaviors (Wing 1997; Gillberg 1993). There is, however, clinical heterogeneity within ASD (Rutter 1978). The clinical symptoms of ASD have a profound impact on daily life and social and economic outcome (e.g., the societal cost of ASD in the United Kingdom exceeds £1 billion) (Jarbrink and Knapp 2001). However, the neurobiological determinants of ASD are poorly understood.

Widespread abnormalities in brain anatomy of people with ASD have been reported (Carper and Courchesne 2005; Bauman and Kemper 2005; McAlonan et al 2005; Piven et al 1990); in particular, frontal, limbic, basal ganglia, parietal, and cerebellar regions are increasingly implicated in the disorder (for review see Bauman and Kemper 2005).

Functional imaging studies in ASD encompass social communication, visual-spatial processing, visual search and attention, motor function, language, and (most recently) executive cognitive function in spatial working memory. Autistic spectrum disorder individuals compared with control subjects are reported to have functional abnormalities in 1) frontostriatal and cingulate regions during socioemotional tasks (Gallagher et al 2000; Critchley et al 2000; Baron-Cohen et al 1999; Happe et al 1996); 2) striate and ventral occipital cortex during visual-attention (Belmonte and Yurgelun-Todd 2003) and visual-motor processing (Mueller et al 2003); 3) occipitotemporal areas during visual search (Ring et al 1999); 4) superior temporal and inferior frontal cortex during language processing (Just et al 2004); 5) the cerebellum during visual-attention tasks (Allen and Courchesne 2003); and 6) dorsolateral prefrontal and anterior cingulate cortex during spatial working memory (Luna et al 2002).

There is an increasing understanding of brain function in people with ASD. There are, however, relatively few studies on the putative anatomicofunctional basis of repetitive, stereotyped behaviors in ASD. It has been proposed that these symptoms may be related to executive function (EF) deficits. Executive function may be fundamentally impaired in ASD, particularly inhibition of response (or inhibitory control) encompassing motor-response inhibition and inhibition of interference (Bishop and Norbury 2005; Ozonoff and Jensen 1999). Further, it has been proposed that these impairments underpin motor and cognitive inflexibility typically observed in ASD (Baron-Cohen 2005; Gillberg 1993). However, more general deficits in EF have also been studied in individuals with ASD (Hughes et al 1994). The authors reported that ASD individuals have difficulty changing their response during cognitive-flexibility tasks, leading to stimulus overselectivity and a repetitive response style (Hughes et al 1994). Neuropsychological studies of EF in individuals with ASD are, however, inconclusive, with some reporting deficits in specific EF tasks, such as set shifting and response inhibition, (Ozonoff and Jensen 1999; Hughes et al 1994) but not others (Griffith et al 1999; Ozonoff et al 1991).

There are no studies on brain function during EF tasks of inhibitory control and set shifting in high-functioning people with ASD, and no one has investigated if brain regions that are functionally different are also anatomically abnormal.

One of the most prominent brain regions implicated in EF is the frontal cortex and its connections to striatal and parietal brain regions (Schroeter et al 2004). Frontostriatal pathways have been reported to be anatomically (Carper and Courchesne 2005; McAlonan et al 2002; Abell et al 1999) and metabolically (Murphy et al 2002) abnormal in adults with ASD compared with control subjects. Further, within the general population, EF deficits are

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associated with frontal lobe pathology, and it is has been proposed that they are the underlying cause of clinical symptoms of autism such as perseveration, rule-bound behaviors, and obsessionality (Russell et al 1999).

Thus, we hypothesized that high-functioning adults with ASD would show differences in frontal brain function while performing EF tasks of inhibitory control and cognitive flexibility and that brain areas that are functionally different in individuals with ASD would be also anatomically abnormal compared with control subjects. To test these hypotheses, we compared the functional neuroanatomy of people with ASD to that of control subjects in three tasks of motor and cognitive inhibitory control: 1) GO/NO-GO motor response-inhibition task; 2) motor version of a spatial STROOP cognitive-interference inhibition task; and 3) set-shifting (SWITCH) task. These three tasks have previously been shown to activate specific frontostriatal pathways: motor response-inhibition in the GO/NO-GO task activated the right prefrontal cortex and the caudate nucleus (Rubia et al 2005, Rubia et al, in press); interference inhibition in the spatial STROOP task activated a left-hemisphere network of dorsolateral prefrontal cortex, anterior cingulate gyrus, parietal lobes, and putamen (Rubia et al 2005; Liu et al 2004; Peterson et al 2002); and the set-shifting (SWITCH) task activated the right inferior prefrontal and parietal cortices and the putamen (Rubia et al 2005; Smith et al 2004). We also compared cortical brain anatomy of people with ASD with that of control subjects using voxel-based morphometry (VBM) analysis (Ashburner and Friston 2000). Furthermore, to determine if functional differences may be partially accounted for by anatomical variation, cortical gray matter differences and functional activation maps of individuals with ASD compared with control subjects were assessed in a preliminary post hoc analysis.

Methods and Materials

Subjects

We included 10 right-handed adult male individuals of normal intelligence with ASD (8 with AS and 2 with high-functioning autism [HFA]) and 12 right-handed male control subjects who did not differ significantly in age or intelligence quotient (IQ) (see Table 1). People with ASD were recruited through the Maudsley Hospital/Institute of Psychiatry, whereas control subjects were recruited locally by advertisement. Asperger Syndrome and HFA were diagnosed by a consultant psychiatrist (D.M.), using ICD-10 criteria (World Health Organization). In addition, where parental informants were available, the Autistic Diagnostic Interview (ADI, Lord et al 1994) was carried out (this was possible in 7 out of 10 ASD individuals; Table 1).

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 18 and 52 years of age at time of scanning.

Every subject underwent a structured clinical examination (including eyesight and routine blood tests) to exclude comorbid medical and psychiatric disorders and biochemical, hematologic, or chromosomal abnormalities (including fragile X syndrome) possibly affecting brain function. None of the participants had a history of major medical illnesses or psychiatric disorders other than ASD. Intelligence quotient was measured using the Wechsler Adult Intelligence Scale-Revised (WAIS-R) short form (Crawford et al 1996). None of the subjects were taking medication.

Neuroimaging

All participants were scanned at the Neuroimaging Unit of the Institute of Psychiatry (IOP), London, United Kingdom using a 1.5 Tesla GE Signa System (General Electric, Milwaukee, Wisconsin).

Table 1. Subject Characteristics

					Autism Diagnostic Interview (ADI)[c]				
Patient	Age at Scanning in Years	IQ[a(full)]	Verbal	Performance	Diagnosis[b]	Social	Nonverbal Communication	Restricted Interests and Repetitive Behaviour[d]	Handedness[e]
1	18	108	97	96	AS	16	12	5	right
2	27	96	93	90	AS	20	14	11	right
3	29	102	100	103	AS	15	11	3	right
4	34	119	108	121	AS	10	14	4	right
5	35	104	104	103	HF	21	10	3	right
6	39	127	112	139	AS				right
7	47	109	99	119	HF	16	13	5	right
8	48	92	90	96	AS				right
9	50	111	100	121	AS				right
10	52	123	87	97	AS	12	12	10	right
All Patients									right
Mean	38	105	99	108		16	13	5	
SD	9	14	8	17		8	4	7	
All Control Subjects						—	—	—	right
Mean	39	106	104	108	—	—	—	—	—
SD	6	13	9	4	—	—	—	—	—

IQ, intelligence quotient; AS, Asperger syndrome; HF, high functioning.
[a]Wechsler intelligence scale.
[b]ICD-10 diagnosis.
[c]Social/nonverbal cut-off for autism: 10/8.
[d]Cut-off for autism: 3.
[e]Based on neurological examination.