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A PRELIMINARY COMPARISON OF VOLUMETRIC CHANGES BETWEEN DYSLEXIA AND ASPERGER SYNDROME

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***Abstract*:** Although shared neuropsychological characteristics between dyslexia and autistic spectrum disorder have been identified, no comparisons at anatomical brain level have been reported. In this study, we examined global and regional grey and white matter changes in adults with dyslexia and patients with Asperger syndrome (AS) in comparison to healthy controls, using voxel-based-morphometry. Results revealed higher levels of global grey matter volume in the Asperger syndrome group in comparison to normal controls but not dyslexia. Further comparisons of grey and white matter could not detect any regional differences between the three groups. From the current data, the hypothesis that regional anatomical abnormalities are strongly implicated in AS and dyslexia could not be supported with the technique used.

***Key words*:** Asperger syndrome, Dyslexia, Neuroimaging

INTRODUCTION

Autism spectrum disorder (ASD) and dyslexia are two of the most frequent neurodevelopmental disorders. While the clinical manifestation of ASD and dyslexia is qualitatively different, a number of similar behavioural, cognitive, and neurobiological impairments in both disorders suggest at least some degree of overlap between them. On the few comparative studies, similar performances have been reported on tests of executive functions (Rumsey & Hamburger, 1990), visuospatial processing (Tsermentseli, O'Brien, & Spencer, 2008), and literacy abilities (White, Frith, Milne, Stuart, Swettenham, & Ramus, 2006). This reported overlap at the neuropsycholog-

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ical level between ASD and dyslexia leads to the assumption of similarities across the two disorders with regard to brain structure.

Most anatomical studies of dyslexia and ASD have used manual-trace approaches in which the user defines a particular region-of-interest (ROI). The ROI analysis method involves defining an area of interest in the brain within which to make measurements. The advantage of this approach is that one can examine an operationally defined region for which there is an a priori hypothesis. For example, many studies have manually traced specific regions of the planum temporale to test the hypothesis that dyslexia is a disorder of planum temporale asymmetry. These studies clearly show that atypical planum temporale symmetry is not a unique characteristic of dyslexia (Best & Demb, 1999; Eckert, Leonard, Richards, Aylward, Thomson, & Berninger, 2003; Leonard, Eckert, Lombardino, Oakland, Kranzler, & Mohr, 2001; Rumsey, Nace, Donohue, Wise, Maisog, & Andreason, 1997), but may reflect more generalized language impairment (Eckert & Leonard, 2000). Disadvantages of manual ROI approaches include difficulty replicating the methods of other research groups because of arbitrary or idiosyncratic definitions for measurements and difficulty obtaining intra-rater and inter-rater reliability for certain measures.

It is not surprising that methods for automated and more objective definition of brain regions have been eagerly sought. In the past decade, investigators have begun to employ voxel-based-morphometry (VBM; Ashburner & Friston, 2000), a fully automated whole-brain measurement technique, to examine structural Magnetic Resonance images (MRI) of the brain. By surveying the whole brain, VBM provides a non-biased measure of highly localised regions that may not be investigated in hypothesis-based studies that employ more labour-intensive ROI techniques. Defined by Ashburner and Friston (2000) as a voxel-wise comparison of the local concentration of grey matter (GM) and white matter (WM) between two or more groups of subjects, VBM tests for residual tissue concentration differences that remain after all subjects' MRI scans are spatially normalised into the same standardised stereotaxic space. GM and WM are segmented out and then smoothed using convolution with a Gaussian kernel.

In order to make structural comparisons between dyslexia and ASD voxel-based VBM was used in the present study. In ASD, VBM studies have reported extensive grey matter changes across frontal, limbic, basal ganglia, parietal and cerebellar regions (Abell, Krams, Ashburner, Passingham, Friston, et al., 1999; McAlonan, Cheung, Cheung, Suckling, Lam, & Tai, 2005; Rojas, Peterson, Winterrowd, Reite, Rogers, & Tregellas, 2006; Waiter, Williams, Murray, Gilchrist, Perrett, & Whiten, 2004) although the directionality of the findings (increase or decrease) has been inconsistent. Similarly, differences between dyslexic and control groups have been found in regions, including the parietotemporal and occipitotemporal regions, infe-

rior frontal gyrus, and cerebellum (Brambati, Termine, Ruffino, Fazio, Cappa, & Perani, 2004; Brown, Eliez, Mevon, Rumsey, White, & Reiss, 2001; Eckert, Leonard, Wilke, Eckert, Richards, et al., 2005; Silani et al., 2005; Steinbrink, Vogt, Kastrup, Muller, Juengling, & Kassubek, 2008). Taken together, the VBM studies published on dyslexia and ASD reveal variable anatomical patterns. These may be relevant for dyslexia and ASD as neurological syndromes but less informative on which abnormalities are truly specific for each condition.

The inconsistency of results reported in VBM studies of ASD and dyslexia precludes any assumptions regarding shared brain abnormalities and therefore a direct comparison of both clinical groups seems to be mandatory. The identification of overlapping and disease-specific cerebral brain abnormalities might help to explain similarities and differences in the neurocognitive profiles of dyslexia and ASD individuals and thereby point to interesting neurobiological phenotypes across different diagnostic categories. The present study was therefore designed to compare for the first time global and regional GM and WM volumes between adults with dyslexia, individuals with ASD (particularly Asperger syndrome) and healthy controls. We only included individuals with Asperger syndrome (AS) because they are better comparisons for dyslexia than high functioning autism as they are characterized by normal language development (Macintosh & Dissanayake, 2004). In addition, this study aimed to re-investigate abnormalities of GM and WM volumes in dyslexia and AS, using advances in VBM analysis.

METHOD

Participants

Fifteen individuals diagnosed with dyslexia, 15 individuals with AS, and 15 healthy normal control participants participated in the study. The groups were matched for chronological age, $F(2, 42) = 0.443$, $p > .05$ and full scale IQ, $F(2, 42) = 1.498$, $p > .05$, as measured with the *WASI-Weschler Abbreviated Scale of Intelligence* (Weschler, 1999). All participants were right-handed Caucasians. Demographics are presented in Table 1. The study was done in accordance with the Declaration of Helsinki and was officially approved by Brunel University's Research Ethics Committee.

Table 1. Demographic characteristics of the experimental groups

	Asperger	Dyslexia	Controls
N	15	15	15
Male/female	10/5	8/7	8/7
Age (years)	25.1 (2.7)	23.0 (2.5)	23.2 (3.1)
Full Scale IQ	124.7 (10.1)	113.0 (13.08)	112.5 (7.0)

The dyslexic participants were recruited from the Disability and Dyslexia Service at Brunel University, UK. They were all university students with a childhood history of specific reading difficulties and had all received a formal diagnosis of dyslexia within the previous two years. A diagnosis of dyslexia was confirmed by a licensed educational psychologist, according to a discrepancy between reading/spelling performance and general cognitive abilities, based on a battery of standardised tests. We did not assess the literacy skills of our participants, as it is quite common with adult dyslexics to show a pattern of remediated symptoms (Hansen, Stein, Orde, Winter, & Talcott, 2001). Individuals in the AS group were referred by two specialized colleges for adults with ASD, accredited by the National Autistic Society, UK. Individuals in the AS group had been diagnosed by qualified clinicians using criteria from the *Diagnostic and Statistical Manual of Mental Disorders –IV (*American Psychiatric Association, 1994). We also inspected their clinical records and developmental history. Exclusion of a history of clinically significant delays in language development was necessary for the diagnosis of Asperger's disorder. Separate research diagnosis with the use of a diagnostic instrument (i.e., Autism Diagnostic Interview & Autism Diagnostic Observation Schedule, Lord et al., 1999) was not carried out as it has been found that there is high degree of agreement between clinical and research diagnosis, with research instruments sometimes leading to overdiagnosis of ASDs (Mazefsky & Oswald, 2006). Typically developing adults were recruited from the student population of Brunel University and according to self-report had no history of learning difficulties diagnosis.

MRI acquisition

MRI brain scans were obtained with a Siemens 3-Tesla scanner. High-resolution whole head 3-D MRI data were collected with a T_1 weighted magnetization-prepared rapid-acquisition gradient echo sequence (MPRAGE) with the following parameters: TR = 1960ms, TE = 3.93 ms, flip angle α = 11 °; FOV = 256 mm; matrix = 180 _ 256 mm^2; 176 slices, slice thickness 3 mm, inter-slice gap = 0, voxel size 1_1_1 mm. Images were visually inspected for artifacts or structural abnormalities unrelated to AS or dyslexia.

Data processing and analysis

We used a standard processing protocol following the unified segmentation approach (Ashburner & Friston, 2005) in Statistical Parametric Mapping (SPM5) (Wellcome Trust Centre for Neuroimaging, London, UK, http://www.fil.ion.ucl.ac.uk/ spm/).

With the unified segmentation approach the steps of spatial normalization, segmentation and modulation are processed simultaneously. Thus, the model avoids the 'circularity problem' of the optimised VBM procedure which was used in SPM2 as the initial image registration does not require initial tissue segmentation and vice versa. Structural T_1 data were partitioned into GM, WM and cerebrospinal fluid (CSF) brain tissue compartments. Finally, the segmented and modulated GM and WM partitions were smoothed with an 8-mm full-width-half-maximum filter and used for statistical analysis.

Total GM and WM volumes were initially calculated by summing modulated voxel intensities for each tissue class. The images representing CSF were not used for VBM as there were no predictions about CSF differences in these groups. The regional-specific differences in GM and WM volumes between the clinical groups and the controls were assessed using analyses of covariance (ANCOVA) with total GM and WM volume as covariates. Voxel level $p < .001$ uncorrected significance levels were initially used for exploratory analysis. We then employed a more stringent threshold of $p < .05$ adjusted for multiple comparisons using the false discovery rate (Genovese, Lazar, & Nichols, 2002).

RESULTS

Global volume

Global measures of grey and white matter were calculated to test for group differences in overall tissue compartment volume on images segmented in native space. The total grey matter volume was significantly different between the three groups, $F(2, 42) = 3.656$, $p < .05$. Tukey's post hoc tests revealed that the group with AS showed increased global gray matter volume (749 ml, $SD = 76.7$, $p < .05$) in comparison to the group of normal controls (666 ml, $SD = 69.6$, $p < .05$) but not in comparison to dyslexics (697 ml, $SD = 59.1$, $p > .05$). The total volume of white matter was not significantly different, $F(2, 42) = 1.116$, $p > .05$, between the groups of AS (478 ml, $SD = 66$), dyslexics (445 ml, $SD = 19.9$) and normal controls (465 ml, $SD = 4.9$). The results are shown in Figure 1.

Regional comparisons

Assessed at significance threshold of $p < .001$, uncorrected for multiple comparisons, scattered areas of grey matter differences were observed between the three

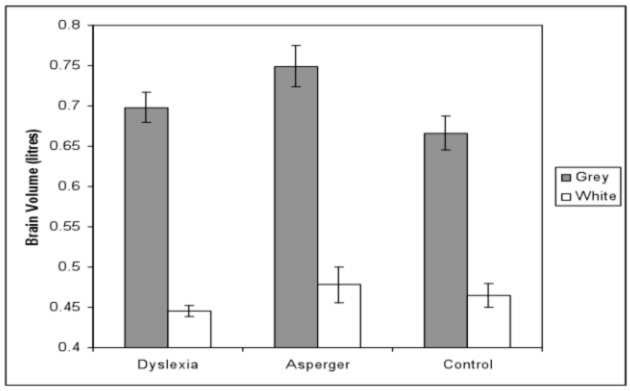

Figure 1. Mean ratings of criticalness for each face type presented for 500 ms in high and low socially anxious participants.

Error bars represent standard error.

groups (Table 2). None of these regional differences remained significant when adjusted for multiple comparisons using the false discovery rate. When small volume corrections (SVC) at $p < .05$ threshold on an arbitrary 5 mm diameter sphere centered on the cluster maximum were applied to the areas that exceeded the uncorrected $p < .001$ threshold, again there were no significant voxels.

Scattered white matter volume differences were also detected between the three groups when assessed at a threshold of $p < .001$, uncorrected for multiple comparisons. Again this difference did not survive adjustment for false discovery rate. When small volume corrections were applied to these areas, there were no significant voxels.

Table 2. Grey Matter Volume differences between the three experimental groups

Brain Region	*Z*	Cluster size	Talairach Co-ordinates		
			x,	y,	z (mm)
Occipital gyrus, BA 18, Left	4.18	10	-52	-82	-6
Temporal gyrus, Left	3.93	5	-46	-58	6
Dorsolateral prefrontal cortex, BA 46, Right	3.56	5	56	26	30
Frontal lobe, sub-gyral, Left	3.45	4	-38	40	12
Frontal lobe, precentral gyrus, Right	4.07	4	48	14	10
Inferior temporal gyrus, Right	3.45	4	48	-14	-34
Posterior cingulated gyrus/parietal cuneus, Left	3.38	4	-22	-74	30
Parietal lobe, precuneus, Left	3.33	4	-14	-64	52
Limbic lobe, uncus, Right	3.26	4	28	-8	-36

Table 3. White Matter Volume differences between the three experimental groups

Brain Region	*Z*	Cluster size	Talairach Co-ordinates x,	y,	z (mm)
Temporal lobe, sub-gyral, Left	4.66	8	-36	-34	-12
Frontal lobe, middle frontal gyrus, BA 6, Left	3.75	6	-38	6	54
Parietal lobe, precuneus, Left	3.92	5	-18	-72	30
Frontal lobe, middle frontal gyrus, Left	3.56	5	-46	-58	6
Temporal lobe, sub-gyral, Left	4.66	4	-36	-34	-12
Lentoform nucleus, putamen, Right	3.85	3	30	-16	6
Frontal lobe, superior frontal gyrus, Left	3.76	3	-18	42	-16
Frontal lobe, middle frontal gyrus BA 6, Left	3.68	3	-40	6	58
Occipital gyrus, BA 18, Right	3.64	3	18	-72	12

DISCUSSION

This study was undertaken to examine the presence of structural differences between adults with dyslexia, adults with AS and normal controls. It also aimed to extend the findings of previous VBM studies of ASD and dyslexia by using state of the art VBM techniques. The results found little indication of anatomical differences between the three groups. Individuals with AS showed increased global grey matter volume, in comparison to normal controls but not dyslexia. No regional grey or white matter volume decreases or increases were found in the clinical groups.

The finding of increased global grey matter volume in AS is consistent with previous reports that showed autistic spectrum disorder to be associated with increased grey matter volume (Abell et al., 1999; Waiter et al., 2004). It has been suggested this may indicate a departure from normal neurodevelopmental processes. Early neurodevelopment is associated with 'pruning' processes, which include programmed cell death (apoptosis), and increased myelination of certain pathways. Normally, neurodevelopmental processes produce a reduction in grey matter associated with apoptosis. Cell bodies in post-mortem samples taken from subjects with autism have been reported to be more closely packed with fewer dendritic branches (Bauman & Kemper, 1994). Others have suggested that ASD may be associated with abnormal apoptosis (Bailey, Luthert, Dean, Hardig, Janota, et al., 1998; Fatemi, Halt, Stary, Realmuto, & Jalali-Mousavi, 2001). It is possible the increased grey matter volume found in this study could reflect a failure of apoptosis in ASD.

Using VBM no regional gray or white matter volume decreases or increases were found in the clinical groups, in contrast to previous reports (Abell et al., 1999; Brambati et al., 2004; Brown et al., 2001; Eckert et al., 2005; McAlonan, 2005; Rojas et al., 2006; Silani et al., 2005; Steinbrink et al., 2008; Waiter et al., 2004) using VBM. This contradiction to previous findings may be explained in part by methodological differences between the current study and previous reports. The results of this study also raise considerations guiding choice of technique, the significance of findings from this method and how the findings from it actually inform our understanding of ASD and dyslexia.

Previous VBM studies on ASD recruited participants from the whole autistic spectrum with a range of severity of ASD. It is possible that findings of structural abnormalities in these investigations were not specific to AS and reflected heterogeneity in their ASD group. The idea that individuals with high functioning autism and AS might be distinct biological entities is not novel. Neuroanatomical measures have revealed differences between high functioning autism and AS and suggest that AS is on the mild end of the autism spectrum (Lotspeich, Kwon, Schumann, Fryer, Goodlin-Jones, & Buonocore, 2004). Indeed, a study (Bird, Catmur, Silani, Frith, & Frith, 2006) that recruited a well-controlled sample of participants with AS did not reveal any voxels in which significant differences were found between AS and controls. It is possible that by meticulous inclusion of AS only individuals without co-morbidities the present study and the study by Bird et al. (2006) excluded the individuals who were likely to show changes in brain structure. In our case, we were interested in the changes of high-achieving individuals *per se,* rather than those more severely impaired. Therefore, it could be postulated that we selected a "super-sample" of AS resistant to neurological complications. We know of no evidence for the true existence of such groups of patients, but this possibility cannot be entirely discounted.

Research on dyslexia has also showed widespread but subtle anatomical changes (Brambati et al., 2004; Brown et al., 2001; Eckert et al., 2005; Silani et al., 2005), which were mainly based on a standard or optimised VBM protocol implemented in previous SPM versions. The only VBM dyslexia study to date that has used SPM5 (Steinbrink et al., 2008), showed a subtle GM reduction only in the superior temporal gyrus which could not be correlated to any reading-related behavioural measures. It is possible that the use of the unified segmentation approach might account for the different results from those of previous VBM studies of ASD and dyslexia.

Previous studies mainly used an optimised pre-processing strategy which is inherently circular. Specifically, the optimised approach involves spatially normalising subjects' brain images to a standard space by matching gray matter in these images to a grey matter reference. Tissue classification in SPM requires the images

to be registered with tissue probability maps. After registration, these maps represent the prior probability of tissue classes being found at each location in an image. Bayes rule can then be used to combine these prior tissue type probabilities derived from voxel intensities to provide the posterior probability (Ashburner & Friston, 2000). This procedure is inherently circular, because the registration requires an initial tissue classification, and the tissue classification requires an initial registration. In SPM5, this circularity is resolved by combining both components into a single generative model (Ashburner & Friston, 2005). This approach provides better results than serial applications of each component. We therefore suggest that, using SPM5, whereby tissue classification, bias correction, and image registration are integrated, no reproducible GM or WM differences between AS, dyslexia and typical development are detectable. It remains to be seen whether larger sample studies using this model in similar populations will produce comparable results.

VBM has been questioned about its potential to be used for understanding the effects of disease on brain morphology as well as for diagnostic or other related purposes (Davatzikos, 2004). In fact, there have been a number of VBM studies to report non-significant results in populations where anatomical defects have been detected with other methods (e.g. Mehta, Grabowski, Trivedi, & Damasio, 2003; Thomann, Wustenberg, Pantel, Essig & Schroder, 2006). According to Davatzikos (2004), VBM analysis is characterised by a significant bias which constitutes inferences about group differences very difficult. With VBM, the anatomical profile of an individual is a collection of the voxel-wise morphological measurements which are then placed into a high-dimensional space, each dimension representing a voxel. When these measurements are smoothed, then each dimension represents a weighted average of a collection of measurements from the vicinity of a voxel. Group differences are then reflected by the degree of separation of the respective anatomical profiles. In this respect, the larger this shift distance is, the greater the effect of this disease is. However, the structural difference between two groups with the same overall magnitude can be interpreted differently by VBM depending on the orientation of the group difference. As Davatzikos (2004) argues, VBM might fail to find group differences because projection onto each dimension separately results in significant group overlap: diseased and normal groups might have different means, but the overlap is high. As a result, effects that are relatively localised will tend to be detected much easier than effects that are relatively more distributed and involve several structures. This could in fact explain why VBM studies of ASD and dyslexia have produced such inconsistent results.

Conclusion

The present study documents no significant regional GM or WM volume deficits in a group of adults with AS and a group of adults with dyslexia. This indicates that there is no evidence of regional structural brain damage in high-achieving populations. It is important to state that the results of the current study do not indicate that there are no anatomical changes in dyslexia or AS in general. Rather, we suggest that the pathological basis of these defects is not regional GM or WM change, as measurable with the technique used.

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