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ORIGINAL ARTICLE

Alzheimer's disease and Down's syndrome: an *in vivo* MRI study

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Background. Individuals with Down's syndrome (DS) are at high risk of developing Alzheimer's disease (AD). However, few studies have investigated brain anatomy in DS individuals with AD.

Method. We compared whole brain anatomy, as measured by volumetric magnetic resonance imaging (MRI), in DS individuals with and without AD. We also investigated whether volumetric differences could reliably classify DS individuals according to AD status. We used volumetric MRI and manual tracing to examine regional brain anatomy in 19 DS adults with AD and 39 DS adults without AD.

Results. DS individuals with AD had significantly smaller corrected volumes bilaterally of the hippocampus and caudate, and right amygdala and putamen, and a significantly larger corrected volume of left peripheral cerebrospinal fluid (CSF), compared to DS individuals without AD. The volume of the hippocampus and caudate nucleus correctly categorized 92% and 92% respectively of DS individuals without AD, and 75% and 80% respectively of DS individuals with AD.

Conclusions. DS individuals with AD have significant medial temporal and striatal volume reductions, and these may provide markers of clinical AD.

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Introduction

Down's syndrome (DS) is associated with trisomy of chromosome 21, and is the most common genetic cause of learning disability (mental retardation), occurring in approximately 1 in 1000 live births (Roizen & Patterson, 2003). Individuals with DS are prone to developing dementia (most commonly Alzheimer's disease; AD) in middle age. The combination of pre-existing learning disability with superimposed dementia in people with DS is difficult to assess and treat, and is an expensive management problem.

The neuropathology of AD and some degree of the gross neuroanatomical changes associated with AD have been reported to occur in the brains of almost all DS people older than 40 years (Malamud, 1972; Wisniewski *et al*. 1985). In addition, the prevalence of clinically detectable dementia in people with DS is reported to rise to 66% in the sixth decade of life (Visser *et al*. 1997). The amyloid precursor protein (APP) gene is localized to chromosome 21. Thus it has been hypothesized that the presence of an extra copy of the APP gene in DS cells leads to abnormalities in APP processing in neuronal membranes, and then to the formation of amyloid plaques, neuronal death and clinical AD (Prasher *et al*. 1998; Folin *et al*. 2003).

The presence of pre-morbid learning disability in people with DS may make additional cognitive deficits associated with the early stages of AD more difficult to detect than in the general population (Miniszek, 1983). Treatment for AD is more successful if it is begun at an early stage; however, there are few non-invasive aids

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to diagnosis. Magnetic resonance imaging (MRI) may provide a technique whereby differences in brain anatomy can be detected and used to aid the early diagnosis of AD in DS.

Four volumetric MRI studies have compared whole brain anatomy in DS individuals with and without dementia (Kesslak *et al*. 1994; Pearlson *et al*. 1998; Aylward *et al*. 1999; Prasher *et al*. 2003). These studies reported that DS individuals with AD, as compared to non-demented DS controls, have a significant reduction in volume of medial temporal lobe/hippocampus (Kesslak *et al*. 1994; Pearlson *et al*. 1998; Aylward *et al*. 1999) and neocortex (Kesslak *et al*. 1994), together with significant enlargement of ventricular cerebrospinal fluid (CSF) (Kesslak *et al*. 1994; Pearlson *et al*. 1998; Prasher *et al*. 2003). These reports are broadly consistent with the pattern of gross brain deficits found in AD in the general population.

These prior MRI studies of DS and dementia were important first steps. However, they examined relatively small numbers of demented DS individuals (ranging from 2 to 11) and most used demented DS participants who were significantly older than the non-demented DS controls (Kesslak *et al*. 1994; Pearlson *et al*. 1998; Aylward *et al*. 1999). Recruiting age-matched samples of DS individuals with and without AD for a MRI study is difficult, as the population of older DS individuals is small, and this is a group of people who often find the demands of MRI scanning difficult. However, age is a potentially important confound because non-demented DS individuals are reported to have significant age-related decreases in regional brain volumes, including medial temporal volumes (Aylward *et al*. 1997; Krasuski *et al*. 2002; Teipel *et al*. 2003, 2004). Despite this, two of the prior MRI studies of demented DS individuals did not correct for age in their statistical analysis (Kesslak *et al*. 1994; Pearlson *et al*. 1998) and thus their results may not be reliable.

To date, no study has investigated whether overall brain anatomy is related to cognitive function in people with DS and AD. Thus, the neurobiological associates of cognitive deficits in DS individuals with dementia/AD are poorly understood. We therefore used volumetric MRI to compare whole brain anatomy in DS individuals with and without AD (correcting for head size, age and gender). We also determined whether brain volumes could reliably classify individuals according to AD status. Furthermore, within DS individuals with AD, we investigated whether brain anatomy was significantly related to cognitive function, as measured by the Cambridge Cognitive Examination (CAMCOG; Huppert *et al*. 1995; Roth *et al*. 1998).

Method

Participants

We studied 19 DS adults with AD, and 39 non-demented, healthy adults with DS. Participants with DS were recruited locally, and from already identified cohorts in Birmingham, Plymouth and Newcastle, UK. DS status was assessed in all participants by karyotyping. Dementia status was assessed using the Diagnostic Criteria for Research-10 (DCR-10; WHO, 1992). As expected, the mean age of the AD group was significantly higher than the healthy DS group: 52 years (range 42–62 years) and 35 years (range 19–66 years) respectively. Nineteen of the 38 healthy DS participants were older than 35 years at the time of scanning. There was also a higher proportion of female participants in the AD group (10 of 19 in the AD group, as compared to 12 of 39 in the healthy DS group). However, the two groups were similar in terms of ethnic origin, apolipoprotein E (apoE) status and handedness (see Table 1).

All participants underwent standard physical, neurological and psychiatric screening, including routine bloods (e.g. renal and liver function tests, full blood count and thyroid function tests) and clinical MRI. Psychiatric screening was performed by a psychiatrist (V.P.) and a psychologist (F.B.). We excluded people with untreated physical disorder affecting brain function, known history of birth trauma or head injury and major psychiatric condition other than AD. In addition, we excluded participants whose clinical MRI scans suggested acquired brain damage.

None of the participants was taking antipsychotic or antidepressant medication at the time of the study; however, nine of the 19 DS participants with AD were taking cholinesterase inhibitors. Some participants were also taking other medications for unrelated physical conditions (e.g. hypertension), but this did not differ significantly between groups.

Multi-Centre Research Ethics Committee (MREC) and Local Research Ethics Committee (LREC) approval was obtained, and after complete description of the study to the participants, written informed consent, or assent, was obtained from the participants and/or their carers.

MRI protocol

All participants were scanned using a 1.5 T GE Signa MR NV/*i* system (General Electric, Milwaukee, WI, USA) at the Maudsley Hospital, London, and were interleaved in the dates of their scans. A vacuum fixation device was used to ensure that participants were both comfortable and restrained from movement during the scanning process. The whole brain was

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Table 1. *Group comparisons for Down's syndrome (DS) adults with Alzheimer's disease (AD), and healthy DS controls. p values are stated after correcting for total cranial volume, age and gender (standard deviations are given in parentheses)*

	DS with AD (uncorrected) ($n=19$)	Healthy DS (uncorrected) ($n=39$)	F (uncorrected)	p (corrected)
Age (years)	52 (11)	35 (11)		
Gender, M/F	9/10	27/12		
CAMCOG total score	30 (15)	55 (22)	8.7	N.A.
Total cranial volume (ml)				
Left	555 (54)	596 (49)	8.3	N.A.
Right	547 (55)	583 (41)	7.8	N.A.
Total	1103 (104)	1179 (86)	8.8	N.A.
WBV				
Left	404 (49)	469 (54)	19.9	0.760
Right	403 (51)	460 (47)	17.8	0.952
Total	808 (98)	922 (91)	19.3	0.758
Hippocampus				
Left	1.7 (0.7)	2.2 (0.4)	13.8	0.014*
Right	1.6 (0.6)	2.3 (0.4)	24.8	0.001*
Total	3.2 (1.3)	4.5 (0.8)	24.9	0.004*
Amygdala				
Left	1.5 (0.5)	1.8 (0.5)	4.6	0.175
Right	1.4 (0.6)	1.8 (0.5)	6.3	0.036*
Total	3.0 (1.1)	3.6 (1.0)	5.6	0.074
Caudate				
Left	2.2 (0.5)	2.8 (0.6)	15.3	0.027*
Right	2.0 (0.4)	2.7 (0.5)	37.1	0.001*
Total	4.2 (0.8)	5.5 (1.0)	26.4	0.005*
Putamen				
Left	3.9 (0.7)	4.7 (0.6)	22.9	0.068
Right	3.5 (0.5)	4.4 (0.4)	37.7	0.012*
Total	7.4 (1.3)	9.2 (1.0)	35.9	0.047*
Striatum				
Left	6.0 (0.9)	7.5 (0.7)	4.2	0.002*
Right	5.6 (0.9)	7.0 (0.7)	41.3	0.003*
Total	11.5 (1.8)	14.6 (1.4)	51.8	0.001*
Frontal lobes				
Left	169 (21)	187 (18)	11.5	0.896
Right	167 (23)	187 (22)	10.9	0.944
Total	336 (43)	373 (41)	10.3	0.792
Prefrontal				
Left	54 (8.8)	61 (9.2)	7.6	0.165
Right	55 (9.4)	61 (9.1)	5.6	0.062
Total	110 (17)	122 (16.7)	6.9	0.090
Temporal lobes				
Left	39 (6.4)	45 (8.0)	10.6	0.848
Right	40 (6.5)	46 (8.6)	7.6	0.674
Total	80 (11.4)	92 (15.5)	9.1	0.703
Parietal lobes				
Left	150 (22)	176 (21)	17.9	0.504
Right	155 (22)	176 (22)	10.4	0.785
Total	309 (41)	352 (41)	12.5	0.873

[*continues overleaf*

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Table 1 (*cont.*)

	DS with AD (uncorrected) ($n=19$)	Healthy DS (uncorrected) ($n=39$)	F (uncorrected)	p (corrected)
Occipital lobes				
Left	48 (11)	55 (18)	2.3	0.475
Right	44 (10)	50 (16)	1.9	0.396
Total	93 (19)	106 (34)	2.2	0.423
Cerebellum				
Left	46 (5.2)	47 (5.2)	0.3	0.196
Right	46 (5.3)	47 (4.9)	0.2	0.214
Total	92 (10.8)	94 (9.7)	0.4	0.173
Lateral ventricles				
Left	12 (6.1)	9.2 (5.7)	3.6	0.557
Right	12 (6.9)	7.3 (4.4)	10.0	0.252
Total	25 (13.8)	16.5 (9.9)	7.9	0.502
Peripheral CSF				
Left	2.9 (1.3)	1.6 (0.9)	19.9	0.006*
Right	2.6 (0.7)	1.8 (1.2)	5.4	0.351
Total	5.3 (1.3)	4.1 (3.0)	3.0	0.842
Total ventricular space				
Left	16 (7.6)	10.9 (6.1)	7.7	0.701
Right	15 (7.0)	9.3 (5.6)	9.9	0.391
Total	31 (14.1)	22.5 (14.8)	4.2	0.770

CAMCOG, Cambridge Cognitive Examination; WBV, whole brain volume; CSF, cerebrospinal fluid; N.A., not applicable.

* Significant at $p<0.05$.

scanned with a three-dimensional (3-D) inversion recovery prepared fast spoiled gradient-recalled (SPGR) acquisition in the steady-state longitudinal relaxation time (T1)-weighted dataset. These T1-weighted images were obtained in the axial plane with 1.5-mm contiguous sections. Repetition time (TR) was 13.8 ms, inversion time was 450 ms, echo time (TE) was 2.8 ms, and the flip angle was 20° with one data average and a $256\times256\times124$ pixel matrix. Image contrast for all datasets was chosen with the aid of a software tool for optimizing image contrast (Simmons *et al*. 1996). Acquisition time was 6 min 27 s.

Volumetric protocol

Volumetric analysis of total and regional brain areas was performed on a reformatted SPGR dataset using Measure software (Barta *et al*. 1997). Right and left hemispheric brain matter, total cranial volume and cerebral ventricles were measured on images aligned along the anterior/posterior commissure line. Measurements were then made, using previously described region of interest boundaries (Murphy *et al*. 1996), of total, right and left total cranial volume, whole brain, frontal, prefrontal, temporal, parietal and occipital lobes, hippocampus, amygdala, cerebellum, caudate, putamen, striatum (caudate + putamen), lateral ventricles, peripheral CSF and total ventricular space (lateral + third ventricles). Images were realigned parallel to the Sylvian fissure for hippocampal and amygdalar measures.

The volume of each region was calculated by multiplying the summed pixel cross-sectional areas by slice thickness. All volumetric measurements were made by a single rater who was blind to the status of each participant. Intra-class reliability was determined for all brain volumes: these were all highly significant (total cranial volume: $r=0.963$; whole brain volumes: $r=0.977$; hippocampus: $r=0.911$; amygdala: $r=0.902$; caudate: $r=0.923$; putamen: $r=0.916$; striatum: $r=0.909$; frontal lobes: $r=0.956$; prefrontal: $r=0.949$; temporal lobes: $r=0.972$; parietal lobes: $r=0.917$; occipital lobes: $r=0.943$; cerebellum: $r=0.969$; lateral ventricles: $r=0.942$; peripheral CSF: $r=0.931$; total ventricular space: $r=0.975$; all p values <0.001).

Cognitive assessment

Cognitive ability was measured using the CAMCOG (Huppert *et al*. 1995; Roth *et al*. 1998). The CAMCOG

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has been validated for use with DS adults (Hon *et al*. 1999) and provides a measure of general cognitive function, including measures of memory, orientation, language, attention, praxis and executive function. The CAMCOG is appropriate for assessing cognitive function in people with learning disability, unlike more standard tests of cognitive function such as the Wechsler Adult Intelligence Scales. CAMCOG subtests, with a small number of exceptions, did not produce ceiling or floor effects. The CAMCOG incorporates, and is highly correlated with, the Mini-Mental State Examination (MMSE; Blessed *et al*. 1991). For each participant cognitive testing was conducted within 6 months of scanning.

Statistical analysis

Analysis of brain volumes was carried out using SPSS 8.0 for Windows (SPSS Inc., Chicago, IL, USA). Normality of distribution was assessed in both groups, and tested for significance using the Kolmogrov–Smirnov statistic. Neither group violated the assumption of normality, therefore parametric tests of difference and correlation were used.

Group differences in brain volumes were tested with one-way analysis of co-variance (ANCOVA), with group as the between-participant factor and total cranial volume, participant age and gender as covariates.

We examined the relevant scatterplots and there was no evidence of non-linearity. Therefore, Pearson's correlation coefficient (two-tailed) was used to assess linear correlations between regional brain volumes and age, in both groups.

Within DS individuals with AD, we also carried out an exploratory *post hoc* analysis (using Pearson's test of correlation) of the relationship between CAMCOG scores and those brain volumes that differed significantly between groups (when corrected for total cranial volume, age and gender).

Our results may have been confounded by medication status, therefore we compared brain anatomy and cognitive function between those demented individuals taking cholinesterase inhibitors to those who were not.

We used logistic regression to assess whether brain volumes could reliably classify individuals according to AD status.

The level of statistical significance was defined as $p < 0.05$ (two-tailed).

Results

Most uncorrected brain volumes (all except occipital lobe and cerebellum) were significantly smaller in the DS + AD group, as compared to the healthy DS group (see Table 1). However, as noted above, brain volumes may be confounded by differences in head size, age and gender.

Mean total cranial volume was significantly larger in the non-demented group (for total cranial volume: $F = 8.8$, df = 1, 57, $p = 0.004$).

As noted earlier, there was a larger proportion of females in the DS + AD group. Within the healthy DS group there were some significant effects of gender on brain volumes: males had significantly larger volumes of left whole brain ($t = 2.23$, $p = 0.032$), left prefrontal lobes ($t = 2.27$, $p = 0.029$), left and right temporal lobes ($t = 4.14$, $p < 0.001$; $t = 3.12$, $p < 0.001$) and right caudate ($t = 2.24$, $p = 0.032$). Within the DS + AD group there were no significant effects of gender on brain volumes or level of cognitive function. In addition, within the DS + AD group there were no significant effects of medication on brain volumes or level of cognitive function.

After correcting for group differences in total cranial volume, age and gender, DS individuals with AD compared to healthy DS individuals had a significantly smaller volume of left and right hippocampus, right amygdala, left and right caudate, right putamen, left and right putamen, and left peripheral CSF (see Table 1).

As expected, DS individuals with AD had significantly lower scores on most cognitive measures, compared to healthy DS individuals, both before and after correcting for age. These included CAMCOG total score ($F = 8.72$, df = 1, 57, $p = 0.005$, after correcting for age) and CAMCOG total memory score ($F = 10.41$, df = 1, 57, $p = 0.02$, after correcting for age).

Within DS individuals with AD, there were no significant correlations between those regional brain volumes that differed significantly between groups and measures of cognitive function (when corrected for total cranial volume, age and gender).

Logistic regression analysis showed that hippocampal volume (and using total cranial volume, age and gender as covariates) was able to correctly categorize 92% of the non-demented DS individuals (specificity) and 75% of DS individuals with AD (sensitivity) (see Fig. 1). Similar analysis showed that caudate volume (again using total cranial volume and age as covariates) were able to correctly categorize 92% of the non-demented DS individuals (specificity) and 80% of DS individuals with AD (sensitivity) (see Fig. 2).

Discussion

In this observational study we found that DS individuals with AD had significantly smaller

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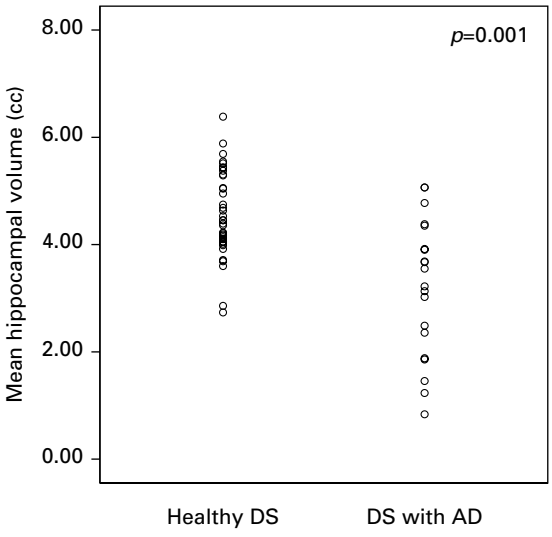

Fig. 1. Mean hippocampal volumes in healthy individuals with Down's syndrome (DS) and individuals with DS and Alzheimer's disease (AD).

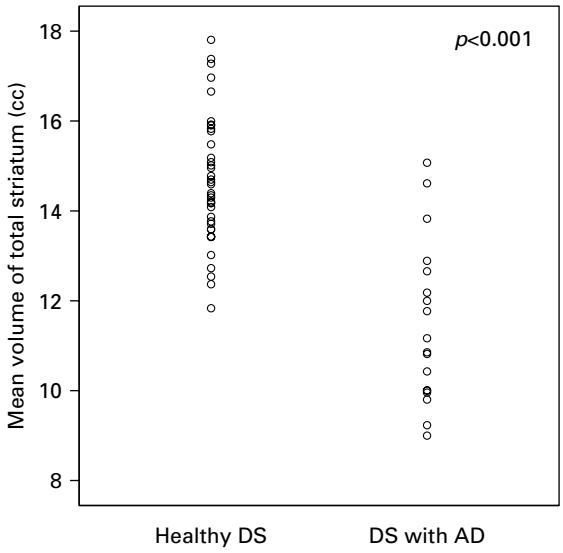

Fig. 2. Mean striatal volumes in healthy individuals with Down's syndrome (DS) and individuals with DS and Alzheimer's disease (AD).

uncorrected volumes of most brain regions we measured, as compared to non-demented DS participants. However, these initial findings were potentially confounded by significant between-group differences in head size, age and gender. To overcome the potential confound of head size, we included total cranial volume as a covariate in our statistical analysis. We also used age as a statistical covariate. This was necessary because some prior volumetric MRI studies of brain ageing in healthy DS individuals have reported significant age-related decreases in volume of a number of brain regions, including hippocampus (Kesslak *et al*. 1994; Krasuski *et al*. 2002), amygdala (Krasuski *et al*. 2002), caudate nucleus (Raz *et al*. 1995) and putamen (Aylward *et al*. 1997). Finally, we included gender as a covariate. This was necessary, first, because the DS + AD group was composed of a greater proportion of females compared to the healthy DS group. Second, there were a small number of sex-related differences in brain volumes within the healthy DS group, although none were present within the DS + AD group.

After correcting for the potential confounds of head size, age and gender, we found that the DS + AD group had a significantly smaller volume of hippocampus, striatal structures (caudate and putamen) and amygdala. Furthermore, we report for the first time that volume of hippocampus and caudate nuclei can distinguish between DS people with and without AD, with good specificity (90%) and reasonable sensitivity (80%).

Another potential confound for our results is that some DS individuals with AD were taking cholinesterase inhibitors and some were not. The reasons for this discrepancy are unknown, but it most probably reflects differences in local prescribing habits. We cannot state whether or not medication status in our DS + AD sample was related to length of illness. This is because it is often difficult to accurately assess the date of onset of dementia in people with DS, and we were not able to retrospectively establish the time of AD onset or the length of illness.

We found no significant differences in any clinical variable between those demented DS participants who were taking cholinesterase inhibitors and those who were not. Nonetheless, it remains possible that medication status was a significant confound for our analysis. However, many people with DS and AD are treated with cholinesterase inhibitors, and therefore our findings may be more generalizable to the whole DS population than if we had excluded these participants.

We carried out multiple statistical tests, and so some of our results may be confounded by type 1 error. Nevertheless, our finding of group differences in regional DS brain anatomy in DS participants with AD is in broad agreement with prior smaller reports. In addition, most of the significant group differences we found survived Bonferroni correction for multiple comparisons (left hippocampus, right caudate, left and right striatum, left peripheral CSF). The Bonferroni correction is a stringent correction for this dataset because volumes of the different brain regions tend to be positively correlated. Thus, it is possible, but unlikely, that our findings can be explained by type 1 error.

We used clinical rather than *post-mortem* criteria for assessing AD. Therefore, we cannot exclude the possibility that some DS participants in the AD group had mixed neuropathology. Nonetheless, the DS individuals with AD that we included were well characterized, and we excluded people with easily detectable physical health problems. Therefore, the group differences we found in brain anatomy most probably reflect the development of AD-type neuropathology, rather than other types of neuropathology.

We used manual delineation methods to measure brain volumes, rather than voxel-based morphometry (VBM), a fully automated technique for examining whole brain morphology. VBM uses statistical modelling assumptions that may not apply to populations with marked abnormalities in brain anatomy. Therefore, VBM analysis of our data may not have been reliable.

As noted above, nearly all older people with DS have the neuropathology of AD, but not all older DS individuals display clinical symptoms of the disorder. Hence, it is very likely that the brains of many of our clinically non-demented DS controls were significantly affected by plaques and tangles. Therefore, the differences we report in brain anatomy cannot be taken to specifically reflect the underlying neuropathology of AD. Rather, these differences in brain anatomy are related to clinical AD status.

Hippocampus and amygdala

Our finding that DS individuals with AD, as compared to healthy DS individuals, had a significantly smaller corrected hippocampal volume is consistent with a report that the hippocampus is one of the brain regions most severely affected by amyloid plaques and non-functioning tumours (NFTs) in the DS brain (Hof *et al*. 1995). It is also consistent with two previous volumetric MRI studies of DS individuals with dementia (Pearlson *et al*. 1998; Aylward *et al*. 1999) and a number of MRI studies of AD patients in the general population (e.g. Double *et al*. 1996; Karas *et al*. 2003; Pennanen *et al*. 2004).

Our results suggest that reduction in hippocampal volume may provide a useful tool for the diagnosis of AD in people with DS, as has been proposed for AD in the general population (e.g. Laakso *et al*. 1996; Yamaguchi *et al*. 2002). For a brain region to be a useful indicator of a disease, it must be relatively unaffected by normal ageing but substantially affected in the diseased state. One previous study reported that hippocampal volume is relatively stable in healthy, non-demented DS adults (Aylward *et al*. 1999), as has also been reported in the general population (e.g. Sullivan *et al*. 1995). However, other volumetric MRI studies of non-demented individuals with DS have reported significant age-related reductions in hippocampal volumes (Kesslak *et al*. 1994; Krasuski *et al*. 2002). In our own sample of non-demented DS individuals there were no significant age-related differences in bulk-volume of the hippocampus. Accordingly, in our dataset hippocampal volume was effective in being able to discriminate between DS individuals with and without AD. Corrected total hippocampal volume was able to correctly categorize 92% of the non-demented DS individuals and 75% of DS individuals with AD. Thus, our results provide preliminary evidence that hippocampal volume may be of diagnostic value for individuals with DS, in particular to exclude the diagnosis of AD. We do not claim that volumetric MRI can be used as a stand-alone diagnostic tool for dementia in DS people. Rather, we suggest that in complex cases measurement of specific brain regions using MRI, when combined with careful clinical examination and recently published scales (Deb *et al*. 2007), will allow more accurate diagnosis and therefore more appropriate treatment.

We also found that DS individuals with AD had a significantly smaller corrected volume of right (but not left) amygdala, as compared to non-demented DS participants. The significance of this difference being only on the left side is unknown. However, this finding is consistent with one previous study that also reported a significant reduction in left, but not right, amygdala volume in demented DS individuals compared to non-demented DS controls (Pearlson *et al*. 1998). More generally, our finding of a reduction in amygdala volume is consistent with volumetric studies of AD in the general population (e.g. Busatto *et al*. 2003).

Caudate and putamen

DS individuals with AD had a significantly smaller volume of caudate, putamen and total striatum (caudate + putamen), as compared to healthy DS controls. Reductions in striatal volumes have not been reported previously in DS individuals with AD. However, significant volume reductions in caudate (but not putamen) have been reported by a number of VBM studies of AD in the general population (Rombouts *et al*. 2000; Frisoni *et al*. 2002; Karas *et al*. 2003).

The caudate and putamen are both classically thought to be involved in organizing and guiding complex motor function (e.g. Marsden, 1982). However, the striatum receives inputs from all cortical regions, and is also thought to be involved in learning and memory (Poldrack *et al*. 1999; Packard &

Knowlton, 2002). It is possible, therefore, that reductions in striatal volumes may contribute to memory and/or other cognitive deficits in DS people with AD.

Within our sample of non-demented DS individuals, putamen volume was subject to a significant age-related decrease, but caudate volume was stable with respect to age. This suggests that reductions in caudate volume are more likely than reductions in putamen volume to provide a diagnostic marker for AD in people with DS. In addition, in our sample corrected total caudate volume was able to correctly categorize 92% of the non-demented DS individuals and 80% of DS individuals with AD. Thus, volume of caudate (but not putamen) may be of diagnostic value to exclude the diagnosis of AD.

CSF

DS individuals with AD had a significantly larger corrected volume of left (but not right) peripheral CSF, as compared to non-demented DS controls. Peripheral CSF is a marker of cortical atrophy. This may suggest that, for unknown reasons, cortical atrophy in people with DS is greater in the left hemisphere than in the right.

We did not find that DS individuals with AD had significant differences in corrected volume of lateral ventricles or total ventricular space (lateral + third ventricles), as compared to non-demented DS controls. Thus, we did not replicate the results of a previous study that reported that DS individuals with AD had a significant increase in total ventricular volume, as compared to age-matched, non-demented DS controls (Prasher *et al*. 2003). Ventricular enlargement is a cardinal feature of AD in the general population. Our failure to detect significantly greater total ventricular volume in DS individuals with AD may indicate that the clinical presentation of AD in DS individuals requires a proportionally smaller reduction in total brain volume than in AD in the general population. Thus, the expression of the clinical phenotype of AD in DS may depend to a greater degree on medial temporal volume loss, which we did detect. In addition, in the general population the clinical presentation of AD may require additional loss of whole brain volume, as non-learning disabled individuals have a greater cognitive 'reserve'. Another possibility is that our DS + AD sample was composed of individuals with the equivalent of relatively mild AD, as more severely demented individuals with DS are generally unable to comply with the demands of MRI scanning. The differences in regional brain anatomy we found may therefore correspond only to mild AD in the general population.

Relationship between brain anatomy and cognitive function

We found that DS individuals with AD had significant reductions in volume of medial temporal regions (hippocampus and amygdala) and striatal structures (putamen and caudate). In healthy populations the hippocampi and amygdalae are implicated in memory function (Tranel & Hyman, 1990; Squire *et al*. 2004). Accordingly, in AD in the general population the early degeneration of the hippocampi and amygdalae is thought to underlie the memory impairments that are typical of (and occur early in) the disorder (e.g. Hyman *et al*. 1990). However, within DS individuals with AD, we found no evidence that regional brain anatomy was significantly related to cognitive function.

One possible explanation for our failure to detect relationships between regional brain anatomy and cognitive function is that our study suffered from a lack of statistical power; that is, that we were limited by the size of our DS + AD sample. Alternatively, cognitive deficits associated with AD in DS individuals may be related to subtle differences in brain anatomy, detectable only using VBM. Another possibility is that cognitive deficits in this population may be more closely related to factors other than differences in brain anatomy. These may include, for example, amyloid plaque density (Wisniewski *et al*. 1985), differences in brain metabolism and perfusion (Azari *et al*. 1994) and/or other neurobiological factors, such as brain *myo*-inositol concentration (Beacher *et al*. 2005). Further (and larger) studies are therefore required to relate other aspects of brain anatomy and metabolism to cognition in both non-demented and demented DS individuals.

Clinical utility of our findings

As this was a cross-sectional study, we could not determine the time course of changes, as opposed to differences, in brain anatomy. That would require a longitudinal approach. Therefore, it remains unclear whether changes in brain anatomy over time could be used to aid the clinical diagnosis of AD in people with DS. In addition, we do not suggest that any between-group differences we identified can be used alone as a diagnostic 'test'. However, the diagnosis of AD in learning disabled populations is usually more difficult than in the general population. We found that that some of the significant between-group differences in brain anatomy were reliable 'biomarkers' for the presence of AD. Thus, in future, the combination of routine medical practice and brain imaging (if practicable) may help to build confidence in clinical diagnosis.

Summary

DS individuals with AD have significant reductions in medial temporal and striatal volumes, and these may provide markers of clinical AD.

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Declaration of Interest

None.

References

Aylward EH, Li Q, Habbak QR, Warren A, Pulsifer MB, Barta PE, Jerram M, Pearlson G (1997). Basal ganglia volume in adults with Down syndrome. *Psychiatry Research* **74**, 73–82.

Aylward EH, Li Q, Honeycutt NA, Warren AC, Pulsifer MB, Barta PE, Chan MD, Smith PD, Jerram M, Pearlson GD (1999). MRI volumes of the hippocampus and amygdala in adults with Down's syndrome with and without dementia. *American Journal of Psychiatry* **156**, 564–568.

Azari NP, Horwitz B, Pettigrew KD, Grady CL, Haxby JV, Giacometti KR, Schapiro MB (1994). Abnormal pattern of cerebral glucose metabolic rates involving language areas in young adults with Down syndrome. *Brain and Language* **46**, 1–20.

Barta PE, Dhingra L, Royall R, Schwartz E (1997). Improving stereological estimates for the volume of structures identified in three-dimensional arrays of spatial data. *Journal of Neuroscience Methods* **75**, 111–118.

Beacher F, Simmons A, Daly E, Prasher V, Adams C, Margallo-Lana ML, Morris R, Lovestone S, Murphy K, Murphy DG (2005). Hippocampal myo-inositol and cognitive ability in adults with Down syndrome: an in vivo ^{1}H-MRS study. *Archives of General Psychiatry* **62**, 1360–1365.

Blessed G, Black SE, Butler T, Kay DW (1991). The diagnosis of dementia in the elderly. A comparison of CAMCOG (the cognitive section of CAMDEX), the AGECAT program, DSM-III, the Mini-Mental State Examination and some short rating scales. *British Journal of Psychiatry* **159**, 193–198.

Busatto GF, Garrido GE, Almeida OP, Castro CC, Camargo CH, Cid CG, Buchpiguel CA, Furuie S, Bottino CM (2003). A voxel-based morphometry study of temporal lobe gray matter reductions in Alzheimer's disease. *Neurobiology of Aging* **24**, 221–231.

Deb S, Hare M, Prior L, Bhaumik S (2007). Dementia screening questionnaire for individuals with intellectual disabilities. *British Journal of Psychiatry* **190**, 440–444.

Double KL, Halliday GM, Kril JJ, Harasty JA, Cullen K, Brooks WS, Creasey H, Broe GA (1996). Topography of brain atrophy during normal ageing and AD. *Neurobiology of Aging* **17**, 513–521.

Folin M, Baiguera S, Conconi MT, Pati T, Grandi C, Parnigotto PP, Nussdorfer GG (2003). The impact of risk factors of Alzheimer's disease in the Down syndrome. *International Journal of Molecular Medicine* **11**, 267–270.

Frisoni GB, Testa C, Zorzan A, Sabattoli F, Beltramello A, Soininen H, Laakso MP (2002). Detection of grey matter loss in mild Alzheimer's disease with voxel based morphometry. *Journal of Neurology, Neurosurgery and Psychiatry* **73**, 657–664.

Hof PR, Bouras C, Perl DP, Sparks DL, Mehta N, Morrison JH (1995). Age-related distribution of neuropathologic changes in the cerebral cortex of patients with Down's syndrome. *Archives of Neurology* **52**, 379–391.

Hon J, Huppert FA, Holland AJ, Watson P (1999). Neuropsychological assessment of older adults with Down's syndrome: an epidemiological study using the Cambridge Cognitive Examination (CAMCOG). *British Journal of Clinical Psychology* **38**, 155–165.

Huppert FA, Brayne C, Gill C, Paykel ES, Beardsall L (1995). CAMCOG – a concise neuropsychological test to assist dementia diagnosis: socio-demographic determinants in an elderly population sample. *British Journal of Clinical Psychology* **34**, 529–541.

Hyman BT, Van Hoesen GW, Damasio AR (1990). Memory-related neural systems in Alzheimer's disease: an anatomic study. *Neurology* **40**, 1721–1730.

Karas GB, Burton EJ, Rombouts SA, van Schijndel RA, O'Brien JT, Scheltens P, McKeith IG, Williams D, Ballard C, Barkhof F (2003). A comprehensive study of gray matter loss in patients with Alzheimer's disease using optimized voxel-based morphometry. *NeuroImage* **18**, 895–907.

Kesslak JP, Nagata SF, Lott I, Nalcioglu O (1994). MRI analysis of age-related changes in the brains of individuals with DS. *Neurology* **44**, 1039–1045.

Krasuski JS, Alexander GE, Horwitz B, Rapoport SI, Schapiro MB (2002). Relation of medial temporal volumes to age and memory function in nondemented adults with Down's syndrome: implications for the prodromal phase of Alzheimer's disease. *American Journal of Psychiatry* **159**, 74–81.

Laakso MP, Partanen K, Riekkinen P, Lehtovirta M, Helkala EL, Hallikainen M, Hanninen T, Vainio P, Soininen H (1996). Hippocampal volumes in Alzheimer's disease, Parkinson's disease with and without dementia, and in vascular dementia: an MRI study. *Neurology* **46**, 678–681.

Malamud N (1972). Neuropathy of organic brain syndromes associated with ageing. In *Advances in Behavioural Biology* (ed. C. M. Gaitz), pp. 63–87. Plenum Press: New York.

Marsden CD (1982). The mysterious motor function of the basal ganglia: the Robert Wartenburge lecture. *Neurology* **32**, 514–539.

Miniszek NA (1983). Development of Alzheimer disease in Down syndrome individuals. *American Journal of Mental Deficiency* **87**, 377–385.

Murphy DG, DeCarli C, McIntosh AR, Daly E, Mentis MJ, Pietrini P, Szczepanik J, Schapiro MB, Grady CL, Horwitz B, Rapoport SI (1996). Sex differences in human brain morphometry and metabolism: an in vivo quantitative magnetic resonanceimaging and positron emission tomography study on the effect of ageing. *Archives of General Psychiatry* **53**, 585–594.

Packard MG, Knowlton BJ (2002). Learning and memory functions of the basal ganglia. *Annual Review of Neuroscience* **25**, 563–593.

Pearlson GD, Breiter SN, Aylward EH, Warren AC, Grygorcewicz M, Frangou S, Barta PE, Pulsifer MB (1998). MRI brain changes in subjects with Down syndrome with and without dementia. *Developmental Medicine and Child Neurology* **40**, 326–334.

Pennanen C, Kivipelto M, Tuomainen S, Hartikainen P, Hänninen T, Laakso MP, Hallikainen M, Vanhanen M, Nissinen A, Helkala EL, Vainio P, Vanninen R, Partanen K, Soininen H (2004). Hippocampus and entorhinal cortex in mild cognitive impairment and early AD. *Neurobiology of Aging* **25**, 303–310.

Poldrack RA, Prabhakaran V, Seger CA, Gabrieli JD (1999). Striatal activation during acquisition of cognitive skill. *Neuropsychology* **13**, 564–574.

Prasher VP, Farrer MJ, Kessling AM, Fisher EM, West RJ, Barber PC, Butler AC (1998). Molecular mapping of Alzheimer-type dementia in Down's syndrome. *Annals of Neurology* **43**, 380–383.

Prasher V, Cumella S, Natarajan K, Rolfe E, Shah S, Haque MS (2003). Magnetic resonance imaging, Down's syndrome and Alzheimer's disease: research and clinical implications. *Journal of Intellectual Disabilities Research* **47**, 90–100.

Raz N, Torres IJ, Briggs SD, Spencer WD, Thornton AE, Loken WJ, Gunning FM, McQuain JD, Driesen NR, Acker JD (1995). Selective neuroanatomical abnormalities in Down's syndrome and their cognitive correlates: evidence from MRI morphometry. *Neurology* **45**, 356–366.

Roizen NJ, Patterson D (2003). Down's syndrome. *Lancet* **361**, 1281–1289.

Rombouts SA, Barkhof F, Witter MP, Scheltens P (2000). Unbiased whole-brain analysis of gray matter loss in Alzheimer's disease. *Neuroscience Letters* **285**, 231–233.

Roth M, Huppert FA, Mountjoy CQ, Tym E (1998). *The Revised Cambridge Examination for Mental Disorders of the Elderly*. Cambridge University Press: Cambridge.

Simmons A, Arridge SR, Barker GJ, Williams SC (1996). Simulation of MRI cluster plots and application to neurological segmentation. *Magnetic Resonance Imaging* **14**, 73–92.

Squire LR, Stark CE, Clark RE (2004). The medial temporal lobe. *Annual Review of Neuroscience* **27**, 279–306.

Sullivan EV, Marsh L, Mathalon DH, Lim KO, Pfefferbaum A (1995). Age-related decline in MRI volumes of temporal lobe gray matter but not hippocampus. *Neurobiology of Aging* **16**, 591–606.

Teipel SJ, Schapiro MB, Alexander GE, Krasuski JS, Horwitz B, Hoehne C, Möller HJ, Rapoport SI, Hampel H (2003). Relation of corpus callosum and hippocampal size to age in nondemented adults with Down's syndrome. *American Journal of Psychiatry* **160**, 1870–1878.

Teipel SJ, Alexander GE, Schapiro MB, Möller HJ, Rapoport SI, Hampel H (2004). Age-related cortical grey matter reductions in non-demented Down's syndrome adults determined by MRI with voxel-based morphometry. *Brain* **127**, 811–824.

Tranel D, Hyman BT (1990). Neuropsychological correlates of bilateral amygdala damage. *Archives of Neurology* **47**, 349–355.

Visser FE, Aldenkamp AP, van Huffelen AC, Kuilman M, Overweg J, van Wijk J (1997). Prospective study of the Alzheimer-type dementia in institutionalized individuals with Down syndrome. *American Journal of Mental Retardation* **101**, 400–412.

Wisniewski KE, Wisniewski HM, Wen GY (1985). Occurrence of neuropathological changes and dementia of Alzheimer's disease in Down's syndrome. *Annals of Neurology* **17**, 278–282.

WHO (1992). *The ICD-10 Classification of Mental and Behavioural Disorders. Clinical Descriptions and Diagnostic Guidelines*. World Health Organization: Geneva.

Yamaguchi S, Meguro K, Shimada M, Ishizaki J, Yamadori A, Sekita Y (2002). Five-year retrospective changes in hippocampal atrophy and cognitive screening test performances in very mild Alzheimer's disease: the Tajiri Project. *Neuroradiology* **44**, 43–48.