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ORIGINAL ARTICLE

Brain anatomy and ageing in non-demented adults with Down's syndrome: an *in vivo* MRI study

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Background. People with Down's syndrome (DS) are at high risk for developing dementia in middle age. The biological basis for this is unknown. It has been proposed that non-demented adults with DS may undergo accelerated brain ageing.

Method. We used volumetric magnetic resonance imaging (MRI) and manual tracing to compare brain anatomy and ageing in 39 non-demented adults with DS and 42 healthy controls.

Results. Individuals with DS had significant differences in brain anatomy. Furthermore, individuals with DS had a significantly greater age-related reduction in volume of frontal, temporal and parietal lobes, and a significantly greater age-related increase in volume of peripheral cerebrospinal fluid (CSF).

Conclusions. Non-demented adults with DS have differences in brain anatomy and 'accelerated' ageing of some brain regions. This may increase their risk for age-related cognitive decline and Alzheimer's disease (AD).

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Introduction

Down's syndrome (DS) is the most common genetic cause of learning disability (mental retardation), and is usually associated with having trisomy of chromosome 21. Volumetric magnetic resonance imaging (MRI) studies of DS have consistently reported that non-demented adults with DS have significantly smaller corrected volume of the cerebellum and hippocampus, as compared to healthy controls (Aylward *et al*. 1999; Pinter *et al*. 2001*a*). In addition, individuals with DS may be more prone to age-related cognitive decline and are at high risk for developing dementia (Visser *et al*. 1997), which most commonly replicates features of Alzheimer's disease (AD). This combination of a pre-existing learning disability with superimposed age-related cognitive decline and dementia is difficult to treat, and is an expensive management problem. However, the neurobiological associates of ageing in DS are poorly understood.

Adults with DS have increased peripheral physiological ageing (Capone, 2001). In addition, *post-mortem* studies have reported that, by 40 years of age, almost all individuals with DS develop amyloid plaques and neurofibrillary tangles in the brain (Mann, 1988). There is preliminary evidence that, within healthy adults with DS, there are significant age-related changes in cerebral blood flow (Rondal & Comblain, 2002) and the amyloidogenic compound *myo*-inositol (Huang *et al*. 1999). One MRI study reported an increase in qualitative markers of brain ageing in healthy adults with DS as compared to healthy controls (Roth *et al*. 1996). Thus, there are several lines of evidence suggesting that non-demented adults with DS may be subject to accelerated brain ageing.

Volumetric MRI studies have reported age-related changes in brain anatomy in non-demented adults with DS, including a significant reduction in volume of the hippocampus (Teipel *et al*. 2003), amygdala and

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posterior hippocampal gyrus (Krasuski *et al*. 2002) and the parietal and frontal cortices (Teipel *et al*. 2004). However, previous volumetric MRI studies of DS did not test for group differences in brain ageing between DS individuals and controls. Hence it is unknown whether non-demented adults with DS have greater loss of brain tissue with increasing age, as compared to the healthy population. We therefore used volumetric MRI to compare whole-brain anatomy in non-demented adults with DS and healthy controls.

We tested the hypotheses that, compared to controls, individuals with DS have: (1) significant differences in brain anatomy; (2) a significantly greater age-related decrease in total brain volume; and (3) (based on prior work) age-related decreases in brain volume that particularly affect frontal, temporal, parietal and hippocampal regions.

Method

Participants

We studied 39 non-demented adults with DS (27 males, 12 females) and 42 healthy controls (27 males, 15 females). Participants with DS were recruited locally from our Behavioural Genetics Service and from already identified clinical cohorts in Birmingham (Greenfields Monyhull Hospital) and Newcastle (Newcastle General Hospital), UK. Healthy controls were recruited locally from staff and students of King's College London. DS status was assessed in all participants by karyotyping. Dementia status was assessed using the Diagnostic Criteria for Research-10 (WHO, 1992). The DS and healthy control groups did not differ significantly in age: the means were 35 (range 18–66, S.D. = 11) and 35 (range 19–66 years, S.D. = 12) years respectively. Twenty-one of the 39 participants with DS were older than 35 years at the time of scanning. The DS and control groups also did not differ significantly in gender, ethnic origin, apolipoprotein E status or handedness.

All participants underwent standard physical, neurological and psychiatric screening, including routine blood tests (e.g. renal and liver function tests, full blood count and thyroid function tests) and clinical MRI. We excluded people with physical or psychiatric disorder affecting brain function (e.g. hypertension), or known history of birth trauma or head injury. We also excluded participants who were taking psychotropic medication at the time of the study. Finally, we excluded participants whose clinical MRI scans suggested significant additional brain damage, for example as indicated by the presence of white matter hyperintensities. The project was approved by the institutional review board and after complete description of the study to the participants, written informed consent, or assent, was obtained from them or their carers.

MRI protocol

Individuals with DS and controls were scanned using a 1.5-T GE Signa NV/*i* MR system (General Electric, USA) at the Maudsley Hospital, London. 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 scanned with a three-dimensional (3-D) inversion recovery prepared fast spoiled gradient-recalled acquisition in the steady state (SPGR) 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 (TI) was 450 ms, echo time (TE) was 2.8 ms, and the flip angle was 20° with one data average and a $256 \times 256 \times 124$ pixel matrix. 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). Left and right 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 left, right and total cranial volume, whole brain, frontal, prefrontal, temporal, parietal and occipital lobes, hippocampus, amygdala, cerebellum, caudate, putamen, lateral ventricles and peripheral cerebrospinal fluid (CSF).

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 (F.B.) 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: $r = 0.969$; whole brain volumes: $r = 0.977$; hippocampus: $r = 0.917$; amygdala: $r = 0.911$; caudate: $r = 0.936$; putamen: $r = 0.925$; striatum: $r = 0.933$; frontal lobes: $r = 0.950$; prefrontal: $r = 0.951$; temporal lobes: $r = 0.977$; parietal lobes: $r = 0.931$; occipital lobes: $r = 0.955$; cerebellum: $r = 0.961$; lateral ventricles: $r = 0.926$; peripheral CSF: $r = 0.932$; total ventricular space: $r = 0.964$; all p's < 0.001).

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Cognitive assessment

Cognitive ability was measured using the Cambridge Cognitive Examination (CAMCOG; Roth *et al*. 1998). The CAMCOG has been validated for use with individuals with DS (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. The CAMCOG did not produce ceiling or floor effects, with the exception of a small number of subtests. The CAMCOG incorporates, and is highly correlated with, the Mini-Mental State Examination (MMSE; Blessed *et al*. 1991).

The British Picture Vocabulary Scale (BPVS; Dunn *et al*. 1997) was used to test receptive vocabulary (which is highly correlated with full-scale IQ), to give an additional indication of overall cognitive function.

For each participant cognitive testing was conducted within 6 months of scanning.

Statistical analysis

Analysis of brain volumes was carried out using SPSS version 8.0 (SPSS Inc., USA). Normality of distribution was assessed in both groups and tested for significance using the Kolmogorov–Smirnov statistic. Neither group violated the assumption of normality, and therefore parametric tests of difference and correlation were used. Group differences in brain volumes were tested with independent sample t tests. Brain size is affected by head size. Thus group differences in brain volumes, expressed as percentages of cranial volume, were also tested with independent sample t tests.

The relevant scatterplots were examined and there was no evidence of nonlinearity. Therefore, linear regression was used to assess the relationships in each of the groups between brain volumes and age, and also between age and overall cognitive function, as measured by the total CAMCOG score. Linear regression was also used to test group × age interactions of brain volumes.

We compared brain ageing in frontal, temporal and parietal lobes and hippocampus, and then carried out further exploratory analyses of other brain regions and CSF volume.

The level of statistical significance was defined as $p<0.05$ (two tailed). We also considered the effect of performing the Bonferroni correction on those group differences that were significant at the 0.05 level.

Results

Regional brain volume differences

Individuals with DS had a significantly smaller cranial volume (i.e. head size) and total brain volume as compared to controls. Individuals with DS also had a significantly smaller percentage volume of left frontal lobe, left and total prefrontal regions and cerebellum bilaterally than controls (see Table 1; for a full version of this table see Table A1 in the Online Appendix). By contrast, individuals with DS had a significantly larger percentage volume bilaterally of parietal lobe, putamen and lateral ventricles, and of the left and total occipital lobe.

The relationship between age and brain volume

Within individuals with DS

Individuals with DS had a significant age-related reduction in most cortical brain regions (see Table 2; for a full version of this table see Table A2 in the Online Appendix). In addition, they had a significant age-related increase in volume of the lateral ventricles bilaterally volume and total peripheral CSF.

Within healthy controls

Within healthy controls there were no significant age-related differences in volume of any brain region, or CSF.

Comparison of brain ageing in DS to healthy controls

Compared to healthy controls, individuals with DS had a significantly greater age-related reduction in volume of the whole brain (see Table 2) and parietal lobes bilaterally, left and total frontal and prefrontal regions, and total temporal lobes (Fig. 1). Furthermore, individuals with DS had a significantly greater age-related enlargement in total volume of peripheral CSF (Fig. 2).

Cognitive function in the DS sample

The DS group had a mean mental age of 7 (range 3–17) years, as measured by the BPVS. The mean total CAMCOG score for the DS group was 55 (S.D. = 22), compared to 119 (S.D. = 3) for the healthy control group. Within individuals with DS, there was no significant age-related difference in overall cognitive function, as measured by the CAMCOG total score ($r = -0.223$, $p = 0.167$).

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Table 1. *Comparison of regional brain volumes (expressed as a percentage of cranial capacity) of non-demented adults with Down's syndrome (DS) and healthy controls*

	Mean percentage of cranial volume				
	DS ($n=39$)	Controls ($n=42$)	Difference	t	p
Whole brain					
Left	78.1	76.3	−1.8	−1.76	0.084
Right	79.2	77.6	−1.6	−1.20	0.234
Total	78.5	76.7	−1.8	−1.87	0.066
Frontal lobes					
Left	31.5	32.8	1.3	2.03	0.047[a]
Right	32.3	33.6	1.3	1.61	0.111
Total	31.8	32.9	1.1	1.85	0.070
Prefrontal lobes					
Left	10.3	11.0	0.7	2.19	0.032[a]
Right	10.6	11.3	0.7	1.83	0.071
Total	10.4	11.1	0.7	2.17	0.033[a]
Temporal lobes					
Left	7.67	7.51	−0.16	−0.63	0.531
Right	7.95	7.75	−0.20	−0.71	0.480
Total	7.80	7.52	−0.28	−1.26	0.210
Parietal lobes					
Left	29.6	28.5	−1.1	−2.00	0.049[a]
Right	30.4	28.8	−1.6	−2.16	0.034[a]
Total	30.0	28.5	−1.5	−2.64	0.010[a]
Occipital lobes					
Left	9.15	7.49	−1.66	−2.90	0.005[a]
Right	8.53	7.49	−1.04	−1.73	0.088
Total	8.83	7.49	−1.34	−2.57	0.013[a]
Hippocampus					
Left	0.384	0.405	0.021	1.10	0.277
Right	0.392	0.372	−0.020	−1.21	0.234
Total	0.389	0.389	0.000	−0.20	0.984
Amygdala					
Left	0.312	0.315	0.003	0.12	0.903
Right	0.316	0.293	−0.023	−1.12	0.269
Total	0.313	0.308	−0.005	−0.30	0.763
Caudate					
Left	0.462	0.477	0.015	0.58	0.562
Right	0.463	0.469	0.006	0.24	0.812
Total	0.464	0.468	0.004	0.15	0.883
Putamen					
Left	0.802	0.642	−0.160	−5.66	<0.001[a]
Right	0.756	0.591	−0.165	−7.40	<0.001[a]
Total	0.781	0.605	−0.176	−8.22	<0.001[a]
Cerebellum					
Left	7.9	10.2	2.3	10.78	<0.001[a]
Right	8.1	10.1	2.0	7.43	<0.001[a]
Total	8.0	10.2	2.2	11.63	<0.001[a]
Lateral ventricles					
Left	1.57	1.00	−0.57	−2.88	0.005[a]
Right	1.26	0.90	−0.36	−2.19	0.032[a]
Total	1.42	1.00	−0.42	−2.35	0.022[a]
Peripheral CSF					
Left	0.271	0.221	−0.050	−1.50	0.138
Right	0.319	0.327	0.008	0.13	0.897
Total	0.349	0.282	−0.067	−1.44	0.156

CSF, Cerebrospinal fluid.

Where regional brain volumes are presented for left or right (rather than total), these are expressed as percentages of cranial volume of that side only, rather than as a percentage of total cranial volume.

[a] Significant group difference.

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Table 2. *Group differences in brain ageing, in non-demented adults with Down's syndrome (DS) and healthy controls*

	Group differences		
	Slope	*t*	*p*
Whole brain			
Left	0.279	3.79	<0.001[a]
Right	0.278	2.66	0.010[a]
Total	0.254	3.73	<0.001[a]
Frontal lobes			
Left	0.134	2.67	0.009[a]
Right	0.126	1.87	0.066
Total	0.136	2.92	0.005[a]
Prefrontal lobes			
Left	0.048	3.79	<0.001[a]
Right	0.055	1.75	0.084
Total	0.056	2.47	0.016[a]
Temporal lobes			
Left	0.037	1.78	0.085
Right	0.045	1.85	0.069
Total	0.037	2.13	0.037[a]
Parietal lobes			
Left	0.144	2.48	0.015[a]
Right	0.178	2.96	0.004[a]
Total	0.116	2.66	0.009[a]
Occipital lobes			
Left	−0.027	−0.52	0.607
Right	−0.073	−1.38	0.171
Total	−0.034	−0.74	0.461
Hippocampus			
Left	0.002	0.97	0.337
Right	0	0.12	0.908
Total	0.002	1.13	0.261
Amygdala			
Left	−0.001	−0.31	0.757
Right	−0.001	−0.62	0.535
Total	0	0.01	0.993
Caudate			
Left	−0.003	−1.12	0.267
Right	0.002	0.78	0.437
Total	−0.001	−0.36	0.719
Putamen			
Left	0.001	0.58	0.562
Right	0.001	0.57	0.569
Total	0.003	1.52	0.134
Cerebellum			
Left	0.008	0.42	0.675
Right	0.017	0.74	0.464
Total	0.023	1.38	0.172
Lateral ventricles			
Left	−0.026	−1.59	0.117
Right	−0.017	−1.2	0.233
Total	−0.022	−1.6	0.114
Peripheral CSF			
Left	0.001	0.39	0.698
Right	−0.009	−1.82	0.074
Total	−0.01	−2.43	0.018[a]

CSF, Cerebrospinal fluid.
[a] Significant group × age interaction.

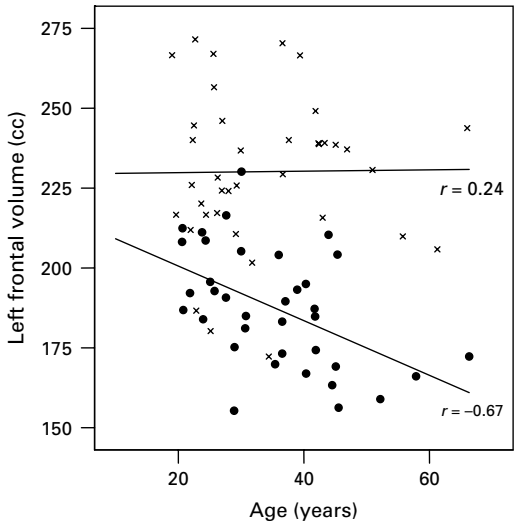

Fig. 1. Age-related differences in volume of the left frontal lobe in non-demented individuals with Down's syndrome (●) and healthy controls (×).

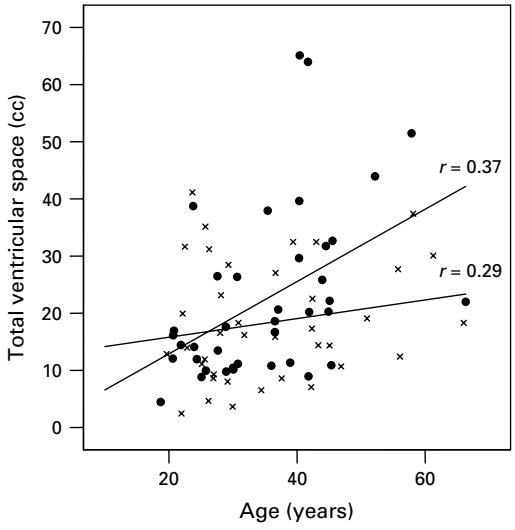

Fig. 2. Age-related differences in total ventricular space in non-demented individuals with Down's syndrome (●) and healthy controls (×).

Discussion

We found significant differences in brain anatomy between non-demented individuals with DS and controls. The between-group differences in regional brain anatomy are broadly consistent with previous (albeit smaller) volumetric MRI studies (Kesslak *et al*. 1994; Raz *et al*. 1995; Aylward *et al*. 1997; Pinter *et al*. 2001*a*). However, we also report, for the first time, evidence that non-demented individuals with DS, compared to healthy controls, have a significantly increased age-related reduction in some brain regions, and an associated significantly greater expansion of CSF; that is,

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non-demented individuals with DS have 'accelerated' brain ageing.

Our sample of individuals with DS did not have significant white matter hyperintensities, as assessed by clinical MRI. This suggests that additional brain damage (for example associated with post-operative hypoxic-ischaemic brain injury) was not a significant confound in our results.

This was a cross-sectional study. Thus we can only report age-related differences and not individual differences in ageing *per se*. Furthermore, we carried out multiple statistical tests, and so some of our results may be confounded by type 1 error. However, our finding of group differences in regional DS brain anatomy is in broad agreement with prior smaller reports. Moreover, of the group comparisons we performed for brain ageing, approximately 50% were significantly different, whereas by chance approximately 5% would be expected. In addition, many of the significant group differences in brain ageing that we found survived Bonferroni correction for multiple comparisons (left occipital lobes, left right and total putamen, left right and total cerebellum, left lateral ventricles). 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 unlikely that our findings can be explained by type 1 error.

To detect subtle differences in grey/white matter it is necessary to use voxel-based morphometry (VBM), a fully automated technique for examining whole-brain morphology. We used manual delineation methods and thus we only report differences in 'bulk volumes' (i.e. grey+white matter). A disadvantage of this method is that it cannot be used to determine the extent to which differences in brain volumes are driven by differences in grey matter or white matter. However, VBM uses statistical modelling assumptions that may not apply to populations with marked abnormalities in brain anatomy, such as people with DS. This method also has the advantage that it yields 'real' volumes in cubic centimetres that can readily be acquired (and compared) in other laboratories. For this reason hand tracing is still considered to be the 'gold standard' for measuring brain volumes.

Despite the limitations of this study, it is the largest volumetric MRI study of brain anatomy in DS to date. This is also the only study to directly compare the effect of age on regional brain anatomy in individuals with DS and healthy controls.

Group differences in regional brain anatomy

We found that individuals with DS had significantly smaller cranial volume, as compared to healthy controls, and significantly smaller 'raw' volume of most of the brain regions we measured (all except the left occipital lobe and putamen). However, some of these group differences in regional brain volume remained significant when expressed as a proportion of cranial volume and so cannot be explained simply by group differences in total head (or brain) size. Compared to controls, individuals with DS had a proportionately smaller volume of frontal regions and cerebellum but a proportionately larger volume of putamen, parietal and occipital lobes. These results are broadly consistent with previous volumetric MRI studies of non-demented individuals with DS (Kesslak *et al*. 1994; Raz *et al*. 1995; Aylward *et al*. 1997; Pinter *et al*. 2001*a*,*b*). Hence our results are probably reliable, and add to the increasing evidence that non-demented individuals with DS have abnormalities in regional brain anatomy.

Brain ageing in DS

We found that individuals with DS, but not controls, had a significant age-related reduction in volume of most cortical brain regions, but not subcortical regions. Furthermore, compared to healthy controls, individuals with DS had a significantly increased age-related reduction in some brain regions, and an associated significantly greater expansion of CSF. Thus non-demented adults with DS have 'accelerated' brain ageing of some regions.

Possible causes of accelerated ageing of the DS brain

The greater ageing we found in these brain regions in individuals with DS may be related to environmental differences (e.g. diet and/or physical health), but are also likely to be related to genetic factors. In full trisomy 21 (the most common form of DS), there is a 50% increased dosage of genes localized to chromosome 21. Some of these genes have been linked to ageing and/or AD, in particular the amyloid precursor protein (APP), superoxide dismutase-1 (SOD-1) and Na^+/*myo*-inositol co-transporter (SLC5A3) genes.

The APP gene produces amyloid precursor protein, which is present in neurones and astrocytes. The normal cellular function of APP is poorly understood, but it may act to protect cells against toxic and oxidative stress. The 'amyloid cascade hypothesis' is currently the dominant theory of the pathogenesis of AD. This holds that the accumulation in the brain of neurotoxic amyloid β-peptide (Aβ), for which APP is a precursor, leads to the formation of neuritic plaques, which in turn causes neuronal death. It has been proposed that the increased dosage of the APP gene in trisomy 21 cells leads to deposition of Aβ in the adult DS brain and increases the risk for AD in individuals with DS.

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This hypothesis is supported by evidence from studies of mouse models of DS (Masliah *et al*. 1996), neuropathological studies of the DS brain (Brooksbank *et al*. 1984) and molecular genetic studies (Prasher *et al*. 1998). Thus, the overexpression of the APP gene may be crucial to the increased brain ageing, and the risk of developing AD in individuals with DS.

Overexpression of the SOD-1 gene may also be related to premature brain ageing in adults with DS. SOD-1 protein is an enzyme that scavenges free superoxide radicals, a product of normal mitochondrial respiration. Some studies have reported increased SOD-1 activity in tissue from DS brains (Brooksbank *et al*. 1984). This may be linked to an increase in oxidative stress in the DS brain (Ianello *et al*. 1999). Oxidative stress damages DNA and it has been proposed to be one of the main determinants of ageing in the general population. It has therefore been proposed that overexpression of the SOD-1 gene may be related to premature brain ageing in adults with DS (Ianello *et al*. 1999).

Overexpression of the SLC5A3 gene has also been implicated in both the learning disability of DS and in the development of AD-type neuropathology. *Myo*-inositol is a polyol that significantly affects neuronal osmolarity and function. In addition, *myo*-inositol concentration, as measured by ^{1}H-MRS, is reported to be increased in the DS brain (Beacher *et al*. 2005). This increase in brain *myo*-inositol concentration in DS is probably a consequence of increased expression of the SLC5A3 gene. *Myo*-inositol is amyloidogenic (McLaurin *et al*. 1998) and people with AD in the general population are reported to have significantly increased brain *myo*-inositol concentration (Firbank *et al*. 2002). Therefore, increased *myo*-inositol concentration in the DS brain may also contribute to the development of AD-type neuropathology and accelerated ageing of the DS brain.

Significance of the regional distribution of accelerated brain ageing

We found that individuals with DS had age-related volume reduction in most cortical brain regions. These were significantly greater than controls in some regions but not in others. The significance of this regional pattern of accelerated brain ageing is unknown, but may include regional differences in the age-related accumulation of amyloid plaques and neurofibrillary tangles. Others have reported that, in individuals with DS, the temporal and frontal cortices and hippocampus are most affected by plaques and tangles (Mann, 1988). However, of these regions we found that individuals with DS had significantly greater age-related volume loss than controls only in frontal and temporal lobes. Hence, the differences we found may not be fully accounted for by greater accumulation of amyloid plaques and neurofibrillary tangles.

There is a good correspondence between those brain regions we found to be most affected by ageing in individuals with DS and those reported by ourselves and others as most affected by ageing in the general population (i.e. frontal, temporal and parietal regions; Resnick *et al*. 2003). This may indicate that the accelerated brain ageing of some brain regions in individuals with DS is due to an accelerated process of 'normal' ageing.

Implications of accelerated regional brain ageing

Accelerated brain ageing in individuals with DS may increase the risk for developing dementia, or modify symptom presentation with the development of dementia, as the disease process would act upon a lesser 'reserve'. For example, a slight age-related decrease in hippocampal volume in adults with DS (which we may have been unable to detect) may increase the risk for developing AD. In our DS sample we found that volumes of the left frontal, prefrontal and parietal regions were significantly reduced, as compared to controls, and were also subject to accelerated ageing. Thus, it is possible that brain regions that are proportionally reduced in volume are also more prone to accelerated ageing. In particular, the process of accelerated ageing on frontal regions (which in DS are already reduced in size) may partially explain why the earliest changes to occur in older adults with DS are reported to be most commonly in personality and behavioural differences, consistent with frontal lobe degeneration (Holland *et al*. 2000).

Preservation of hippocampal volume in individuals with DS

We did not find a significant age-related decrease in the volume of the hippocampus in the DS group. This is perhaps surprising because, as noted above, in older individuals with DS the hippocampus is reported to be particularly affected by plaques, neurofibrillary tangles and neuronal loss (Hof *et al*. 1995). Similarly, in AD in the general population, the hippocampus is one of the brain regions earliest and most severely affected by atrophy. Consistent with these findings, several previous MRI studies have reported a significant age-related decrease in hippocampal volume in our DS sample (Kesslak *et al*. 1994; Krasuski *et al*. 2002; Teipel *et al*. 2003). However, our failure to observe a significant age-related decrease in hippocampal volume in the individuals with DS we studied is consistent with other previous volumetric MRI studies of non-demented adults with DS (Raz *et al*. 1995; Aylward *et al*. 1999; Teipel *et al*. 2004).

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Furthermore, many older individuals with DS are reported to develop personality and behavioural changes, consistent with frontal lobe atrophy, without memory impairments suggestive of hippocampal atrophy (Holland *et al*. 2000).

Cognitive function in individuals with DS, and brain ageing in controls

We did not detect a significant age-related reduction in cognitive function in our DS sample. In addition, the sensitivity of our study was limited by its cross-sectional nature and by its sample size. Thus it is possible that individuals with DS in our sample were subject to age-related cognitive decline, but that we were unable to detect this. Nevertheless, our findings do suggest that measurable loss of brain tissue precedes easily detectable cognitive decline in individuals with DS.

In contrast to the DS group, within controls there were no significant age-related differences in any measure of brain volume (or cognitive function) across the age range we studied. This is consistent with previous studies of cognitive ageing in healthy individuals over the age range we investigated (Lindeboom & Weinstein, 2004).

Summary

We found that individuals with DS had significant differences from controls in brain anatomy. In addition, individuals with DS, but not controls, had a significant age-related reduction in the volume of most brain regions. Moreover, the ageing of some brain regions was significantly greater in individuals with DS than in controls. This may render individuals with DS more vulnerable to, and/or modify the clinical symptomatology of, age-related brain disease.

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Declaration of Interest

None.

Note

Supplementary material accompanies this paper on the Journal's website (http://journals.cambridge.org/psm).

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