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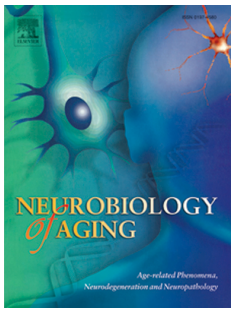


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# The Down syndrome brain in the presence and absence of fibrillar β–amyloidosis

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## Abstract

People with Down syndrome (DS) have a neurodevelopmentally distinct brain and invariably develop amyloid neuropathology by age 50. This cross-sectional study aimed to provide a detailed account of DS brain morphology and the changes occuring with amyloid neuropathology. Forty-six adults with DS underwent structural and amyloid imaging—the latter using Pittsburgh Compound–B (PIB) to stratify the cohort into PIB–positive (n=19) and PIB–negative (n=27). Age-matched controls (n=30) underwent structural imaging. Group differences in deep grey matter volumetry and cortical thickness were studied. PIB-negative people with DS have neurodevelopmentally atypical brain, characterised by disproportionately thicker frontal and occipitoparietal cortex and thinner motor cortex and temporal pole with larger putamina and smaller hippocampi than controls. In the presence of amyloid neuropathology, the DS brains demonstrated a strikingly similar pattern of posterior dominant cortical thinning and subcortical atrophy in the hippocampus, thalamus and the striatum, to that observed in non-DS Alzheimer's disease. Care must be taken to avoid underestimating amyloid–associated morphological changes in DS due to disproportionate size of some subcortical structures and thickness of the cortex.

Keywords: Alzheimer's disease, amyloid, cortical thickness, Down syndrome, grey matter volume

## Abbreviations

AD – Alzheimer's disease; CAMCOG - Cambridge Examination for Mental Disorders in Older people with DS and Others with Intellectual Disabilities; DS – Down syndrome; MRI – magnetic resonance imaging; PET – positron emission tomography; PIB – Pittsburgh Compound-B.

# 1 Introduction

People with Down syndrome (DS) are known to have developmentally altered brain structure caused by trisomy of chromosome 21. Children with DS present with delayed maturation of the central nervous system, which has been linked to prenatal arrest of neurogenesis and synaptogenesis (Schmidt-Sidor *et al.*, 1990; Wisniewski, 1990). Post–mortem studies in adults with DS have found several brain abnormalities, including reduced gross brain weight, a lower number and depth of cerebral sulci, enlarged ventricles and hypoplasia of several brain structures such as the brainstem, cerebellum, frontal and temporal lobes. In contrast, subcortical structures are shown to be relatively preserved (de la Monte and Hedley-Whyte, 1990; Dierssen, 2012; Dierssen and Ramakers, 2006; Lott and Dierssen, 2010; Delabar *et al.*, 2006). Imaging studies in adults with DS have corroborated the post–mortem findings by showing widespread cerebral hypoplasia and ventricular enlargement in comparison to typically developing individuals [Supplementary Table 1, Kesslak *et al.* (1994); Raz *et al.* (1995); Roth *et al.* (1996); Frangou *et al.* (1997); Aylward *et al.* (1997b); Pearlson *et al.* (1998); Aylward *et al.* (1997a); Aylward *et al.* (1999); Pinter *et al.* (2001); Krasuski *et al.* (2002); Teipel *et al.* (2003); White *et al.* (2003); Prasher *et al*. (2003); Teipel *et al*. (2004); Beacher *et al.* (2009); Beacher *et al*. (2010); Koran *et al.* (2014)]. The vast majority of neuroimaging studies, however, are based on region–of–interest volumetry, which is only able to detect volumetric changes in predetermined regions. There is a need to study the structural morphology of the whole DS brain in a more unbiased way.

In addition to the developmental abnormalities, people with DS are at high risk for early–onset Alzheimer's disease (AD) and have been found to deposit β–amyloid plaques from about 40 years of age (Mann *et al.*, 1990; Mann *et al.*, 1984; Annus *et al.*, 2016). Similar to sporadic AD, significant amyloid binding with PET is found before any signs of cognitive or functional decline in DS (Landt *et al.*, 2011; Handen *et al.*, 2012; Hartley *et al.*, 2014; Annus

*et al.*, 2016). Yet previous structural imaging studies (see Supplementary Table 1) have aimed to characterise the developmental alterations of the adult DS brain by studying non–demented individuals; such studies are, therefore, potentially confounded through the aggregation of amyloid positive and negative participants. For instance, four previous neuroimaging studies (Pearlson *et al.*, 1998; Aylward *et al.*, 1999; Prasher *et al.*, 2003; Beacher *et al.*, 2009) aimed to characterise cerebral atrophy associated with AD in DS by comparing cognitively stable individuals to those with a clinical diagnosis of dementia. It is highly likely, however, that a sizable proportion of cognitively stable individuals already had amyloidosis and it is known from the general population (Desikan *et al.*, 2010; Dickerson *et al.*, 2009; Dickerson and Wolk, 2011) that abnormalities in cortical structure occur at presymptomatic stages of AD. As such, the present cross-sectional study aimed to characterise the morphology of the adult DS brain in the absence of amyloid deposits and to describe the changes seen in the presence of fibrillar β–amyloid neuropathology.

## 2 Materials and methods

### 2.1 Study design and participants

Forty–six adults with DS and 30 typically developing participants (controls) took part in the present study. The DS cohort is the same as that reported in a previous amyloid PET study (Annus *et al.*, 2016) with the exception of two amyloid negative and one amyloid positive participant, whose magnetic resonance imaging (MRI) scans were of inferior quality (motion artefact evident on visual inspection) and hence unsuitable for reliable morphometric analysis. Adults with DS were identified via clinical and social services for people with intellectual disabilities in England and Scotland and via the DS Association (UK), whereas volunteers with typical neurodevelopment were recruited from the local community via

advertisement. Control participants were screened to exclude neurological and major psychiatric illness and developmental disorders. All study participants were screened for contraindications to MRI. Written consent was obtained from typically developing controls and all adults with DS with capacity to consent. Verbal assent was obtained from participants with DS lacking capacity and a written assent was provided by an appointed consultee, in accordance with the UK Mental Capacity Act (2005). Ethics and research and development approvals were granted by the National Research Ethics Committee of East of England – Norfolk and Cambridgeshire and Peterborough NHS Foundation Trust, respectively.

## 2.2 Clinical assessments

All participants with DS had previously received a clinical diagnosis of DS based on the characteristic phenotype with full trisomy 21 confirmed in 33 DS participants by karyotyping. All participants with DS were assessed for dementia using the Cambridge Examination for Mental Disorders in Older people with DS and Others with Intellectual Disabilities informant interview as described previously (Annus *et al.*, 2016) and allocated into categories of “Stable cognition”, “Cognitive decline” and “Dementia”. Dementia was diagnosed in accordance with the International Classification of Diseases-10 criteria and diagnosis of “Cognitive decline” was given to participants with evidence of functional decline in one or more cognitive domains, while insufficient to satisfy the full criteria for dementia. All DS participants, except three who had severe dementia and were untestable, were administered the cognitive function assessment – CAMCOG – part of the Cambridge Examination for Mental Disorders in Older people with DS and Others with Intellectual Disabilities. With the exception of one demented individual who was receiving Donepezil, no participants were using anti-dementia medications.

## 2.3 Magnetic resonance imaging acquisition

All participants underwent an anatomical MRI scan on a Siemens Verio 3T scanner with 12 channel head coil (Siemens AG, Erlangen, Germany) using the 3D T1–weighted magnetisation–prepared, rapid gradient–echo pulse sequence with the following parameters: repetition time / echo time / inversion time / flip angle = 2300ms/ 2·98ms/ 900ms/ 9°, 256x240x176 matrix dimensions, and 1x1x1 $mm^3$ voxel size. Receiver bandwidth and echo spacing were 240 Hz/pixel and 7.1 ms, respectively and parallel acceleration was disabled. The imaging protocol included whole–brain, T2–weighted, half–Fourier acquisition, single–shot turbo spin echo sequence (repetition time/ echo time/ flip angle/ turbo factor = 1500ms/ 79ms/ 150°/ 256; 0.9x0.7x4.0 $mm^3$ voxel size) to assess for vascular pathology and incidental lesions. For all acquisitions, the field of view was aligned in stereotactic space, with the axial plane aligned to the anterior commissure – posterior commissure line and the sagittal plane to the interhemispheric fissure.

## 2.4 Positron emission tomography using [11C]–Pittsburgh Compound–B

Details of the PIB PET data acquisition and processing have been published previously (Annus *et al.*, 2016). Briefly, PIB PET images were acquired in 3D mode on a GE Advance scanner (General Electric Medical Systems, Milwaukee, WI, USA) for 90 minutes post–PIB injection in 58 frames. Only participants with DS were assessed for amyloid. Cortical regional PIB analysis was based on Brodmann areas, whereas subcortical regions of interest were based on deep grey matter parcellations using FIRST (Patenaude *et al.*, 2011) and included the striatum (caudate nucleus and putamen), amygdala, thalamus, and hippocampus. For each region of interest, non–displaceable binding potential was obtained using a basis function implementation of the simplified reference tissue model (Gunn *et al.*, 1997) with

superior cerebellar grey matter as reference region. PIB positive and PIB negative groups were assigned on the basis of striatal non–displaceable binding potential, which had previously revealed a bimodal distribution with clear separation of positive and negative groups (Annus *et al.*, 2016). Of the 46 participants with DS, 19 were PIB–positive.

## 2.5 Image processing

### 2.5.1 Cortical thickness analysis

Cortical thickness analysis was conducted using FreeSurfer (v5.3, available from https://surfer.nmr.mgh.harvard.edu). The detailed procedure for surface reconstruction and estimation of cortical thickness has been described previously (Dale *et al.*, 1999; Fischl *et al.*, 1999; Fischl and Dale, 2000). Image processing involved automated non-uniformity bias correction, skull stripping, segmentation of the white matter and estimation of the grey/white matter boundary. Segmented and skull–stripped data of all participants were visually inspected for parcellation errors and topological defects in the grey/white matter boundary were manually corrected. The grey/white boundary served as a starting point for a deformable surface algorithm to compute the grey/white and pial surfaces, from which cortical thickness is calculated as the closest distance from the grey/white matter boundary to the pial surface at each vertex on the tessellated surface. Thickness measurements were mapped on the inflated surface of each participant's brain reconstruction for visualisation of data across the entire cortical surface. The thickness measurements using this technique have been shown to be both valid (Rosas *et al.*, 2002) and reliable (Dickerson *et al.*, 2008). Each participant's brain was then morphed and aligned to a spherical common surface template using a high–resolution surface–based averaging technique that aligns cortical folding patterns by individual sulci and gyri. Prior to analysis, the data was smoothed with a 25mm full–width at

half–maximum Gaussian kernel, the rationale for using a large kernel size has been published previously (Diaz-de-Grenu *et al.*, 2014). Statistical analysis was performed using the QDEC module implemented in FreeSurfer. For each hemisphere, General Linear Model was applied to estimate variations in cortical thickness at each vertex of the surface. Statistical surface maps were created using a vertex–wise statistical threshold of $p<0.05$ corrected for false-discovery rate at $q<0.05$. Covariate of interest analysis in FreeSurfer demonstrated no significant gender or total intracranial volume (TIV) specific regional differences in cortical thickness between PIB–negative group and neurotypical controls, resulting in the exclusion of both covariates from the statistical models (data not shown). Furthermore, β–amyloid has been shown to be a function of age in people with DS (Annus *et al.*, 2016) and by controlling for age, the true effects of Alzheimer's disease would be removed. A subgroup analysis was conducted in age–matched PIB–negative and PIB–positive group by including all individuals, who were in the age bracket of 39–48 years representing the time from first evidence of amyloid binding to the whole cohort being positive on PIB PET [for detailed results, see Annus *et al.* (2016)].

### 2.5.2 Deep grey matter volumetry

Deep brain regions of interest were defined by constructing a mask of these structures using FIRST [Patenaude *et al.* (2011), available from: http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FIRST]. Individual structural neuroimaging data was registered by a two–stage affine transformation to a standard Montreal Neurological Institute space with $1mm^3$ resolution using 12 degrees of freedom, after which the registered data was fitted with ‘a surface mesh’ modelled using a multivariate Gaussian model based on the shape and intensity information from the normalised T1–images (Patenaude *et al.*, 2011). The segmentation was performed on all

subcortical structures using the run_first_all wrapper with default settings and visually inspected for errors and misregistrations. As a result, nucleus accumbens, brain stem and globus pallidus were excluded from the analyses due to their small size, poor segmentation and high frequency of calcified lesions, respectively. Volumes of the structures of interest (putamen, caudate nucleus, thalamus, hippocampus and amygdala) for each hemisphere were calculated and corrected for TIV (Jack *et al.*, 1989). To limit the number of statistical tests, volumes of the left and right hemisphere structures were averaged for group comparisons. TIV and total brain volumes were determined by summing the relevant tissue classes using Statistical Parametric Mapping (Pengas *et al.*, 2009). All calculated volumes were normally distributed across study groups (Shapiro–Wilk test, all $p>0.05$), thus parametric tests in SPSS Statistics 22.0 (IBM, Corp.) were implemented for statistical analyses. Between–group differences were assessed using One-way ANOVA, whereas independent group and correlation analyses were conducted using Independent sample t–test (all two–tailed) and Pearson's correlation test, respectively. The relationship between categorical variables was assessed using Chi–squared test. A significance level of $p<0.05$ was used for all inferences with results reported as mean and standard deviation.

## 3. Results

### 3.1 Demographics and summary measures

Participant demographics are provided in Table 1. Participants in the PIB–negative group were significantly younger than controls ($t(48)= –4.311$, $p<0.001$) and the PIB–positive group ($t(37)= –6.722$, $p<0.001$), whereas controls and PIB–positive group were of similar ages ($t(47)=1.491$, $p=0.143$). The Control group had significantly larger TIV than PIB–negative ($t(55)=7.370$, $p<0.001$) and PIB–positive ($t(47)=5.535$, $p<0.001$) individuals with

DS, while there was no difference in TIV between the two DS groups (t(44)=0.735, p=0.466). The PIB–positive group had significantly lower TIV–corrected total brain volume than PIB–negative group (t(44)= –5.304, p<0.001), as well as controls (t(47)= –4.444, p<0.001). PIB–negative and control groups had similar TIV–corrected total brain volume (t(55)= –0.189, p=0.850; Fig. 3). Furthermore, on average the isocortex in the PIB–negative group was 4.3% thicker than in controls and 4.9% thicker than in the PIB–positive group, whereas PIB–positive and control group had similar mean global cortical thickness (0.56% lower in PIB–positive, Supplementary Fig. 1). No differences were observed in the cognitive function test CAMCOG between PIB–negative and PIB–positive groups (t(41)= –1.057, p=0.297). Note, however, that three individuals in the PIB–positive group were untestable because of dementia—for this reason analyses were also run excluding these three individuals in order to contrast PIB–positive and PIB–negative participants matched for CAMCOG performance. Excluding these three severely demented individuals did not influence the findings reported for the overall PIB–positive group (Table 1). Interestingly, even the cognitively stable participants in the PIB–positive group had significantly lower TIV–corrected total brain volume (1,087.98 ± 72.82 $cm^3$ vs 1,148.05 ± 31.27 $cm^3$, respectively; t(29)= –3.232, p=0.003) and lower mean global cortical thickness (2.58 ± 0.10 mm vs 2.68 ± 0.10mm, respectively; t(29)=2.425, p=0.022) than cognitively stable participants in the PIB–negative group.

[TABLE 1 HERE]

## 3.2 Cortical thickness

### 3.2.1 PIB–negative Down syndrome vs Controls

The vertex–wise analysis in the PIB–negative group compared with controls demonstrated highly significant cortical thinning in the precentral gyrus; significant thinning was also found in the temporal pole with additional small areas in subgenual anterior cingulate and retrosplenial cortex (Fig. 1). Widespread cortical thickness increases relative to controls were evident in medial and lateral prefrontal cortex; parietal, precuneus and posterior cingulate cortex; postcentral gyrus; occipital and postero-inferior temporal cortex. Controlling for age differences between PIB–negative and Control group did not alter the main findings (see Supplementary Fig. 2).

[FIGURE 1 HERE]

### 3.2.2 PIB–positive Down syndrome vs PIB–negative Down syndrome

Vertex–wise analysis of cortical thickness in the PIB–positive compared to PIB–negative group revealed large confluent clusters of cortical thinning in parieto–temporo-occipital cortices, posterior cingulate and precuneus cortices along with some small and scattered changes in prefrontal areas. The extent of cortical thinning was more marked in the right hemisphere. In contrast, there were some small, weakly significant areas of greater thickness in the PIB–positive group in the right sub-genual cortex and left precentral gyrus (Fig. 2).

Removal of the three PIB-positive DS individuals, who were too advanced to complete the CAMCOG, did not alter the reported findings (data not shown). While PIB–negative group was significantly younger than PIB–positive, matching the groups for age is problematic because, by definition, transition to amyloid positivity is a function of age in people with DS [see Annus *et al.* (2016)]. Nonetheless, the age bracket from 39 to 48 years contained an overlap of PIB–positive (n=9) and PIB–negative (n=13) participants that were matched for age ($t(20)=1.481$, $p=0.154$). Reducing the power by only looking at this subgroup meant that the significance of the changes diminished, however at $p(uncorr)<0.05$ a similar atrophy pattern to that seen in the full cohort contrast was evident (Supplementary Fig. 3).

[FIGURE 2 HERE]

## 3.3 Deep grey matter volumetry

Compared to controls, the PIB–negative group had significantly larger TIV–corrected putamina ($t(55)= 5.351$, $p<0.001$) and smaller hippocampi ($t(55)=4.951$, $p<0.001$), whereas no volumetric differences were identified in the caudate nucleus and thalamus. The results remained unaltered, when corrected for differences in age between the two groups (data not shown). Relative to the PIB–negative group, the PIB–positive group demonstrated significantly atrophic caudate nucleus ($t(44)=2.323$, $p<0.05$), putamen ($t(44)= 5.52$, $p<0.001$), thalamus ($t(44)= 3.277$, $p=0.01$) and hippocampus ($t(44)= 4.258$, $p<0.001$), whereas only

thalamic ($t(47)= 4.289$, $p<0.001$) and hippocampal volumes ($t(47)= 8.361$, $p<0.001$) were smaller when compared to controls. There were no significant differences in the TIV–corrected volumes of amygdala ($F(3,75)= 0.878$, $p=0.42$) across the three groups (Fig. 3). Furthermore, the inclusion of three severely demented individuals in the PIB–positive group, who were untestable on the CAMCOG assessment, had no impact on the deep grey matter volumetry findings in the PIB–positive group (unfilled circles, Fig. 3).

[FIGURE 3 HERE]

## 4 Discussion

The present study demonstrated a distinct neurodevelopmental phenotype of the DS brain with evidence of a thicker cortical ribbon particularly in the frontal and occipital lobes and thinner motor cortex. Development of fibrillar β–amyloidosis in people with DS is associated with a widespread posterior cortical thinning and subcortical atrophy in a pattern highly concordant with that seen in sporadic (Dickerson *et al.*, 2009; Fjell *et al.*, 2014; Jack *et al.*, 2009) and familial AD (Fortea *et al.*, 2010; Cash *et al.*, 2013). This study is the first of its kind to provide a comprehensive analysis of the cortical and subcortical landscape of the adult DS brain in groups clearly defined according to amyloid status.

### 4.1 The structure of the Down syndrome brain without amyloid

It is expected that the DS brain differs qualitatively from that of the typically-developing population. The aim of the contrast of amyloid-negative DS to healthy controls was to map these differences and, therefore, to aid interpretation of the changes that then occur in the DS brain in the presence of amyloid. With a mean age of 46 years, it was considered highly unlikely that the control group would be contaminated with amyloid-positive participants. In line with previous work (see Supplementary Table 1), adults with DS presented with significantly lower TIV compared to neurotypical controls. The current findings indicate, however, that the DS brain is not simply a downscale model of the typically developed brain but has a distinct topography of regions that are disproportionally smaller or larger with respect to the smaller brain size. In the absence of amyloid, the brain of people with DS is characterised by atypically and disproportionally thicker cortex in the frontal, parietal, occipitotemporal and posterior cingulate areas. Furthermore, people with DS have neurodevelopmentally thinner motor cortices and temporal poles. The present findings are in line with a recent report of increased cortical thickness in the frontal, parietal and occipital lobes in children and young adults with DS [mean age 15 years, range 5–24 years; Lee *et al.* (2015)], demonstrating that a largely thicker cortex is present already in childhood and persists into adulthood in individuals with DS. However, the authors only focused on the pattern of thicker cortex in the DS youth in comparison to typically developing youth and did not investigate the reverse contrast, thus possibly missing the pattern of cortical thinning described in the present study. Interestingly, the regions that are atypically thicker in DS are characterised by pronounced cortical thinning during brain development in adolescents without trisomy 21 (Vandekar *et al.*, 2015). This suggests a delay in the cortical thinning in DS and that the abnormalities in the development and maturation of the cortex extend beyond early development well into adulthood.

In deep grey matter structures, the most striking differences between people with DS and neurotypical controls was in the striatum – specifically that the putamen was disproportionately enlarged in amyloid negative adults with DS. Disproportionally greater volume of the putamen has been previously found in a morphometry study of children (Menghini *et al.*, 2011) and in non–demented adults with DS (Beacher *et al.*, 2010; Aylward *et al.*, 1997b), when compared to typically developing individuals. This again points to a neurodevelopmental origin of the observed structural enlargement, in line with the findings of increased cortical thickness as a result of abnormal cortical development and maturation in DS.

The hippocampi were disproportionally smaller in PIB–negative individuals with DS compared to neurotypical controls – a finding consistent with previous in vivo volumetry reports (Menghini *et al.*, 2011; Smigielska–Kuzia *et al.*, 2011; Kesslak *et al.*, 1994; Raz *et al.*, 1995; Krasuski *et al.*, 2002; White *et al.*, 2003). As the current study was cross-sectional, it cannot address whether this reduction in hippocampal volume in adults with DS is developmental (hypoplasia) or acquired (atrophy). It would seem, however, to almost certainly represent hypoplasia because past studies have found decreased hippocampal volume in adults under the age of 30 years (Raz *et al.*, 1995), as well as in adolescents (Menghini *et al.*, 2011) and children (Smigielska–Kuzia *et al.*, 2011) with DS. Although these past studies did not include amyloid imaging, it seems reasonable to assume, based on amyloid PET (Annus *et al.*, 2016) and pathology (Mann and Esiri, 1989) studies, that such participants would have been amyloid negative. The rest of the subcortical structures, including the thalamus and the amygdala, did not exhibit any DS specific characteristics in the absence of PIB binding and were neurodevelopmentally proportional to those of typically developing controls.

## 4.2 The PIB positive Down syndrome brain

A significant reduction in TIV–corrected total brain volume was observed in the PIB–positive group, when compared to the PIB–negative group. In addition to marked volumetric differences, amyloid positive individuals also presented with significantly lower mean global cortical thickness than their amyloid negative counterparts. This reduction in both volume and cortical thickness was significant even in the cognitively stable PIB–positive participants, demonstrating that, in keeping with sporadic (Becker *et al.*, 2011; Aizenstein *et al.*, 2008) and familial AD (Klunk *et al.*, 2007; Villemagne *et al.*, 2009), volume loss and cortical thinning is measurable before any clinical signs of cognitive decline in people with DS. The neocortex of PIB–positive adults with DS exhibited a pattern of posterior dominant cortical thinning mapped to the parieto–temporo-occipital cortices laterally and to the medial posterior cingulate and precuneus cortices. This pattern of reduced thickness in DS was highly similar to that observed in sporadic and familial AD (Boxer *et al.*, 2003; Cash *et al.*, 2013; Du *et al.*, 2007; Fjell *et al*., 2014; Gili *et al*., 2011). The volumes of putamen and caudate were significantly lower in PIB–positive individuals with DS compared to either the PIB–negative group or typically developing controls. This result highlights the importance of amyloid stratification in DS – the striatal volume reduction would be missed entirely if one examined volumetric changes in PIB–positive DS only in comparison to a neurotypical control group. The striatum has been receiving increasing interest in the field of AD, particularly as it has been shown to be the first site of PET amyloid binding in the familial forms of early onset AD (Klunk *et al.*, 2007; Koivunen *et al.*, 2008; Remes *et al.*, 2008; Villemagne *et al.*, 2009; Pievani *et al.*, 2013) and recently in people with DS (Annus *et al.*, 2016; Handen *et al.*, 2012).

The PIB–positive group demonstrated significant reduction in the thalamic volume, when compared to amyloid negative individuals. PIB positivity was also associated with marked

hippocampal volume reduction, when contrasted to PIB–negative DS group. As already noted, the TIV–corrected hippocampal volumes in PIB–negative individuals with DS were, in turn, significantly smaller than controls. Hippocampal atrophy is an expected finding in AD, though it is interesting to note that the effect size was comparable to that for putaminal atrophy (Fig. 3) in the amyloid–positive DS group. Given that many of the amyloid–positive individuals in the present series were asymptomatic, these findings suggest that atrophy becomes measurable very early after the conversion to amyloid positivity, although this hypothesis would need to be proven in a longitudinal sample.

### 4.3 Limitations

The present study is the first in characterising the brain morphology in neuropathologically clearly defined groups of amyloid positive and negative adults with DS. There were, however, inevitable age differences between the PIB–negative and PIB–positive group as a result of age–dependent threshold of amyloidosis in the DS population (Annus *et al.*, 2016). As such, it is not possible to control for the differences in age in the statistical models without removing the effects of amyloid. Although the lack of age–matched groups is a limitation of the present study, repeating the cortical thickness analysis in smaller (n=22) but age–matched groups of 39–48 year–olds yielded similar results (Supplementary Fig. 3). Although the significance (expectedly) diminished, the results were consistent with the full group analysis suggesting that they were not spurious and, in turn, making it very unlikely that the whole group results were merely driven by between–group age differences. Three individuals in the PIB-negative group were diagnosed with dementia (n=2/3) or cognitive decline (n=1/3) albeit having no evidence of amyloidosis in PIB-PET. Diagnosing dementia in people with intellectual disabilities (including DS) is a challenge with an acknowledged risk of

uncertainty, particularly exacerbated by the presence of underlying intellectual disability, frequent lack of information about individual's premorbid level of functioning and difficulties in communication and therefore heavy reliance on informant opinion (Burt et al., 1998; for discussion see Annus et al., 2016). Furthermore, changes associated with amyloid deposition in DS are described using a cross–sectional dataset. While longitudinal studies are needed to understand better the relationship between sub/cortical atrophy and amyloidosis, the present findings have highlighted that, in the presence of confirmed amyloidosis, the pattern of cortical thinning is similar across AD regardless of aetiology. Finally, it will be of interest in future studies with greater power to examine the severity of atrophy stratified not just for amyloidosis, but also with respect to clinical status (i.e. stable cognition/cognitive decline/dementia); in the present cohort (see Table 1) such a stratification resulted in groups that were too small to reliably address this issue.

## 5 Conclusion

This study is the first to describe the cortical landscape of the adult DS brain in distinct neuropathologically defined groups. Adults with DS presented with significant neuroanatomical differences from typically developing controls, which were further exacerbated in those individuals with evidence of amyloid pathology on a PIB PET scan. In the absence of amyloid, people with DS had smaller brain volume but with atypically thicker cortex in the frontal and occipitoparietal cortices and thinner motor cortex and temporal pole compared to controls. The data also demonstrated that, compared to the general population, people with DS had disproportionately larger putamina and smaller hippocampi, likely a result of abnormal brain development and maturation. In the presence of amyloidosis, adults with DS demonstrated posterior dominant cortical thinning as well as atrophy in the hippocampi, thalami and the striatum in a strikingly similar pattern as observed in sporadic and familiar AD. The data further showed that people with DS can tolerate significant

cortical atrophy in the presence of amyloid without deleterious effects on their cognitive function. The present study has highlighted the importance of first understanding the neuroanatomical characteristics of the DS brain before any assessments of the effects of amyloid are undertaken. Thus, care must be taken when characterising amyloid–related structural changes in individuals with DS to avoid underestimation of the observed morphology due to disproportionate size of some deep grey matter structures and increased thickness of the cortex.

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## Disclosure Statement

The authors report no conflict of interest.

## 7 References

Aizenstein, H. J., Nebes, R. D., Saxton, J. A., Price, J. C., Mathis, C. A., Tsopelas, N. D., Ziolko, S.K., James, J.A., Snitz, B.E., Houck, P.R., Bi, W., Cohen, A.D., Lopresti, B.J., DeKosky, S.T., Halligan, E.M., Klunk, W.E.. Frequent amyloid deposition without significant cognitive impairment among the elderly. Arch Neurol 2008. 65, 1509-17.

Annus, T., Wilson, L. R., Hong, Y. T., Acosta–Cabronero, J., Fryer, T. D., Cardenas–Blanco, A., Smith, R., Boros, I., Coles, J.P., Aigbirhio, F.I., Menon, D.K., Zaman, S.H., Nestor, P.J., Holland, A.J.The pattern of amyloid accumulation in the brains of adults with Down syndrome. Alzheimers Dement 2016. 12, 538-45.

Aylward, E. H., Habbak, R., Warren, A. C., Pulsider, M.B., Barta, P.E., Jerram, M., Pearlson, G.D. Cerebellar volume in adults with Down syndrome. Arch Neurol 1997a. 54, 209-12.

Aylward, E. H., Li, Q. A., Habbak, R., Warren, A., Pulsifer, M. B., Barta, P. E., Jerram, M., Pearlson, G.D. Basal ganglia volume in adults with Down syndrome. Psychiatry Res Neuroimaging 1997b. 74, 73-82.

Aylward, E. H., Li, Q., Honeycutt, N. A., Warren, A. C., Pulsifer, M. B., Barta, P. E., Chan, M.D., Smith, P.D., Jerram, M., Pearlson, G.D. .MRI volumes of the hippocampus and amygdala in adults with Down's syndrome with and without dementia. Am J Psychiatry 1999. 156, 564-8.

Beacher, F., Daly, E., Simmons, A., Prasher, V., Morris, R., Robinson, C., Lovestone, S., Murphy, K., Murphy, D.G.M. Alzheimer's disease and Down's syndrome: an in vivo MRI study. Psychol Med 2009. 39, 675-84.

Beacher, F., Daly, E., Simmons, A., Prasher, V., Morris, R., Robinson, C., Lovestone, S., Murphy, K., Murphy, D.G.M. Brain anatomy and ageing in non-demented adults with Down's syndrome: an in vivo MRI study. Psychol Med 2010. 40, 611-9.

Becker, J. A., Hedden, T., Carmasin, J., Maye, J., Rentz, D. M., Putcha, D., Fischl, B., Greve, D.N., Marshall, G.A., Salloway, S., Marks, D., Buckner, R.L., Sperling, R.A., Johnson, K.A. Amyloid-beta associated cortical thinning in clinically normal elderly. Ann Neurol 2011. 69, 1032-42.

Boxer, A., Rankin, K., Miller, B., Schuff, N., Weiner, M., Gorno-Tempini, M. Cinguloparietal atrophy distinguishes Alzheimer disease from semantic dementia. Arch Neurol 2003. 60, 949 - 56.

Burt, D. B., Loveland, K. A., Primeaux-Hart, S., Chen, Y.-W., Phillips, N. B., Cleveland, L. A., Lewis, K. R., Lesser, J., Cummings, E. Dementia in adults with Down syndrome: Diagnostic challenges. Am J Ment Retard 1998. 103, 130-45.

Cash, D. M., Ridgway, G. R., Liang, Y. Y., Ryan, N. S., Kinnunen, K. M., Yeatman, T., Malone, I.B., Benzinger, T.L.S., Jack, C.R., Thompson, P.M., Ghetti, B.F., Saykin, A.J., Masters, C.L., Ringman, J.M., Salloway, S.P., Schofield, P.R., Sperling, R.A., Cairns, N.J., Marcus, D.S., Xiong, C., Bateman, R.J., Morris, J.C., Rossor, M.N., Ourselin, S., Fox, N.C., DIAN.The pattern of atrophy in familial Alzheimer disease Volumetric MRI results from the DIAN study. Neurology 2013. 81, 1425-33.

Dale, A. M., Fischl, B., Sereno, M. I. Cortical surface-based analysis: I. Segmentation and surface reconstruction. Neuroimage 1999. 9, 179-94.

De La Monte, S. M., Hedley-Whyte, E. T. Small cerebral hemispheres in adults with Down's syndrome: contributions of developmental arrest and lesions of Alzheimer's disease. J Neuropathol Exp Neurol 1990. 49, 509-20.

Delabar, J. M., Aflalo-Rattenbac, R., Creau, N. Developmental defects in trisomy 21 and mouse models. Scientific World J 2006. 6, 1945-64.

Desikan, R. S., Sabuncu, M. R., Schmansky, N. J., Reuter, M., Cabral, H. J., Hess, C. P., Weiner, M.W., Biffi, A., Anderson, C.D., Rosand, J., Salat, D.H., Kemper, T.L., Dale, A.M., Sperling, R.A., Fischl, B. Selective disruption of the cerebral neocortex in Alzheimer's disease. PLoS One 2010. 5, e12853.

Diaz-de-Grenu L.Z., Acosta-Cabronero J., Chong Y.F., Pereira J.M., Sajjadi S.A., Williams G.B., Nestor P.J. A brief history of voxel-based grey matter analysis in Alzheimer's disease. J Alzheimers Dis. 2014. 38, 647-59.

Dickerson, B. C., Fenstermacher, E., Salat, D. H., Wolk, D. A., Maguire, R. P., Desikan, R., Pacheco, J., Quinn, B.T., Van der Kouwe, A., Greve, D.N., Blacker, D., Albert, M.S., Killiany, R.J., Fischl, B. Detection of cortical thickness correlates of cognitive performance: Reliability across MRI scan sessions, scanners, and field strengths. Neuroimage 2008. 39, 10-18.

Dickerson, B. C., Bakkour, A., Salat, D. H., Feczko, E., Pacheco, J., Greve, D. N., Grodstein, F., Wright, C.I., Blacker, D., Rosas, H.D., Sperling, R.A., Atri, A., Growdon, J.H., Hyman, B.T., Morris, J.C., Fischl, B., Buckner, R.L. The cortical signature of Alzheimer's disease: regionally specific cortical thinning relates to symptom severity in very mild to mild AD dementia and is detectable in asymptomatic amyloid-positive individuals. Cereb Cortex 2009. 19, 497-510.

Dickerson, B. C., Wolk, D. A. Dysexecutive versus amnesic phenotypes of very mild Alzheimer's disease are associated with distinct clinical, genetic and cortical thinning characteristics. J Neurol Neurosurg Psychiatry 2011. 82, 45-51.

Dierssen, M. Down syndrome: the brain in trisomic mode. Nat Rev Neurosci 2012. 13, 844-58.

Dierssen, M., Ramakers, G. J. A. Dendritic pathology in mental retardation: from molecular genetics to neurobiology. Genes Brain Behav 2006. 5, 48-60.

Du, A.-T., Schuff, N., Kramer, J. H., Rosen, H. J., Gorno-Tempini, M. L., Rankin, K., Miller, B.L., Weiner, M.W. Different regional patterns of cortical thinning in Alzheimer's disease and frontotemporal dementia. Brain 2007. 130, 1159-66.

Fischl, B., Dale, A. M. Measuring the thickness of the human cerebral cortex from magnetic resonance images. PNAS 2000. 97, 11050-5.

Fischl, B., Sereno, M. I., Dale, A. M. Cortical surface-based analysis: II: inflation, flattening, and a surface-based coordinate system. Neuroimage 1999. 9, 195-207.

Fjell, A. M., Westlye, L. T., Grydeland, H., Amlien, I., Espeseth, T., Reinvang, I., Raz, N., Dale, A.M., Walhovd, K.B., ADNI. Accelerating cortical thinning: unique to dementia or universal in aging? Cereb Cortex 2014. 24, 919-34.

Fortea, J., Sala-Llonch, R., Bartres-Faz, D., Bosch, B., Llado, A., Bargallo, N., Molinuevo, J.L., Sanchez-Valle, R. Increased cortical thickness and caudate volume precede atrophy in PSEN1 mutation carriers. J Alzheimers Dis 2010. 22, 909-22.

Frangou, S., Aylward, E., Warren, A., Sharma, T., Barta, P., Pearlson, G. Small planum temporale volume in Down's syndrome: a volumetric MRI study. Am J Psychiatry 1997. 154, 1424-9.

Gili, T., Cercignani, M., Serra, L., Perri, R., Giove, F., Maraviglia, B. Regional brain atrophy and functional disconnection across Alzheimer's disease evolution. J Neurol Neurosurg Psychiatry 2011. 82, 58 - 66.

Gunn, R. N., Lammertsma, A. A., Hume, S. P., Cunningham, V. J. Parametric imaging of ligand-receptor binding in PET using a simplified reference region model. Neuroimage 1997. 6, 279-87.

Handen, B. L., Cohen, A. D., Channamalappa, U., Bulova, P., Cannon, S. A., Cohen, W. I., Mathis, C.A., Price, J.C., Klunk, W.E. Imaging brain amyloid in nondemented young adults with Down syndrome using Pittsburgh compound B. Alzheimers Dement 2012. 8, 496-501.

Hartley, S. L., Handen, B. L., Devenny, D. A., Hardison, R., Mihaila, I., Price, J. C., Cohen, A.D., Klunk, W.E., Mailick, M.R., Johnson, S.C., Christian, B.T. Cognitive functioning in relation to brain amyloid-beta in healthy adults with Down syndrome. Brain 2014. 137, 2556-63.

Jack, C. R., Twomey, C. K., Zinsmeister, A. R., Sharbrough, F. W., Petersen, R. C., Cascino, G. D. Anterior temporal lobes and hippocampal formations: normative volumetric measurements from MR images in young adults. Radiology 1989. 172, 549-54.

Jack, C. R., Lowe, V. J., Weigand, S. D., Wiste, H. J., Senjem, M. L., Knopman, D. S., Shiung, M.M., Gunter, J.L., Boeve, B.F., Kemp, B.J., Weiner, M., Petersen, R.C.. Serial PIB and MRI in normal, mild cognitive impairment and Alzheimer's disease: implications for sequence of pathological events in Alzheimer's disease. Brain 2009. 132, 1355-65.

Kesslak, J. P., Nagata, S. F., Lott, I., Nalcioglu, O. Magnetic resonance imaging analysis of age-related changes in the brains of individuals with Down's syndrome. Neurology 1994. 44, 1039-45.

Klunk, W. E., Price, J. C., Mathis, C. A., Tsopelas, N. D., Lopresti, B. J., Ziolko, S. K., Bi, W., Hoge, J.A., Cohen, A.D., Ikonomovic, M.D., Saxton, J.A., Snitz, B.E., Pollen, D.A., Moonis, M., Lippa, C.F., Swearer, J.M., Johnson, K.A., Rentz, D.M., Fischman, A.J.,

Aizenstein, H.J., DeKosky, S.T. Amyloid deposition begins in the striatum of presenilin-1 mutation carriers from two unrelated pedigrees. J Neurosci 2007. 27, 6174-84.

Koivunen, J., Verkkoniemi, A., Aalto, S., Paetau, A., Ahonen, J.-P., Viitanen, M., Någren, K., Rokka, J., Haaparanta, M., Kalimo, H., Rinne, J.O. PET amyloid ligand [11C]PIB uptake shows predominantly striatal increase in variant Alzheimer's disease. Brain 2008. 131, 1845-53.

Koran, M. E., Hohman, T. J., Edwards, C. M., Vega, J. N., Pryweller, J. R., Slosky, L. E., Crockett, G., Villa de Rey, L., Meda, S.A., Dankner, N., Avery, S.N., Blackford, J.U., Dykens, E.M., Thornton-Wells, T.A. Differences in age-related effects on brain volume in Down syndrome as compared to Williams syndrome and typical development. J Neurodev Disord 2014. 6, 8.

Krasuski, J. S., Alexander, G. E., Horwitz, B., Rapoport, S. I., Schapiro, M. B. Relation of medial temporal lobe volumes to age and memory function in nondemented adults with Down's syndrome: Implications for the prodromal phase of Alzheimer's disease. Am J Psychiatry 2002. 159, 74-81.

Landt, J., D'abrera, J. C., Holland, A. J., Aigbirhio, F. I., Fryer, T. D., Canales, R., Hong, Y.T., Menon, D.K., Baron, J.C., Zaman, S.H. Using positron emission tomography and carbon 11-labeled Pittsburgh Compound B to image brain fibrillar beta-amyloid in adults with Down syndrome: safety, acceptability, and feasibility. Arch Neurol 2011. 68, 890-6.

Lee, N. R., Adeyemi, E. I., Lin, A., Clasen, L. S., Lalonde, F. M., Condon, E., Driver, D.I., Shaw, P., Gogtay, N., Raznahan, A., Giedd, J.N. Dissociations in cortical morphometry in youth with Down syndrome: evidence for reduced surface area but increased thickness. Cereb Cortex 2015. doi:10.1093/cercor/bhv107.

Lott, I. T., Dierssen, M. Cognitive deficits and associated neurological complications in individuals with Down's syndrome. Lancet Neurol 2010. 9, 623-33.

Mann, D. M. A., Esiri, M. M. The pattern of acquisition of plaques and tangles in the brains of patients under 50 years of age with Down's syndrome. J Neurol Sci 1989. 89, 169-79.

Mann, D. M. A., Jones, D., Prinja, D., Purkiss, M. S. The prevalence of amyloid (A4) protein deposits within the cerebral and cerebellar cortex in Down's syndrome and Alzheimer's disease. Acta Neuropathol 1990. 80, 318-27.

Mann, D. M. A., Yates, P. O., Marcyniuk, B. Alzheimer's presenile dementia, senile dementia of Alzheimer's type and Down's syndrome in middle age form an age related continuum of pathological changes. Neuropathol Appl Neurobiol 1984. 10, 185-207.

Menghini, D., Costanzo, F., Vicari, S. Relationship between brain and cognitive processes in Down syndrome. Behav Genet 2011. 41, 381-93.

Mullins, D., Daly, E., Simmons, A., Beacher, F., Foy, C., Lovestone, S., Hallahan, B., Murphy, K.C., Murphy, D.G. Dementia in Down’s syndrome: an MRI comparison with Alzheimer’s disease in the general population. J Neurodev Disord 2013. 5, 19.

Patenaude, B., Smith, S. M., Kennedy, D. N., Jenkinson, M. A Bayesian model of shape and appearance for subcortical brain segmentation. Neuroimage 2011. 56, 907-22.

Pearlson, G. D., Breiter, S. N., Aylward, E. H., Warren, A. C., Grygorcewicz, M., Frangou, S., Barta, P.E., Pulsifer, M.B. MRI brain changes in subjects with Down syndrome with and without dementia. Dev Med Child Neurol 1998. 40, 326-34.

Pengas, G., Pereira, J. M. S., Williams, G. B., Nestor, P. J. Comparative reliability of total intracranial volume estimation methods and the influence of atrophy in a longitudinal semantic dementia cohort. J Neuroimaging 2009. 19, 37-46.

Pievani, M., Bocchetta, M., Boccardi, M., Cavedo, E., Bonetti, M., Thompson, P. M., Frisoni, G.B. Striatal morphology in early-onset and late-onset Alzheimer's disease: a preliminary study. Neurobiol Aging 2013. 34, 1728-39.

Pinter, J. D., Eliez, S., Schmitt, J. E., Capone, G. T., Reiss, A. L. Neuroanatomy of Down's syndrome: A high-resolution MRI study. Am J Psychiatry 2001. 158, 1659-65.

Prasher, V., Cumella, S., Natarajan, K., Rolfe, E., Shah, S., Haque, M. S. Magnetic resonance imaging, Down's syndrome and Alzheimer's disease: research and clinical implications. JIDR 2003. 47, 90-100.

Raz, N., Torres, I. J., Briggs, S. D., Spencer, W. D., Thornton, A. E., Loken, W. J., Gunning, F.M., McQuain, J.D., Driesen, N.R., Acker, J.D. Selective neuroanatomic abnormalities in Down's syndrome and their cognitive correlates: evidence from MRI morphometry. Neurology 1995. 45, 356-66.

Remes, A. M., Laru, L., Tuominen, H., Aalto, S., Kemppainen, N., Mononen, H., Nagren, K., Parkkola, R., Rinne, J.O. Carbon 11-labeled pittsburgh compound B positron emission tomographic amyloid imaging in patients with APP locus duplication. Arch Neurol 2008. 65, 540-4.

Rosas, H. D., Liu, A. K., Hersch, S., Glessner, M., Ferrante, R. J., Salat, D. H., van der Kouwe, A., Jenkins, B.G., Dale, A.M., Fischl, B. Regional and progressive thinning of the cortical ribbon in Huntington's disease. Neurology 2002. 58, 695-701.

Roth, G. M., Sun, B., Greensite, F. S., Lott, I. T., Dietrich, R. B. Premature aging in persons with Down syndrome: MR findings. Am J Neuroradiol 1996. 17, 1283-89.

Schmidt-Sidor, B., Wisniewski, K. E., Shepard, T. H., Sersen, E. A. Brain growth in Down syndrome subjects 15 to 22 weeks of gestational age and birth to 60 months. Clin Neuropathol 1990. 9, 181-90.

Smigielska-Kuzia, J., Bockowski, L., Sobaniec, W., Sendrowski, K., Olchowik, B., Cholewa, M., Lukasiewicz, A., Lebkowska, U. A volumetric magnetic resonance imaging study of brain structures in children with Down syndrome. Neurol Neurochir Pol 2011. 45, 363-9.

Teipel, S. J., Schapiro, M. B., Alexander, G. E., Krasuski, J. S., Horwitz, B., Hoehne, C., Moller, H.J., Rapoport, S.I., Hampel, H. Relation of corpus callosum and hippocampal size to age in nondemented adults with Down's syndrome. Am J Psychiatry 2003. 160, 1870-8.

Teipel, S. J., Alexander, G. E., Schapiro, M. B., Moller, H. J., Rapoport, S. I., Hampel, H. Age-related cortical grey matter reductions in non-demented Down's syndrome adults determined by MRI with voxel-based morphometry. Brain 2004. 127, 811-24.

Vandekar, S. N., Shinohara, R. T., Raznahan, A., Roalf, D. R., Ross, M., Deleo, N., Ruparel, K., Verma, R., Wolf, D.H., Gur, R.C., Gur, R.E., Satterthwaite, T.D. Topologically dissociable patterns of development of the human cerebral cortex. J Neurosci 2015. 35, 599-609.

Villemagne, V. L., Ataka, S., Mizuno, T., Brooks, W. S., Wada, Y., Kondo, M., Jones, G., Watanabe, Y., Mulligan, R., Nakagawa, M., Miki, T., Shimada, H., O'Keefe, G.J., Masters, C.L., Mori, H., Rowe, C.C. High striatal amyloid beta-peptide deposition across different autosomal Alzheimer disease mutation types. Arch Neurol 2009. 66, 1537-44.

Weis, S., Weber, G., Neuhold, A., Rett, A. Down syndrome: MR quantification of brain structures and comparison with normal control subjects. Am J Neuroradiol 1991. 12, 1207-11.

White, N. S., Alkire, M. T., Haier, R. J. A voxel-based morphometric study of nondemented adults with Down Syndrome. Neuroimage 2003. 20, 393-403.

Wisniewski, K. E. Down syndrome children often have brain with maturation delay, retardation of growth, and cortical dysgenesis. Am J Med Gen Suppl 1990. 7, 274-81.

Tables

Table 1. Participant demographics

| | | Controls | PIB–negative | PIB–positive | PIB–positive excl. 3 non-CAMCOG participants |
|---|---|---|---|---|---|
| n, f/m | | 30, 14/16 | 27, 13/14 | 19, 8/11 | 16, 6/10 |
| Age, range (years) | | 46.2 ± 9.7, 30–64 | 37.1 ± 6, 28–48 | 49.7 ± 6.5, 39–65 | 48.1 ± 5.1, 39 – 56 |
| Global cortical thickness (mm) | | 2.57 ± 0.09 | 2.68 ± 0.10 | 2.55 ± 0.12 | 2.56 ± 0.12 |
| TIV ($cm^3$) | | 1,421.71 ± 140.58 | 1,178.71 ± 103.13 | 1,203.40 ± 124.10 | 1,203.03 ± 115.00 |
| TIV–corrected TBV* ($cm^3$) | | 1,151.26 ± 59.52 | 1,148.86 ± 29.87 | 1,067.08 ± 72.05 | 1,070.26 ± 73.94 |
| Stable cogn./Cogn. decline/ Dement. | | N/A | 24 / 1 / 2 | 7 / 5 / 7 | 7 / 5 / 4 |
| CAMCOG score (max 109), range | | N/A | 76, 38 – 102 | - | 74, 17 – 95 |
| ApoE† | ε2/ε3 | N/A | 4 | 3 | 2 |
| | ε3/ε3 | N/A | 15 | 6 | 6 |
| | ε3/ε4 | N/A | 4 | 6 | 6 |
| | ε2/ε4 | N/A | 1 | 1 | 1 |

Table 1 Data is shown as mean ± standard deviation and range, if applicable. f/m – females/males ratio; N/A – not applicable; Stable cogn. – Stable cognition; Cogn. decline –

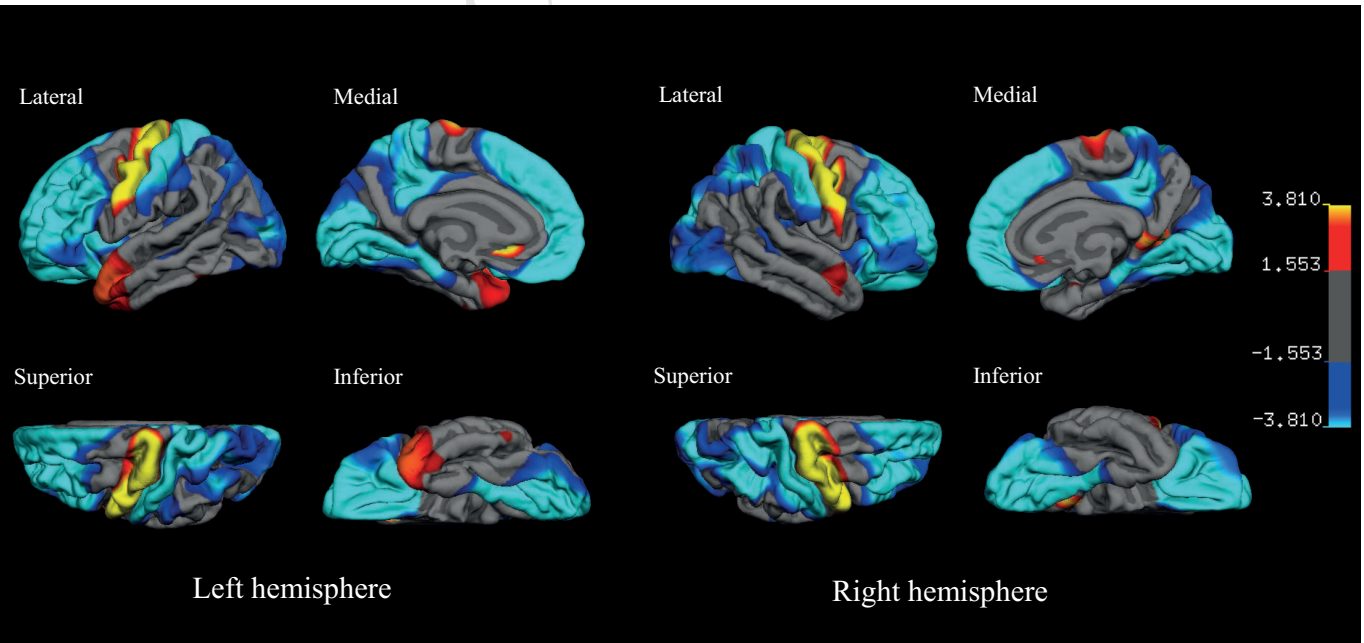
Cognitive decline; Dement. – Dementia; TIV – Total intracranial volume; TBV – Total brain volume; ApoE – apolipoprotein E allele. * (Jack *et al.*, 1989). † Three individuals in the PIB–negative group and three in the PIB–positive group did not undergo ApoE genotyping.

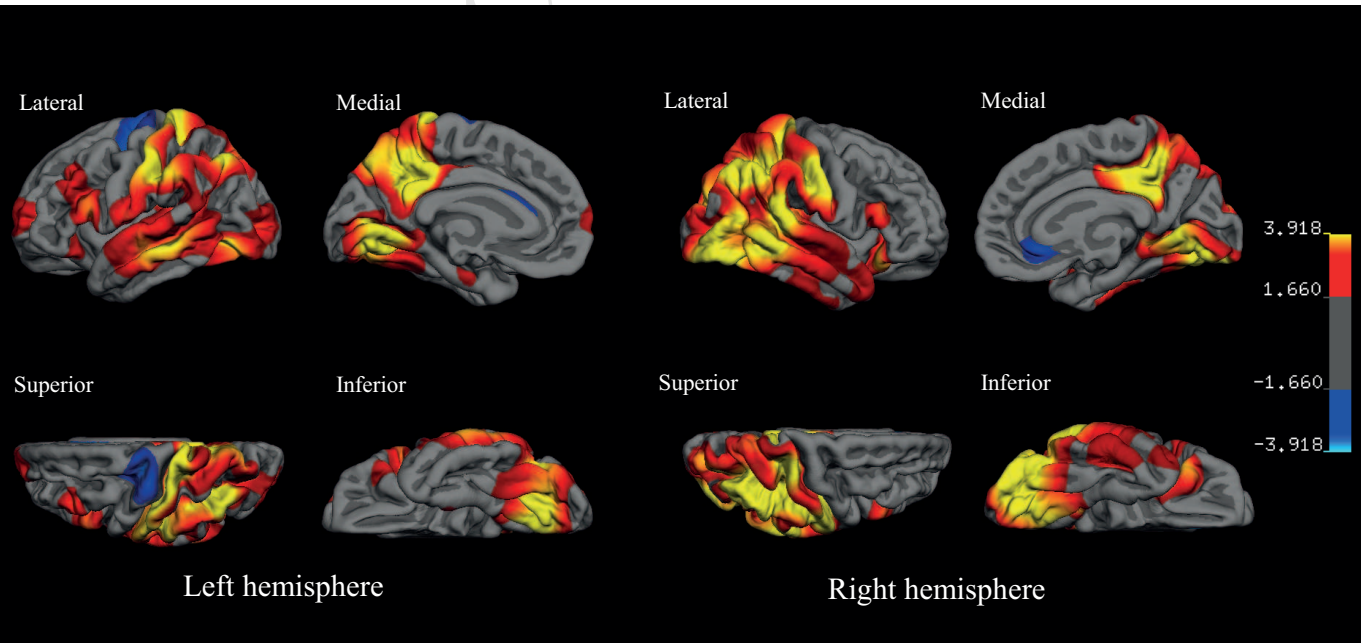
## Figure captions

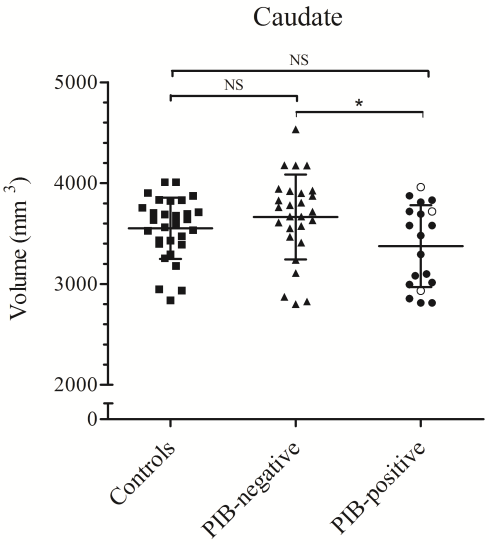
Figure 1 The cortical signature of the Down syndrome brain without amyloid pathology: regional variations in cortical thickness across the hemispheres in the PIB–negative group (n=27) in comparison to control group (n=30). The colour scale on the right represents the significance of the thickness difference as –log10(p–value) with red-yellow indicating thinner cortex and blue-light blue indicating thicker cortex in the PIB–negative group relative to controls. The results are false-discovery rate corrected at $p<0.05$.

Figure 2 The cortical signature of the Down syndrome brain with amyloid pathology: regional variations in cortical thickness in the PIB–positive group (n=19), when compared to PIB–negative group (n=27). The colour scale on the right represents the significance of the difference in thickness as –log10(p–value) with red–yellow indicating thinner cortex and blue-light blue indicating thicker cortex in the PIB–positive group relative to PIB–negative group. The results are false-discovery rate corrected at $p<0.05$.

Figure 3 Volumes of the deep grey matter structures and total brain in the control, PIB–negative and PIB–positive groups. Unfilled circles in the PIB–positive group represent the three individuals who had too advanced dementia to be able to perform the CAMCOG cognitive assessment. Figure legend: *** – $p<0.001$, * – $p<0.05$, NS – non–significant. All tests are two sample t–test results (two-tailed) following one–way ANOVA.






Caudate
Volume (mm 3)
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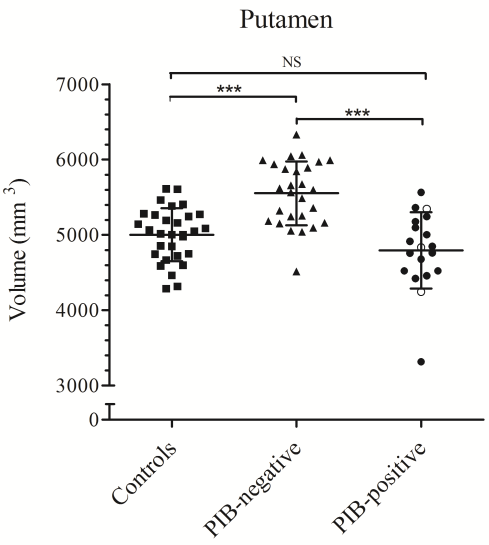
4000
3000
2000
0
NS
NS
*
Controls
PIB-negative
PIB-positive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***
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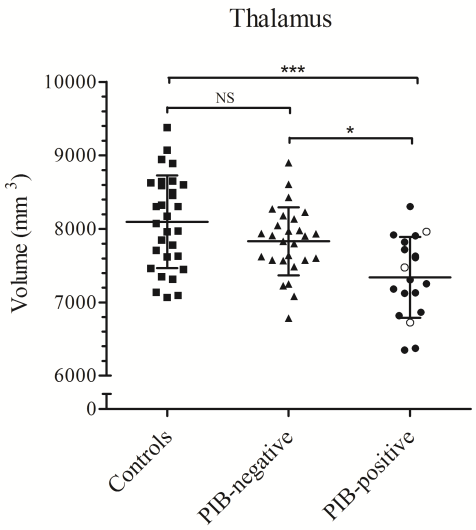
PIB-positive


Thalamus
Volume (mm 3)
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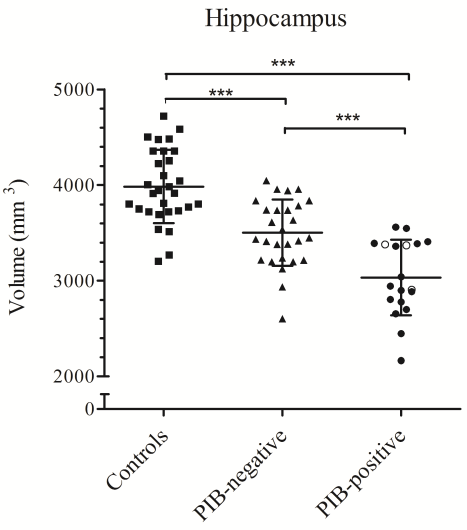
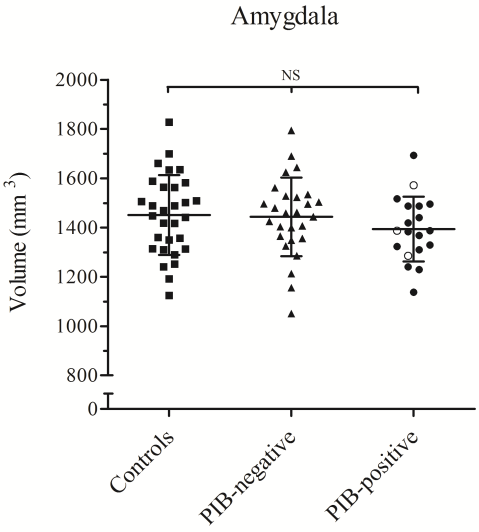
9000
8000
7000
6000
0
***
NS
*
Controls
PIB-negative
PIB-positive


Hippocampus
Volume (mm 3)
5000
4000
3000
2000
0
***
***
***
Controls
PIB-negative
PIB-positive


Amygdala
Volume (mm 3)
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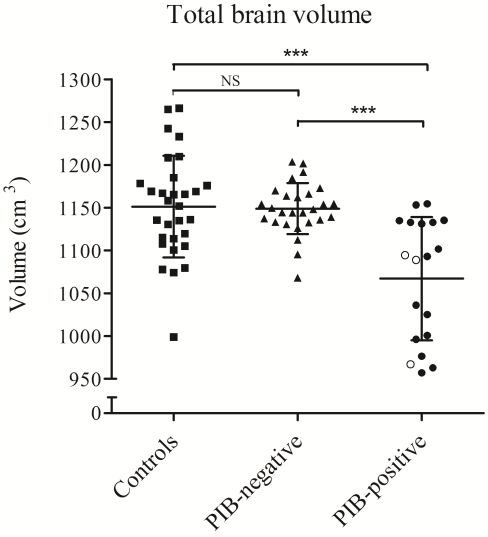
1800
1600
1400
1200
1000
800
0
NS
Controls
PIB-negative
PIB-positive


Total brain volume
Volume (cm 3)
1300
1250
1200
1150
1100
1050
1000
950
0
***
NS
***
Controls
PIB-negative
PIB-positive

## Highlights

- Adults with Down syndrome have neurodevelopmentally distinct cortical anatomy.
- Frontal cortices are atypically thicker with large putamina and small hippocampi.
- Amyloidosis is associated with posterior cortical thinning and subcortical atrophy.
- Pattern of cortical thinning resembles Alzheimer's disease in general population.
- Care must be taken in assessing amyloid-related structural changes in Down syndrome.