Neurobiology of Aging 53 (2017) 11–19

Contents lists available at ScienceDirect

Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging

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

Tiina Annus [a,*], Liam R. Wilson [a], Julio Acosta-Cabronero [b,c], Arturo Cardenas-Blanco [b], Young T. Hong [d], Tim D. Fryer [d], Jonathan P. Coles [e], David K. Menon [e], Shahid H. Zaman [a,f], Anthony J. Holland [a,f], Peter J. Nestor [b]

[a] Cambridge Intellectual and Developmental Disabilities Research Group, Department of Psychiatry, University of Cambridge, Douglas House, Cambridge, UK
[b] German Center for Neurodegenerative Diseases (DZNE), Magdeburg, Germany
[c] Wellcome Trust Centre for Neuroimaging, Institute of Neurology, University College London, London, UK
[d] Wolfson Brain Imaging Centre, Department of Clinical Neurosciences, University of Cambridge, Cambridge, UK
[e] Division of Anaesthesia, Department of Medicine, University of Cambridge, Cambridge, UK
[f] Cambridgeshire and Peterborough NHS Foundation Trust, Elizabeth House, Fulbourn Hospital, Fulbourn, Cambridge, UK

ARTICLE INFO

Article history:
Received 4 July 2016
Received in revised form 1 January 2017
Accepted 6 January 2017
Available online 17 January 2017

Keywords:
Alzheimer's disease
Amyloid
Cortical thickness
Down syndrome
Gray matter volume

ABSTRACT

People with Down syndrome (DS) have a neurodevelopmentally distinct brain and invariably developed 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 gray matter volumetry and cortical thickness were studied. PIB-negative people with DS have neurodevelopmentally atypical brain, characterized 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 striatum, to that observed in non-DS Alzheimer's disease. Care must be taken to avoid underestimating amyloid-associated morphologic changes in DS due to disproportionate size of some subcortical structures and thickness of the cortex.

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). Postmortem 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; Delabar et al., 2006; Dierssen, 2012; Dierssen and Ramakers, 2006; Lott and Dierssen, 2010). Imaging studies in adults with DS have corroborated the postmortem findings by showing widespread cerebral hypoplasia and ventricular enlargement in comparison to typically developing individuals (Supplementary Table 1, Aylward et al., 1997a,b 1999; Beacher et al., 2009, 2010; Frangou et al., 1997; Kesslak et al., 1994; Koran et al., 2014; Krasuski et al., 2002; Pearlson et al., 1998; Pinter et al., 2001; Prasher et al., 2003; Raz et al., 1995; Roth et al., 1996; Teipel et al., 2003, 2004; White et al., 2003). 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

* Corresponding author at: Cambridge Intellectual and Developmental Disabilities Research Group, Department of Psychiatry, University of Cambridge, Douglas House, 18b Trumpington Road, Cambridge CB2 8AH, UK. Tel.: +44 1223 746127; fax: +44 1223 746033.
E-mail address: t.annus@cantab.net (T. Annus).

http://dx.doi.org/10.1016/j.neurobiolaging.2017.01.009

(Annus et al., 2016; Mann et al., 1984, 1990). Similar to sporadic AD, significant amyloid binding with positron emission tomography (PET) is found before any signs of cognitive or functional decline in DS (Annus et al., 2016; Handen et al., 2012; Hartley et al., 2014; Landt et al., 2011). Yet, previous structural imaging studies (see Supplementary Table 1) have aimed to characterize 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, 4 previous neuroimaging studies (Aylward et al., 1999; Beacher et al., 2009; Pearlson et al., 1998; Prasher et al., 2003) aimed to characterize 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 and Wolk, 2011; Dickerson et al., 2009) that abnormalities in cortical structure occur at presymptomatic stages of AD. As such, the present cross-sectional study aimed to characterize 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 2 amyloid-negative and 1 amyloid-positive participant, whose magnetic resonance imaging (MRI) scans were of inferior quality (motion artifact 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, whereas insufficient to satisfy the full criteria for dementia. All DS participants, except 3 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 1 demented individual who was receiving Donepezil, no participants were using antidementia 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 magnetization–prepared, rapid gradient echo pulse sequence with the following parameters: repetition time/echo time/inversion time/flip angle = 2300 ms/2.98 ms/900 ms/9°, 256 × 240 × 176 matrix dimensions and 1 × 1 × 1 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 = 1500 ms/79 ms/150°/256; 0.9 × 0.7 × 4.0 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 gray matter parcelations 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 gray matter as reference region. PIB-positive and PIB-negative groups were assigned on the basis of striatal nondisplaceable 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 and Dale, 2000; Fischl et al., 1999). Image processing involved automated nonuniformity bias correction, skull stripping, segmentation of the white matter, and estimation of the gray/white matter boundary. Segmented and skull-stripped data of all participants were visually inspected for parcelation errors, and topological defects in the gray/white matter boundary were manually corrected. The gray/white boundary served as a starting point for a deformable surface algorithm to compute the gray/white and pial surfaces, from which cortical thickness is calculated as the closest