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Authors
Abrahamson, Eric E
Head, Elizabeth
Lott, Ira T
et al.

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Neuropathological correlates of amyloid PET imaging in Down syndrome

Eric E. Abrahamson[1,2], **Elizabeth Head**[4], **Ira T. Lott**[5], **Benjamin L. Handen**[3], **Elliott J. Mufson**[6], **Bradley T. Christian**[7], **William E. Klunk**[2,3], **Milos D. Ikonomovic**[1,2,3]

[1]Geriatric Research Education and Clinical Center, VA Pittsburgh Healthcare System, University of Pittsburgh, Pittsburgh PA

[2]Department of Neurology University of Pittsburgh, Pittsburgh PA

[3]Department of Psychiatry, University of Pittsburgh, Pittsburgh PA

[4]Department of Pathology and Laboratory Medicine UC Irvine School of Medicine, Orange CA

[5]Department of Neurology, UC Irvine School of Medicine, Orange CA

[6]Department of Neurobiology, Barrow Neurological Institute, Phoenix AZ

[7]Departments of Medical Physics and Psychiatry, Waisman Center, University of Wisconsin-Madison, Madison, WI

Abstract

Down syndrome (DS) results in an over-production of amyloid-β (Aβ) peptide associated with early onset of Alzheimer's disease (AD). DS cases have Aβ deposits detectable histologically as young as 12–30 years of age, primarily in the form of diffuse plaques, the type of early amyloid pathology also seen at pre-clinical (i.e., pathological aging) and prodromal stages of sporadic late onset AD. In DS subjects aged >40 years, levels of cortical Aβ deposition are similar to those observed in late onset AD and in addition to diffuse plaques involve cored plaques associated with dystrophic neurites (neuritic plaques) which are of neuropathological diagnostic significance in AD. The purpose of this review is to summarize and discuss findings from amyloid PET imaging studies of DS in reference to post-mortem amyloid based neuropathology. PET neuroimaging applied to subjects with DS has the potential to a) track the natural progression of brain pathology, including the earliest stages of amyloid accumulation, and b) determine whether amyloid PET biomarkers predict the onset of dementia. In addition, the question that is still incompletely understood and relevant to both applications is the ability of amyloid PET to detect Aβ deposits in their earliest form.

Correspondence to: Milos Ikonomovic, M.D., University of Pittsburgh School of Medicine, Thomas Detre Hall of the WPIC, Room 1421, 3811 O'Hara Street, Pittsburgh, PA 15213-2593. Phone: (412) 802-3004; Fax: (412) 647-2777; ikonomovicmd@upmc.edu.

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Keywords

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1. Introduction

[C-11]Pittsburgh Compound-B (PiB) and related F-18 labeled amyloid PET ligands have high affinity for amyloid-β (Aβ) fibrils in extracellular plaques, a major neuropathological hallmark of Alzheimer's disease (AD). While altered metabolism of the Aβ precursor protein (APP) and/or impaired brain clearance of Aβ are hypothesized to be responsible for plaque deposition in the majority of late-onset AD cases (>65 years of age), genetic abnormalities due to autosomal dominant mutations in familial AD (FAD) are known to cause amyloid pathology with an early disease onset (<50 years of age). Down syndrome (DS), a genetic disorder due to an extra copy of chromosome 21, which harbors the gene encoding APP, also results in an over-production of Aβ peptide associated with early onset of AD (Mori et al., 2002; Russo et al., 1997; Teller et al., 1996). DS cases have Aβ plaques detectable histologically as young as 12 to 30 years of age, primarily in the form of diffuse Aβ plaques, the type of early amyloid pathology also seen at pre-clinical (i.e., pathological aging) and prodromal stages of sporadic AD. In DS subjects aged >40 years, levels of cortical Aβ deposition are similar to those observed in sporadic, late onset AD (Davidson et al., 2018; Head et al., 2016; Lemere et al., 1996; Liu et al., 2006; Mann, 1988a; Mann and Esiri, 1989; Wisniewski et al., 1989) and in addition to diffuse plaques involve cored plaques associated with dystrophic neurites (neuritic plaques) which are of neuropathological diagnostic significance in AD. Understanding structural properties, biochemical constituents, and evolution of morphologically diverse Aβ plaques and other AD-related pathology within and between brain regions in relation to age and development of dementia is needed to guide interpretation of amyloid PET imaging of subjects with DS (Head et al., 2018; Neale et al., 2018). Compared to the extensive number of amyloid PET studies performed in AD (Cohen et al., 2019), there are relatively few amyloid PET studies of DS (Mak et al., 2019; Cohen et al., 2018; Lao et al., 2018; Annus et al., 2017; Cole et al., 2017; Rafii et al., 2017; Annus et al., 2016; Lao et al., 2016; Matthews et al., 2016; Jennings et al., 2015; Sabbagh et al., 2015; Hartley et al., 2014; Handen et al., 2012; Landt et al., 2011), even fewer longitudinal studies (Tudorascu et al., 2018; Hartley et al., 2017; Lao et al., 2017), and only one imaging-to-autopsy analysis (Sabbagh et al., 2011). Building upon the understanding that AD and DS brains/pathology are not the same, the purpose of this article is to summarize amyloid PET imaging studies of people with DS in the context of neuropathology defined at autopsy, to guide interpretation of future investigations in larger numbers of subjects with DS over longer periods of time. Post-mortem characterization of amyloid PET in DS compared to AD is particularly germane at this point in time given the increasing role of neuroimaging in anti-amyloid intervention trials. In addition, the ability to track amyloid accumulation in relation to dementia onset and rate of impairment is critical for understanding the natural progression of pathology in DS, including the earliest stages of amyloid deposition, and whether amyloid PET biomarkers can predict the onset of dementia.

2. Overview of amyloid plaque pathology and PET imaging of AD

Neuropathology studies of AD brain tissue describe at least five morphologically-distinct Aβ plaque types: diffuse, stellate/focal, primitive, classic (also referred to as cored or neuritic), and burnt-out (sometimes referred to as isolated cores or burnt out plaques) (Wisniewski, 1989; Yamaguchi, 1989; Schmidt, 1995). These lesions consist primarily of Aβ fibrils structurally organized into physiologically insoluble β-pleated sheets, with Aβ fibril packing density differing between morphologically-defined plaque subtypes. Diffuse Aβ plaques consist of varying ratios of amorphous “pre-amyloid” material and loosely-dispersed Aβ fibrils, while the core region of classic and burnt out Aβ plaques consist of densely packed Aβ fibrils. The latter two plaque types are defined by birefringence when labeled with the amyloid binding dye Congo red, a characteristic reflecting the high packing density of amyloid fibrils in these plaque types. In preclinical AD (i.e., pathological aging), diffuse Aβ plaques predominate (Mochizuki et al., 1996; Mufson et al., 1999) and are also referred to as plaques A, pre-amyloid deposits, type 3 plaques, pre-plaques, or very primitive plaques, among others [see (Allsop et al., 1989; Yamaguchi et al., 1988b)]. Diffuse Aβ plaques have scarce, loosely dispersed bundles of Aβ-immunoreactive amyloid fibrils when viewed at the ultrastructural level (Yamaguchi et al., 1990; Yamaguchi et al., 1989) and due to the absence of a dense amyloid core they are not congophilic (Tagliavini et al., 1988; Yamaguchi et al., 1988b). Moreover, Allsop and colleagues stated that “these ‘pre-plaques’ can be detected as an area of granular staining after an immunohistochemical reaction with antibodies to β-protein; they show no abnormal neurites demonstrable by silver impregnation, and no amyloid detectable by Congo red” (Allsop et al., 1989). Diffuse plaques in the cerebral cortex appear composed of both amorphous extracellular electron dense material, corresponding to Aβ-immunoreactive granular amorphous deposits detected using light microscopy (Yamaguchi et al., 1988a; Yamaguchi et al., 1988b) and, in some brain regions, loosely bundled Aβ fibrils (Ikeda et al., 1989a; Yamaguchi et al., 2000; Yamaguchi et al., 1990; Yamazaki et al., 1991). Biochemical studies suggest that diffuse plaques contain unstructured Aβ aggregates and protofibrils, some of which are amino-truncated Aβ forms in including the nonamyloidogenic Aβ17–42 also referred to as pre-amyloid (Gowing et al., 1994; Huang et al., 2000; Lalowski et al., 1996). Although not considered congophilic, diffuse plaques lose argyrophilia after treatment with formic acid suggesting that a β-sheet amyloid structure is present (albeit in small amounts), in agreement with ultrastructural studies (Yamaguchi et al., 1988a; Yamaguchi et al., 1988b).

Until recently, definite diagnosis of AD was possible only post-mortem, based on histopathological evidence of neuritic Aβ plaques and intracellular lesions composed of hyper-phosphorylated tau protein (i.e., neurofibrillary tangles, NFT). The discovery and application of carbon-11 labeled Pittsburgh Compound-B (PiB) (Klunk et al., 2004) and related fluorine-18 labeled amyloid PET ligands Florbetapir (Amyvid) (Clark et al., 2011; Wong et al., 2010), Florbetaben (Neuraceq) (Sabri et al., 2015), and Flutemetamol (Vizamyl) (Vandenberghe et al., 2010) has allowed for detection and quantification of amyloid burden in brains of living subjects. Recent clinical pathological studies reported that neuritic Aβ plaques are primarily responsible for binding of amyloid PET ligands in AD, supported by a high correspondence between ante-mortem amyloid PET retention levels and region-

matched frequencies of neuritic plaques determined post-mortem (Clark et al., 2012; Curtis et al., 2015; Hatsuta et al., 2015; Sabri et al., 2015; Salloway et al., 2017). While cortical Aβ plaques can be present in subjects with amyloid PET retention below detection levels, these are typically non-neuritic and diffuse (Cairns, 2011; Ikonomovic, 2012). However, a recent clinical-pathological study demonstrated several cases that were amyloid-PET positive, but post-mortem analysis revealed insufficient amounts of cortical neuritic plaques marked by Bielschowsky silver histology (Salloway et al., 2017). These false positive cases had significant amounts of cortical diffuse Aβ plaques detected immunohistochemically, suggesting that both diffuse and neuritic Aβ plaques can contribute to amyloid PET signal (Ikonomovic et al., 2016; Ikonomovic et al., 2018). Other studies also support that moderate to frequent striatal (and cortical) diffuse Aβ plaques are PET detectable (Beach et al., 2016). For a more in-depth review of amyloid PET imaging in AD the reader is referred to Mathis et al., 2017.

3. Neuropathology substrates of amyloid PET ligands in the DS brain

3.1. Amyloid-β plaques and amyloid PET in DS

Neuropathology studies demonstrate diffuse Aβ plaques as the earliest and predominant plaque type in DS brains (Ikeda et al., 1989c; Mann and Esiri, 1989; Mann et al., 1986). Unlike the late onset of Aβ plaques in sporadic AD (>65 years), plaques have been detected post-mortem in the brains of people with DS as early as the twenties and thirties (Ikeda et al., 1989c; Mann and Esiri, 1989). In DS there is “a transitional period usually between 20 and 40 years of age during which the complete absence of plaques (and tangles) changes into a presence in virtually all patients” (Ikeda et al., 1989c; Mann and Esiri, 1989; Mann et al., 1986). A variety of immunohistochemical and silver histology methods demonstrated the predominance of diffuse Aβ plaques in the cerebral cortex, parahippocampal gyrus, and hippocampus of a limited number of young DS cases: nine cases age 12–38 years (Lemere et al., 1996), one case age 23 years (Liu et al., 2006), three cases age 31–38 years (Ikeda et al., 1994), 18 cases age 8–38 years (Leverenz and Raskind, 1998), six cases age 12–38 years (Burger and Vogel, 1973), and in four cases age 31–38 years (Mann et al., 1990a; Mann et al., 1990b). In contrast, DS cases older than 40 years consistently have high densities of both diffuse and classic/neuritic Aβ plaques in neocortex, hippocampus, caudate/putamen, thalamus, amygdala, and cerebellum (Armstrong and Smith, 1994; Burger and Vogel, 1973; Davidson et al., 2018; Hof et al., 1995; Ikeda et al., 1989a; Ikeda et al., 1989b; Kida et al., 1995a; Kida et al., 1995b; Lemere et al., 1996; Leverenz and Raskind, 1998; Liu et al., 2006; Malamud, 1972; Mann, 1988a; Mann et al., 1989; Mann and Esiri, 1989; Mann and Iwatsubo, 1996; Mann et al., 1990a; Mann et al., 1990b; Mann et al., 1986; Motte and Williams, 1989; Olson and Shaw, 1969; Whalley, 1982; Wisniewski et al., 1985b). For an overview of the progression of regional AD pathology in subjects with DS aged 0–76 years, as summarized by Mann and colleagues, see Figure 1 (Davidson et al., 2018). Some structural aspects of Aβ plaques differ between DS and late onset AD. For example, Aβ fibril packing density in all plaque types appears to be lower in DS compared to AD (Ikeda et al., 1989c; Mann and Esiri, 1989; Mann et al., 1986). In this regard it was noted that “...the proportion of amorphous plaque cores is dissimilar in the two diseases (Allsop et al., 1986; Masters et al., 1985). In DS, cores are larger than in AD and the amyloid fibrils are

less compact, with Congo red birefringence poorly defined and often lacking. In situ [i.e., post-mortem] analyses revealed large, amorphous type plaques [i.e., diffuse plaques] to be more common in DS than in AD" (Mann, 1988a, Mann, 1988b). These observations were replicated in a confocal study using antibodies targeting Aβ (Schmidt et al., 1995).

3.2. Regional variability of amyloid-β plaques and PET retention in DS: focus on the striatum

Recent studies demonstrated feasibility of [C-11]PiB imaging of early amyloid pathology in DS (Handen et al., 2012; Landt et al., 2011) (Figure 2). While amyloid PET retention is detectable in all cortical regions of adults with DS, several studies identified the striatum as a region with earliest and most prominent signal retention (Annus et al., 2016; Cohen et al., 2018; Handen et al., 2012), similar to that observed in a [C-11]PiB PET study of presenilin-1 (PS1) mutation carriers (Klunk et al., 2007). A recent study reported a striatal-predominant retention pattern visualized by [C-11]PiB PET in the oldest (ages 38 and 44) of seven non-demented adults with DS (age 20–44 years) (Handen et al., 2012). Other studies reported that [C-11]PiB PET retention was higher in the striatum compared to cerebral cortex of subjects with DS regardless of their cognitive and amyloid status (Lao et al., 2018; Lao et al., 2017). Furthermore, most [C-11]PiB PET positive subjects with DS were PiB-positive in the striatum, while in several cases the striatum was the only positive region (Annus et al., 2016; Hartley et al., 2014; Lao et al., 2016). In a cohort of 49 subjects with DS age 25–65 years, nine stages of amyloid deposition were described using [C-11]PiB PET (Annus et al., 2016), with the striatum being the first region to exhibit positivity (approximately age 40 years), followed by frontal and cingulate areas, temporal and parietal cortex, sensorimotor cortex, occipital cortex, and non-striatal subcortical areas (thalamus, parahippocampal cortical area, and amygdala). This hierarchical model of amyloid deposition derived from PET imaging datasets does not agree completely and is not necessarily expected to agree with cross-sectional neuropathology studies of DS. Autopsy studies of DS brains suggest that amyloid deposition in the striatum occurs contiguously or, more likely, after the appearance of cerebral cortical plaques (discussed below). The latter scenario is similar to the hierarchy of amyloid deposition described in sporadic AD and currently used to stage amyloid severity in this disease (Braak and Braak, 1990; Thal et al., 2002). Supporting this is a post-mortem immunohistochemical analysis of 56 brains from subjects with DS ranging in age from newborn to 76 years that identified cerebral cortical regions (typically temporal neocortex) as early sites of amyloid deposition while amyloid in subcortical regions (including the striatum) appeared 20–30 years later in life (Davidson et al., 2018; Mann, 1988a). An overview of the data from a recent review by Mann and colleagues (Davidson et al., 2018; Mann, 1988a) shows absence of striatal amyloid in 15 (27%) cases, all aged 50 years or less, however 7 of these striatal-negative cases (47%) had amyloid plaques in the temporal cortex (Figure 1). In the entire cohort, only 4 cases (7%, all over 55 years) had greater amyloid load in the striatum than in the temporal cortex, while 20 cases (36%) had greater amyloid load in temporal cortex than in the striatum, and 16 (29%) cases had comparable amyloid load in the two brain regions. These results suggest that amyloid pathology in DS follows a regional evolution similar to the Thal phases (Braak and Braak, 1990; Thal et al., 2002) seen in sporadic AD, with neocortical regions including temporal cortex affected earlier than subcortical regions, including the striatum.

Discrepancies between in vivo PET and post-mortem pathology observations in DS could be due to low sensitivity of amyloid PET for the initial stages of cortical amyloid deposition, or they may reflect the age of subjects examined relative to the time of onset and progression rate of plaque types in different brain areas. Based on neuropathology observations in DS, at early ages neocortical diffuse plaques precede striatal diffuse plaques, but these infrequent diffuse deposits are likely not readily detectable by PET. In agreement with this, PiB PET retention is detectable starting with the striatum from ~40 years of age, which is several decades later than the age at which the onset of neocortical diffuse amyloid is detected on post-mortem examination. Over time, the DS striatum may accumulate larger amounts of diffuse amyloid compared to neocortex, and this would be reflected on PET imaging as earlier striatal positivity, but not on pathological staging at autopsy (i.e., Thal phases) which is based on the frequencies of all Aβ-immunoreactive plaques from diffuse to classic (Braak and Braak, 1990; Thal et al., 2002). After age ~50 years, amyloid pathology in DS closely resembles sporadic AD because by this age cortical Aβ plaques in DS include the full spectrum of typical AD pathology and plaque load has likely plateaued. Thus, the positive amyloid PET signal in striatum is likely due to radioligands' binding to diffuse Aβ plaques which predominate in this brain region. Recently, it was suggested that striatal amyloid positivity may be useful for pathology-based clinical staging of AD, as increased sensitivity of [F-18]Flutemetamol PET was observed with higher histological density thresholds for striatal amyloid deposits (Beach et al., 2016).

A similar discrepancy between amyloid PET retention and post-mortem neuropathology has been observed in neocortical regions. In a recent clinical-neuropathological study of [F-18]Flutemetamol, false positive results were resolved by taking into account Aβ-immunoreactive diffuse plaques instead of relying exclusively on the frequency of Bielschowsky silver-stained neuritic plaques (Ikonomovic et al., 2018). Whether additional factors such as region-specific differences in vasculature and white matter content affect amyloid PET ligands kinetics and contribute to greater retention in the striatum is currently unknown. Overall, a distinction should be made between use of amyloid PET imaging for clinical disease staging or for tracking the natural history of amyloid deposition (including initial sites of deposition) in the disorder. There is a need for amyloid PET and neuropathology studies in larger numbers of DS subjects. In addition, longitudinal PET studies will more closely dissect the role of striatal amyloid PET signal in the pathological and clinical progression of DS and AD.

3.3. Post-translational amyloid-β modifications can influence amyloid PET imaging in DS

It has been reported, in an autopsy study of a 72-year old subject with probable AD and neuropathology-confirmed end-stage AD, that despite severe amyloid pathology there was diminished high affinity [H-3]PiB binding and lack of [H-3]PiB autoradiography signal in cortical areas (Rosen et al., 2010). Further biochemical analysis of this case revealed large amounts of Aβ oligomers as well as C- and N-terminal truncated Aβ species (termed PiB refractory), strikingly similar to reports of truncated Aβ species in diffuse plaques in cerebellar cortex of AD and DS cases (Kida et al., 1995b; Lalowski et al., 1996). However, plaques with intact N-terminal portion of Aβ were also reported in the cerebellum (Iwatsubo et al., 1996). This PiB refractory case was also characterized by extensive vessel-associated

diffuse Aβ deposits resembling severe dyshoric lesions [see (Richard et al., 2010) for discussion of dyshoric amyloid] with moderate numbers of classic plaques (Rosen et al., 2010). Interestingly, this case had no known genetic mutation of APP or presenilin genes. Small numbers of sporadic AD cases whose predominant pathology type is dyshoric amyloid could be refractory to amyloid PET imaging. Thus, large amounts of plaques with N- or C- terminal truncated Aβ species could influence amyloid PET imaging in DS. An autopsy study of 29 DS cases aged 3–73 years reported Aβ42 and Aβ40 immunoreactive diffuse plaques in temporal cortex from seven cases <30 years (12, 15, 16, 17, 21, 27, 29 years). However, when these same cases were examined using antibodies targeting N-terminus pyroglutamate-modified Aβ (AβpE3), plaques were present only in cases older than 27 years (Lemere et al., 1996). This suggests intact amino terminus in the initial stages of Aβ fibrillization in DS. Another autopsy study of DS cases >36 years and using an array of antibodies targeting multiple N-terminus modifications of Aβ (including pyroglutamate-modified species) as well as antibodies targeting Aβ with intact N-terminus reported immunoreactivity with all antibodies in diffuse plaques in both the striatum and cerebellum (Iwatsubo et al., 1996). An ELISA analysis of Aβ concentrations in DS frontal cortex found Aβ1–40 in concentrations higher than AβpE3 which in turn were higher than concentrations of Aβ1–42 (Hosoda et al., 1998). How different species and concentrations of proteolytically-modified (or intact) Aβ influence the interaction of fibrillar Aβ deposits with amyloid PET ligands in DS is currently in need of further investigation.

3.4. Amyloid PET and age in DS

Amyloid PET positivity in DS correlates with age (Annus et al., 2016; Handen et al., 2012; Hartley et al., 2014; Jennings et al., 2015; Lao et al., 2016; Lao et al., 2018; Sabbagh et al., 2015), in agreement with post-mortem neuropathology analyses (Davidson et al., 2018; Ikeda et al., 1989c; Lemere et al., 1996; Leverenz and Raskind, 1998; Mann, 1988a; Mann et al., 1990a; Mann et al., 1986; Motte and Williams, 1989). Hartley and colleagues reported 22 PiB positive and 41 PiB negative non-demented DS (DS/no dementia) subjects ranging in age from 30–53 years (Hartley et al., 2014), with chronological age accounting for 39% of variability in [C-11]PiB retention. Another study of DS/no dementia reported 17 PiB positive (mean age 44.9 years) and 51 PiB negative subjects (mean age 35 years), with SUVR values correlating with age only in the PiB negative group (Lao et al., 2016). When all participants were combined, the brain region showing the strongest correlation with age was the putamen, and when prevalence of amyloid positivity was assessed, both the striatum and precuneus cortex showed the highest values in the youngest participants (age range 36–40 years), suggesting that these brain regions retain amyloid PET ligands early in the course of amyloid pathology progression in DS (Lao et al., 2016). However, as discussed earlier, patterns of amyloid PET ligand retention likely do not fully recapitulate patterns described in neuropathology studies at least at initial stages of amyloid deposition in DS. In a smaller study including DS/no dementia/PiB negative (n=16, mean age 35 years), DS/no dementia/PiB positive (n=5, mean age 47 years), and DS/dementia/PiB positive subjects (n=3, mean age 49 years) the same group reported correlations of SUVR with age (all participants combined) in multiple neocortical areas and striatum (Lao et al., 2018). Correlations between [18-F]Florbetapir PET amyloid and age were reported in a small study including DS/no dementia (n=10, mean age 36 years) and DS/dementia (n=5, mean age 50

years) subjects (Sabbagh et al., 2015). Another study employed machine learning to predict brain age from structural MRI data in DS/PiB positive (n=19, mean age 50 years) and DS/PiB negative subjects (n=27, mean age 37 years) (Cole et al., 2017), and found a correlation between age-related brain atrophy and amyloid deposition (Cole et al., 2017). A non-linear correlation of [C-11]PiB binding potential and age was also seen in a study of DS/PiB positive (n=20, mean age 50 years) and DS/PiB negative subjects (29, mean age 36 years), with a sharp increase in binding potential observed at approximately 45–50 years of age (Annus et al., 2016). Though beyond the scope of the current review, several DS studies report correlations of age with brain volume reductions (neurodegeneration), fluorodeoxyglucose PET (metabolism), and a PET ligand for neurofibrillary tangles (Annus et al., 2017; Lao et al., 2018; Matthews et al., 2016; Rafii et al., 2017; Sabbagh et al., 2015). The correlation between amyloid accumulation and age in DS underscores the need to control for chronological age in studies attempting to discriminate amyloid patterns in DS/dementia from DS/no dementia, addressed in the following section. Further, morphological differences in brain structure in the DS population require the use of standardized brain atlases specific to this population. T1W MRI- and PiB-based normative templates were developed to account for structural differences with the non-DS population (Lao et al., 2019). The structural brain morphology template (based upon the segmented T1W images) confirmed reductions in gray matter volume in the frontal cortex, hippocampus and cerebellum in DS (Coyle et al., 1986). Other methods implemented to improve the quality of spatial normalization for this population utilized MRI sequences to minimize motion artifacts (Kecskmeti et al., 2018) and applied both morphological and PiB-based brain templates (Lao et al., 2019) with volume averaging strategies for longitudinal studies of amyloid accumulation in DS.

3.5. Amyloid PET and dementia in DS

Collectively, studies indicate that the age of onset of amyloid PET positivity in DS varies but appears to precede dementia (Jennings et al., 2015; Lao et al., 2016). Only a few PET studies tested the hypothesis that temporal and anatomical pattern of amyloid deposition in DS/dementia is distinct from DS/no dementia. Sabbagh and colleagues reported greater mean cortical and striatal [F-18]Florbetapir retention in DS/dementia (n=5, mean age 50 years) compared to DS/no dementia subjects (n=10, mean age 36 years) after adjusting for age, with both groups having higher retention values than controls (Sabbagh et al., 2015). Lao (2018) reported [C-11]PiB values above threshold levels in both DS/dementia (n=3, mean age 49 years, all PiB positive) and DS/no dementia subjects (16 PiB negative, mean age 35 years; 5 PiB+, mean age 47 years). Interestingly, the DS/no dementia/PiB positive group had [C-11]PiB retention levels exceeding threshold cutoffs in anterior cingulate, frontal cortex, and striatum, and levels at threshold cutoffs in the precuneus cortex, lateral parietal cortex, and temporal cortex. In contrast, the DS/dementia/PiB positive group had [C-11]PiB PET levels higher than cutoff values in all regions examined despite similar mean age when compared to the DS/no dementia/PiB positive group (Lao et al., 2018). Another [C-11]PiB PET study of DS/no dementia/PiB negative (n=41, mean age 35 years) and DS/no dementia/PiB positive (n=22, mean age 44 years) found that PET amyloid status did not influence between-person differences in cognition independent of age (Hartley et al., 2014). In a recent investigation, elevated [C-11]PiB binding potential was detected in 13 of 16 DS

participants with cognitive impairment or dementia, whereas comparable positivity was seen in only 7 of 33 cognitively stable participants (Annus et al., 2016). Considering these data, there is currently limited evidence to establish amyloid signature in DS/dementia compared to DS/no dementia beyond greater amyloid load which could reflect faster amyloid accumulation in the former group, conclusions supported by post-mortem studies (Wisniewski and Rabe, 1986). However, a recent study reported that amyloid loads were similar in the frontal cortex between demented and nondemented people with DS (Perez et al., 2019). Nevertheless, results from studies employing multiple imaging modalities (MRI and PET) in people with DS provide intriguing support for the idea that imaging signatures of structural MRI, glucose metabolism (FDG PET), and amyloid progression are capable of identifying distinct patterns of DS from those of AD dementia and cognitively normal people (Matthews et al., 2016).

3.6. Other pathologies and their potential value in interpreting amyloid PET signal in DS

3.6.1. Cerebral amyloid angiopathy—Cerebral amyloid angiopathy (CAA) refers to deposition of Aβ in brain vasculature and is a common neuropathology finding in DS (Belza and Urich, 1986; Davidson et al., 2018; Donahue et al., 1998; Frost et al., 2013; Kalaria et al., 1996; Mendel et al., 2010; Naito et al., 2008; Wisniewski et al., 1985a). As in amyloid plaques, Aβ in CAA also contributes to amyloid PET ligand retention in vivo (Bacskai, 2007; Lockhart 2007). Although variable, severity of CAA lesions in DS was reported to be higher than in sporadic AD (Head et al., 2017; Mann et al., 2018), a finding also reflected in studies of CAA-associated MRI neuroimaging features in DS (Carmona-Iragui et al., 2017). However, the time of onset of CAA lesions in DS, and its implications for amyloid PET imaging are not well-understood. In a cross-sectional neuropathology study of DS, the presence of CAA in relation to age lagged behind the first appearance of amyloid plaques in cerebral cortex and temporal lobe and more closely paralleled the time course of tau pathology (Davidson et al., 2018). Relevant to amyloid PET imaging which often uses cerebellum grey matter as a reference region, severe CAA in the cerebellum is a common finding in DS (Davidson et al., 2018). Interestingly, some AD cases with extensive capillary CAA are refractory to amyloid PET ligands (Rosen et al., 2010). Whether the same may occur in a subset of DS subjects remains to be determined to better understand the contribution of CAA to amyloid PET imaging in DS.

3.6.2. Tau, alpha-synuclein, and TDP-43 pathology—Tau pathology in the form of hyperphosphorylated, fibrillar tau protein aggregates in neurofibrillary tangles (NFT), dystrophic neurites, and neuropil threads typical of AD (Braak et al., 1986; Goedert, 1996; Kowall and Kosik, 1987) is also a major pathological feature of DS (Davidson et al., 2018; Mann, 1988b; McKenzie et al., 1996; Whalley, 1982; Wisniewski et al., 1985b). Autopsy studies of DS brain reported that amyloid precedes tau pathology in the cerebral cortex and in subcortical nuclei of the forebrain including the hippocampus and amygdala (Burger and Vogel, 1973; Davidson et al., 2018; Head et al., 2003; Hof et al., 1995; Mann, 1988b; Mann and Esiri, 1989; Mann et al., 1986; Margallo-Lana et al., 2007; Murphy et al., 1990; Whalley, 1982; Wisniewski et al., 1985b). While amyloid can be present without histologically-detectable tau pathology (Davidson et al., 2018; Whalley, 1982), the converse has not been reported, further indicating that amyloid positivity is an earlier phenomenon or

a prerequisite for tau pathology in DS. Similar to AD, tau pathology in DS was detected first in the temporal lobe, in the hippocampus/entorhinal cortex (Hyman and Mann, 1991; Mann, 1988a; Mann and Yates, 1987; Mann et al., 1986; Motte and Williams, 1989), though early involvement of brainstem monoamine-producing neuron systems was also reported (Davidson et al., 2018; Mann and Esiri, 1989). In DS subjects age 40 years and older, tau pathology is (almost) invariably present and co-distributed with amyloid (Mann, 1988b) in some cases at densities higher and with distributions wider than AD (Crapper et al., 1975; Yoshimura et al., 1990). Collectively, studies of DS cases greater than 40 years old led Mann to conclude that "frontal, temporal and parietal cortex are all favoured for plaque formation whereas the visual, motor and somatosensory cortex are much less affected. Former regions are also severely affected by tangle formation as are neurones in certain subcortical areas, locus caeruleus, nucleus basalis of Meynert, dorsal raphe, ventral tegmentum and occasionally some cells in the substantia nigra. Olfactory nuclei and tracts are also often affected by tangles and sometimes by plaques" (Mann, 1988a). These patterns roughly reflect evolution of tau pathology in AD (Braak and Braak, 1991). A recent article comparing demented and nondemented cases with DS found that NFT and neuropil thread densities in frontal cortex were significantly greater in DS with dementia compared to DS without dementia, while densities of tau pathology in the striatum were similar between groups (Perez et al., 2019). Moreover, ultrastructure of tau filaments in DS closely resemble those in AD (Ellis et al., 1974; Schochet et al., 1973). It has been reported that 3-repeat, but not 4-repeat tau mRNA is upregulated in DS (Oyama et al., 1994), however more studies are needed to clarify abundance of different tau species in DS. In summary, age- and region-related initiation and evolution of tau pathology, its ultrastructural characteristics, and its relation to amyloid pathology in DS are similar to AD. Hence, when amyloid PET scan of a DS subject is positive, the underlying amyloid pathology likely coexists with tau pathology. Further insight into the relationship of the two pathologies in DS and AD could be gained by imaging studies combining amyloid PET with tau PET tracers in the same people (Rafii et al., 2017). Studies of DS also reported accumulation of alpha-synuclein aggregates in Lewy bodies and neurites in neocortex and amygdala (Davidson et al., 2018; Lippa et al., 1999) and TDP-43 in dentate gyrus granule cells (Davidson et al., 2018; Lippa et al., 1999). Though none of currently available amyloid PET ligands binds to tau, alpha-synuclein, or TDP-43 aggregates, the relationship of these lesions to amyloid is an important avenue of investigation, in relation to development of dementia in people with DS, especially if PET ligands specific for alpha-synuclein and TDP-43 are developed successfully (Mathis et al., 2017).

4. Post-mortem neuropathology validation of amyloid PET imaging in DS

4.1. Imaging-to-autopsy studies of amyloid PET ligands in DS

Multiple studies of AD, MCI, and aged non-demented controls demonstrated high correspondence between post-mortem amyloid pathology and ante-mortem amyloid PET imaging using [C-11]PiB (Bacskai et al., 2007; Burack et al., 2010; Ikonomovic et al., 2008; Kadir et al., 2011; Kantarci et al., 2012; Sojkova et al., 2011) and related F-18 labeled ligands Florbetapir (Clark et al., 2012) and Flutemetamol (Curtis et al., 2015; Ikonomovic et al., 2016; Ikonomovic et al., 2018; Thal et al., 2018). In contrast, little work has been done

to elucidate neuropathology substrates of amyloid PET ligands in DS cases. In a case study, correspondence between cortical [F-18]Florbetapir retention and post-mortem amyloid plaques was examined in a 55-year old white male with DS/dementia (Sabbagh et al., 2011). All cortical regions analyzed showed highly positive [F-18]Florbetapir retention, similar to end-stage late-onset AD, with strongest signal observed in the striatum as well as in cerebral cortical regions including anterior cingulate, frontal, precuneus, and parietal cortex followed by temporal cortex and posterior cingulate cortex. Histological analysis of amyloid pathology in the same subject post-mortem agreed with region-matched ante-mortem PET data, showing frequent Aβ deposits in diffuse and neuritic plaques as well as CAA in regions of high ligand retention. These preliminary results highlight the need for additional imaging-to-autopsy studies of subjects with DS including those at younger ages and with intact cognition.

4.2. Biochemical characterization of amyloid PET ligands in post-mortem DS brain tissues

As autopsy brains of amyloid PET-imaged DS people become available, it will be important to more precisely evaluate the anatomical correspondence between ante-mortem amyloid PET retention levels and region-matched post-mortem amyloid load at different stages of disease progression. Until that time, one useful approach to characterize amyloid PET ligands in DS brain tissues involves post-mortem in vitro binding assays and tissue autoradiography studies using tritiated versions of C-11 and F-18 amyloid ligands. A recent study of a series of 31 DS cases 40 years and older reported variable but higher-than-control in vitro [H-3]PiB binding in homogenates of frontal cortex (LeVine et al., 2017). In a follow-up study, we examined [H-3]PiB binding level and concentration of insoluble (formic acid-soluble) fibrillar Aβ1–42 peptide in dorsolateral prefrontal cortex (BA46) from DS subjects with neuropathologically confirmed AD (DS+AD, n=18; ages 43–63 years), compared to normal controls and AD cases. Like the (LeVine et al., 2017) study, [H-3]PiB binding levels were variable, but most cases were above the values detected in normal aged controls (NC, n=9; ages 78–92 years) (Figure 3A). Furthermore, the average [H-3]PiB binding in DS+AD was higher than the average in AD cases (n=21; 76–101 years) although there was overlap (Figure 1A). Fibrillar Aβ1–42 peptide concentration measured in the same frontal cortex homogenates was also higher in DS+AD compared to NC and AD (Figure 3B), and it correlated with [H-3]PiB retention (Figure 3C). These results indicate that frontal cortex in older DS+AD subjects has higher concentration of fibrillar Aβ1–42 and more PiB-detectable amyloid burden compared to typical AD cases.

4.3. Histological characterization of amyloid PET ligands in post-mortem DS brain

Another method for characterizing amyloid PET ligands in DS autopsy brain tissues involves histological techniques with fluorescent derivatives of PET ligands. Previous studies used CN-PiB, a highly fluorescent derivative of PiB (Ikonomovic et al., 2006; Styren et al., 2000) in imaging-to-autopsy studies of [C-11]PiB (Ikonomovic et al., 2012; Ikonomovic et al., 2008). The same methodology was recently applied to autopsy studies of DS, demonstrating that Aβ plaques are detectable using CN-PiB histofluorescence in post-mortem DS brain tissue (LeVine et al., 2017; Perez et al., 2019). Examples of CN-PiB-labeled diffuse plaques in the striatum and mixed diffuse and classic plaques in the frontal

cortex of a DS+AD case is illustrated in Figure 4. We extended these observations by assessing CN-PiB-labeled Aβ plaque load separately in diffuse and classic, cored/neuritic plaques (based on morphological characteristics and overall intensity of CN-PiB fluorescence) in the frontal cortex from the same 18 DS cases with neuropathology confirmed AD (43–63 years) from our biochemical study (Figure 3) compared to aged controls (74–93 years; n=8) and AD (76–100 years; n=16). CN-PiB-labeled amyloid load (as % area coverage positive for CN-PiB fluorescence) in diffuse plaques was greater in DS than in controls but lower than in AD cases (Figure 5A), and when classic, cored/neuritic plaques were quantified, DS cases had on average higher loads than both control and AD cases (Figure 5B), in agreement with results of our biochemical analyses (Figure 3).

5. Technical considerations

Regardless of the ambiguous ultrastructural features of diffuse plaques, in AD striatum these deposits are associated with amyloid PET ligand retention when present at moderate to frequent densities (Beach et al., 2016). In addition, diffuse Aβ plaques in the striatum are PET-detectable in pre-symptomatic and symptomatic FAD (Klunk et al., 2007). In post-mortem DS cases, diffuse plaques are detectable and possibly predominant at the transitional period described by Mann (Mann, 1988a). The anterior ventral aspect of the striatum appears to retain amyloid PET ligands most robustly, and consequently this region has been targeted as a region-of-interest in many PET studies. This is logical, but further anatomical precision in ROI selection could yield valuable insights into potential differences in amyloid PET signal across patients in relation to their pre-mortem cognitive status (i.e., presence or absence of dementia). In a study of late onset AD, Ishibashi (2014) adapted a “striatum area” parcellation scheme from PET imaging studies of the dopaminergic circuit in this area (Martinez et al., 2003; Mawlawi et al., 2001). According to this scheme “the striatum was anatomically divided into five subregions: ventral striatum (VST), dorsal caudate rostral to the anterior commissure (AC) [pre-commissural dorsal caudate (preDCA)], dorsal putamen rostral to the AC [pre-commissural dorsal putamen (pre-DPU)], caudate caudal to the AC [post-commissural caudate (post-CA)], and putamen caudal to the AC [post-commissural putamen (post-PU)]” (Ishibashi et al., 2014). If this scheme is applied in parallel with careful neuropathological descriptions of amyloid plaque types at the light and electron microscopic levels, in relation to cognitive status and age in DS, the full potential of the striatum in identifying early stages of the disease, or cases with dementia susceptibility might be revealed.

From a neuropathology perspective, more care is needed in the choice of anti-Aβ antibodies used for immunohistochemical determination of Aβ plaque type and load, especially in future imaging-to-autopsy analyses of DS cases younger than 40 y. The poor sensitivity of certain variations of silver histology methods in detecting diffuse (probably Type 3) plaques in early reports of amyloid in DS likely resulted in this technique missing many of the diffuse Aβ deposits subsequently observed using more sensitive immunohistochemical procedures. However, immunohistochemical procedures appear to vary in their sensitivity depending on the Aβ antibody used in the assay. Only a few studies showed robust labeling of high densities of neocortical diffuse Aβ plaques in adolescent, teenage, and young adult DS cases, and these studies employed Aβ antibodies that have not been used frequently in

autopsy studies of DS, including an antibody against Aβ42 [“BC42” against Aβ37–42 (Lemere et al., 1996)] and Aβ N-terminal amino acid directed antibodies [NAB228 against Aβ1–11 (Liu et al., 2006) and 10D5 recognizing an epitope within Aβ amino acids 3–7; (Leverenz and Raskind, 1998)]. Another study robustly labeled cerebellar diffuse plaques with antibody 4G8 but not 6E10 which in part reflects the high amounts of nonamyloidogenic Aβ17–42 (p3 fragment) considered pre-amyloid in diffuse cerebellar Aβ deposits (Lalowski et al., 1996). A recent study indicated no difference between demented and nondemented subjects with DS based on an analysis of frontal cortex using Aβ/APP (6E10) and Aβ (MOAB2) immunohistochemistry as well as X-34 and CN-PiB fluorescence (Perez et al., 2019). However, in subjects with DS and dementia, cortical APP/Aβ and X-34 plaque load was significantly higher than Aβ and CN-PiB plaque load. Future investigations should include a panel of antibodies proven successful in marking diffuse Aβ plaques in DS and AD (i.e., NAB228 or 10D5) as well as antibodies generated against the large array of possible N- and C- terminal truncated Aβ species or other possible Aβ species.

6. Conclusions

There is a need for longitudinal PET studies of large series of DS cases assessing amyloid in the neocortex as well as in discrete striatal areas (e.g., (Ishibashi et al., 2014)) to compare to future imaging-to-autopsy studies. In addition, significant advances have been made in tau PET imaging of AD, and this knowledge combined with amyloid PET and other modalities (volumetric MRI, FDG PET) will continue to enhance our ability to detect pathology and monitor its progression in living people with DS (Neale et al., 2017; Rafii et al., 2017; Rafii, 2018). One caveat encountered frequently in post-mortem validation studies of PET imaging ligands in AD is long time intervals between imaging and autopsy, which is difficult to avoid except in cohorts of subjects at end-of-life (which must be ethically justified). A distinction should be made between use of amyloid PET (in combination with other imaging modalities, such as [F-18]FDG as well as volumetric and diffusion MRI) as a biomarker for amyloid and its use to investigate the early stages of the natural course of history of amyloid deposition in DS. In DS as in FAD, use of amyloid PET is effective in identifying older subjects with *substantial* fibrillar Aβ deposition in most plaque types and is therefore valuable as a biomarker for classic AD amyloid pathology in these people. However, utility of amyloid PET may be limited in the earliest stages of the natural history of amyloid in DS subjects younger than 25 years, due to presence of low levels of diffuse plaques with very small amounts of Aβ fibrils. Nevertheless, the ability of amyloid PET to detect early Aβ deposits in young DS brains needs further investigation. In contrast to gold standard neuropathology analyses, PET imaging studies are more limited in their sensitivity and specificity. This is particularly important to keep in mind when attempting to draw conclusions about regional order of pathology onset and progression using PET imaging which lacks necessary resolution to overcome the challenges due to regional variations in amyloid deposits with wide variety of morphological, structural, and biochemical profiles that could affect the binding of imaging ligands. In contrast, amyloid PET can measure amyloid deposition in the entire brain, whereas neuropathological assessment is limited for practical reasons to small sampling of the brain, which can lead to biased findings. Regarding the proposed striatal-predominant amyloid PET positivity in younger (<40 years

old) DS subjects, it remains to be determined if this region is the anatomical nidus of amyloid pathology in these subjects or whether this is the first region where amyloid becomes “PET-detectable.” Until this is resolved, caution is needed when drawing conclusions from amyloid PET imaging studies (especially based on cross-sectional analyses) - the proposed order of regional pathology may simply reflect the anatomical locations where amyloid PET ligands are most readily retained in younger cases independent of the natural course of the patho-anatomical evolution of amyloid lesions which are variably detectable with currently used amyloid PET tracers.

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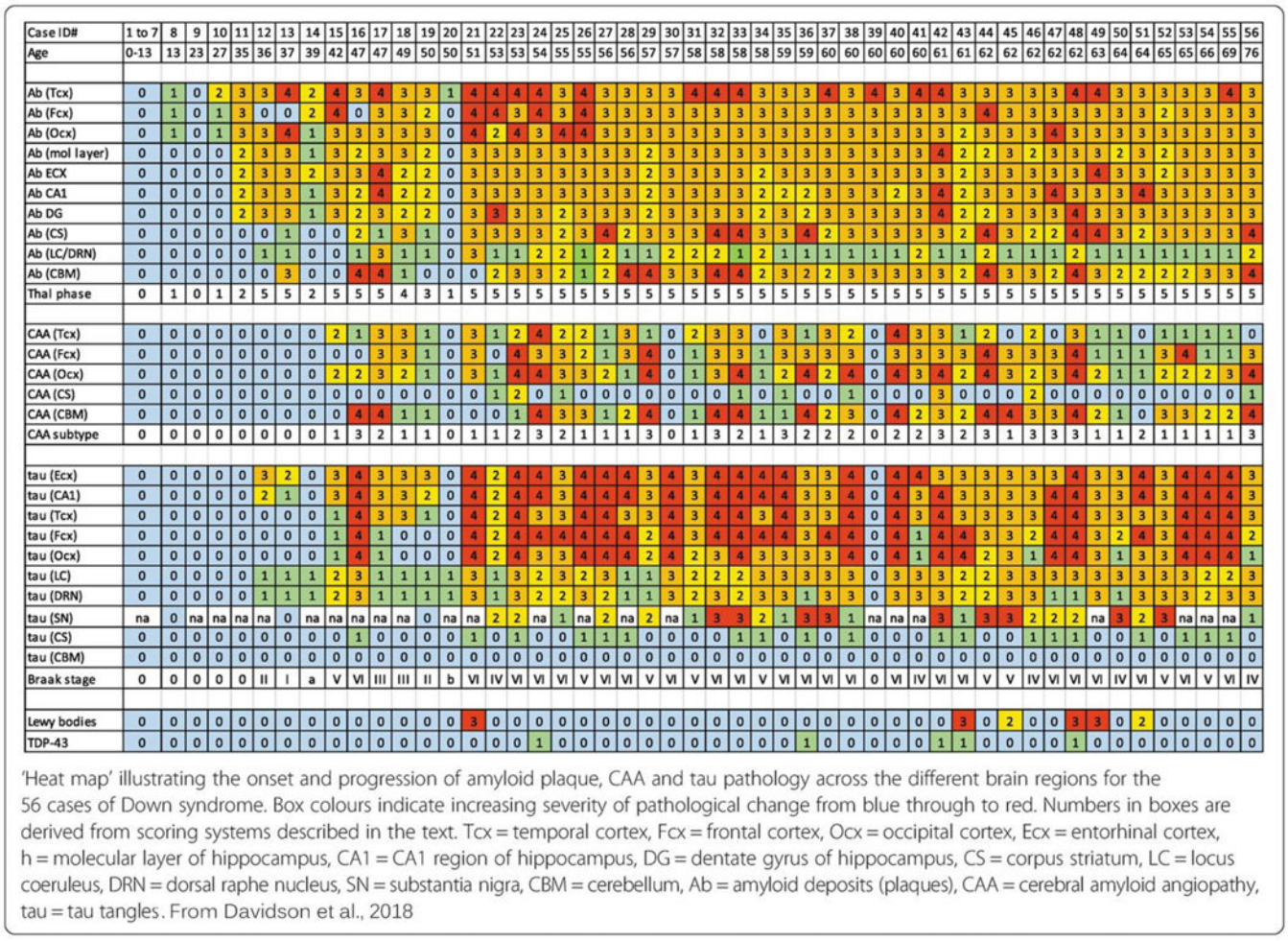

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Age	0-13	13	23	27	35	36	37	39	42	47	47	49	50	50	51	53	53	54	55	55	56	56	57	57	58	58	58	58	59	59	60	60	60	60	60	60	61	61	62	62	62	62	63	64	64	65	65	66	69	76
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Ab ECX	0	0	0	0	2	3	3	2	3	3	4	2	2	0	3	3	3	3	3	3	3	3	2	3	3	3	3	2	3	3	3	3	3	3	3	3	2	3	3	3	3	4	3	3	2	3	3	3	3	3
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Ab (CS)	0	0	0	0	0	0	1	0	0	2	1	3	1	0	3	3	3	3	2	3	4	2	3	3	3	4	4	3	3	4	2	3	3	3	3	3	2	4	3	2	2	4	4	3	2	3	3	3	3	4
Ab (LC/DRN)	0	0	0	0	1	1	0	0	1	3	1	1	0	3	1	1	2	2	1	2	1	1	2	2	2	1	2	1	1	1	1	1	1	1	2	1	1	2	1	1	1	2	1	1	1	1	1	1	1	2
Ab (CBM)	0	0	0	0	0	0	3	0	0	4	4	1	0	0	0	2	3	3	2	1	2	4	4	3	3	4	4	2	3	2	2	3	3	3	3	3	2	4	3	3	2	4	3	2	2	2	2	3	3	4
Thal phase	0	1	0	1	2	5	5	2	5	5	5	4	3	1	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
CAA (Tcx)	0	0	0	0	0	0	0	0	2	1	3	3	1	0	3	1	2	4	2	2	1	3	1	0	2	3	3	0	3	1	3	2	0	4	3	3	1	2	0	2	0	3	1	1	0	1	1	1	1	0
CAA (Fcx)	0	0	0	0	0	0	0	0	0	0	3	3	1	0	3	0	4	3	3	2	1	3	4	0	1	3	3	1	3	3	3	3	0	3	3	3	3	4	3	3	3	4	1	1	1	3	4	1	1	3
CAA (Ocx)	0	0	0	0	0	0	0	0	2	2	3	2	1	0	3	1	4	4	3	3	2	1	4	0	1	3	4	1	2	4	2	4	0	4	3	4	2	4	3	2	3	4	2	1	1	2	2	2	3	4
CAA (CS)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	2	0	1	0	0	0	0	0	0	0	1	0	1	0	0	1	0	0	0	3	0	0	0	2	0	0	0	0	0	0	0	0	0	1
CAA (CBM)	0	0	0	0	0	0	0	0	0	4	4	1	1	0	0	0	1	4	3	3	1	2	4	0	1	4	4	1	1	4	2	3	0	4	2	3	2	4	4	3	3	4	2	1	0	3	3	2	2	4
CAA subtype	0	0	0	0	0	0	0	0	1	3	2	1	1	0	1	1	2	3	2	1	1	1	3	0	1	3	2	1	3	2	2	2	0	2	2	3	2	3	1	3	3	3	1	1	2	1	1	1	1	3
tau (Ecx)	0	0	0	0	0	3	2	0	3	4	3	3	3	0	4	2	4	4	3	4	4	4	3	4	3	4	4	4	4	3	3	4	0	4	4	3	3	3	3	3	3	4	3	3	4	3	4	4	4	3
tau (CA1)	0	0	0	0	0	2	1	0	3	4	3	3	2	0	4	2	4	4	3	4	4	4	3	4	3	4	4	4	4	3	3	4	0	4	3	4	3	3	3	3	3	4	4	3	3	4	3	4	4	3
tau (Tcx)	0	0	0	0	0	0	0	0	1	4	3	3	1	0	4	2	4	3	3	4	4	3	3	4	3	4	4	3	4	3	3	3	4	0	4	3	4	3	3	3	3	4	4	3	3	3	3	4	4	3
tau (Fcx)	0	0	0	0	0	0	0	0	1	4	1	0	0	0	4	2	4	4	4	4	4	4	2	4	3	4	4	4	4	3	3	4	4	0	4	1	4	4	3	3	2	4	4	3	2	4	3	4	4	2
tau (Ocx)	0	0	0	0	0	0	0	0	1	4	1	0	0	0	4	2	4	3	3	4	4	4	2	4	2	3	4	3	3	3	3	4	0	4	1	4	4	2	3	1	4	4	3	1	3	3	4	4	4	1
tau (LC)	0	0	0	0	0	1	1	1	2	3	1	1	1	1	3	1	3	2	3	2	3	1	1	3	2	2	2	3	3	3	3	3	0	3	3	3	2	2	3	3	3	3	3	3	3	3	2	2	3
tau (DRN)	0	0	0	0	0	1	1	1	2	3	1	1	1	1	3	1	3	2	2	3	2	1	1	3	2	3	2	3	3	1	3	3	0	3	3	3	2	2	3	3	1	1	3	1	3	3	3	2	3	3
tau (SN)	na	0	na	na	na	na	0	na	na	na	na	na	0	na	na	2	2	na	1	na	2	na	2	na	1	3	3	2	1	3	3	1	na	na	na	3	1	3	3	2	2	2	na	3	2	3	na	na	na	1
tau (CS)	0	0	0	0	0	0	0	0	0	1	0	0	0	0	1	0	1	0	0	1	1	1	0	0	0	0	1	1	0	1	0	1	0	0	0	1	1	1	0	0	1	1	1	0	0	1	0	1	1	0
tau (CBM)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Braak stage	0	0	0	0	0	II	I	a	V	VI	III	III	II	b	VI	IV	VI	VI	VI	V	VI	VI	V	VI	V	VI	VI	V	VI	VI	VI	0	VI	IV	VI	VI	V	V	IV	VI	VI	VI	VI	IV	VI	V	VI	V	VI	IV
Lewy bodies	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	0	2	0	0	3	3	0	2	0	0	0	0	0	0
TDP-43	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	1	0	0	0	0	1	0	0	0	0	0	0	0	0

'Heat map' illustrating the onset and progression of amyloid plaque, CAA and tau pathology across the different brain regions for the 56 cases of Down syndrome. Box colours indicate increasing severity of pathological change from blue through to red. Numbers in boxes are derived from scoring systems described in the text. Tcx = temporal cortex, Fcx = frontal cortex, Ocx = occipital cortex, Ecx = entorhinal cortex, h = molecular layer of hippocampus, CA1 = CA1 region of hippocampus, DG = dentate gyrus of hippocampus, CS = corpus striatum, LC = locus coeruleus, DRN = dorsal raphe nucleus, SN = substantia nigra, CBM = cerebellum, Ab = amyloid deposits (plaques), CAA = cerebral amyloid angiopathy, tau = tau tangles. From Davidson et al., 2018

Figure 1.

Heat map illustrating the regional progression of amyloid, tau, Lewy bodies, and TDP-43 pathology in subjects with DS aged 0–76 years. From Davidson et al., 2018.

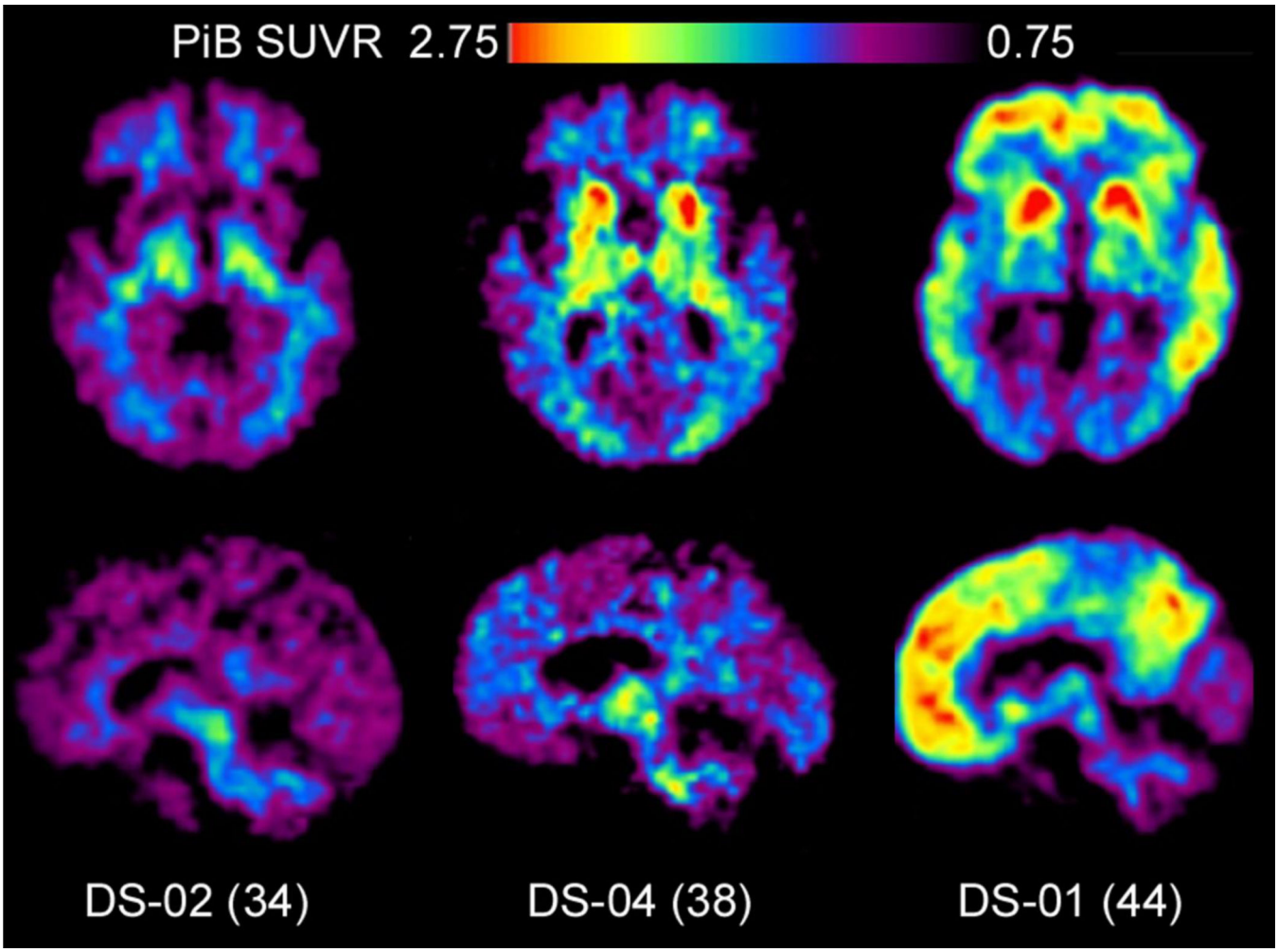

Figure 2.

Pittsburgh compound B (PiB) standardized uptake value ratio (SUVR) images of subjects with DS showing different levels of ligand retention (the axial images are shown at the top and the sagittal images at the bottom). **Left:** Amyloid-negative 34 year-old DS subject showing only nonspecific PiB retention in white matter; **Middle:** Moderately amyloid-positive 38 year-old DS subject showing early striatal PiB retention; and **Right:** Heavily amyloid-positive 44 year-old DS subject which is very similar to those seen in late-onset AD, but with a predominant striatal signal. Adapted from Handen et al., 2012.

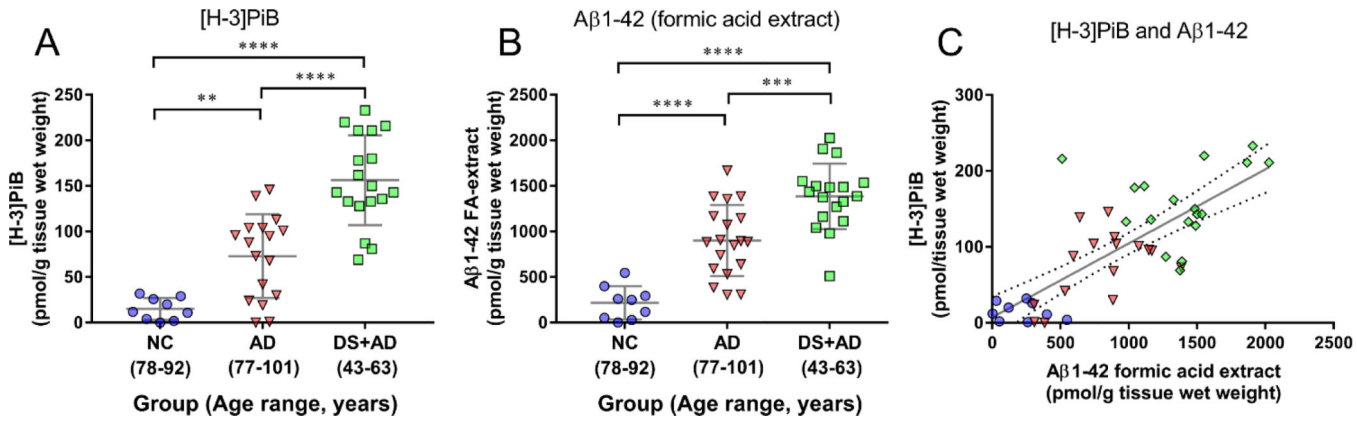

Figure 3.

Biochemical analyses of [H-3]PiB binding and concentration of formic acid-extracted (insoluble) 42 amino acid-long amyloid-β peptide (Aβ1–42) in the frontal cortex (BA10) from subjects with normal cognition (NC, age range 78–92 years) and Alzheimer's disease (AD, age range 76–101 years) from the Rush Religious Order Study brain bank compared to adults with Down syndrome and AD (DS+AD, range 43–63 years) from the University of California Irvine brain bank. **(A)** [H-3]PiB binding differed between groups ($F(2, 41) = 35.76$, $P < 0.0001$; Tukey multiple comparisons, NC < AD, DS; AD < DS). **(B)** Concentration of insoluble Aβ1–42 differed between groups ($F(2, 43) = 34.5$, $P < 0.0001$; Tukey multiple comparisons, NCI < mild AD, mod/sev AD, DS; mild AD, mod/sev AD < DS). **(C)** Insoluble Aβ1–42 and [H-3]PiB binding correlated across groups by linear regression analysis ($Y = 0.09746*X + 7.256$, R square = 0.59, $P < 0.0001$). **0.01 < P<0.05; ***0.0001 < P< 0.001; ****P < 0.0001.

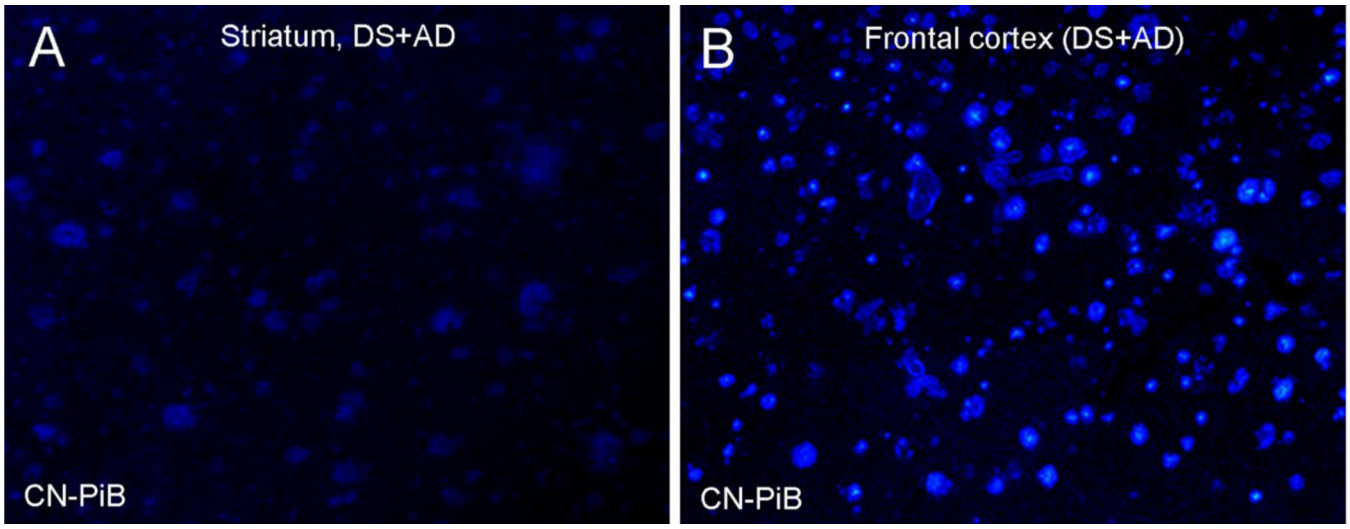

Figure 4.

Representative images of CN-PiB fluorescence in diffuse plaques in the striatum **(A)** and both diffuse and cored plaques as well as cerebral amyloid angiopathy in the frontal cortex of a 57-year old female with DS and confirmed AD pathology **(B)** from the University of California Irvine brain bank. Scale bar = 200 μm.

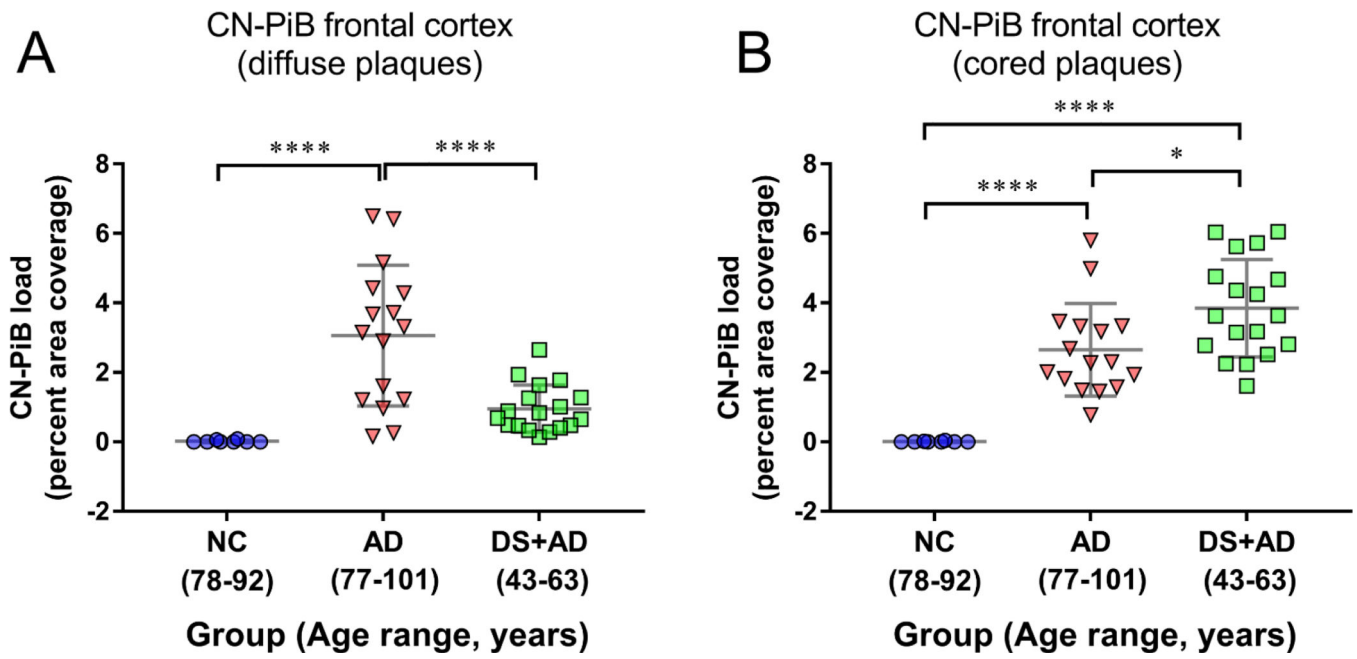

Figure 5.

CN-PiB positive plaque load (expressed as percent area coverage) analyzed separately for diffuse **(A)** and cored **(B)** plaques in the frontal cortex from cases with normal cognition (NC, age range 74–93 years) and Alzheimer's disease (AD, age range 76–100 years) from the Rush Religious Order Study brain bank compared to adults with Down syndrome and AD (DS+AD, range 43–63 years) from the University of California Irvine brain bank. CN-PiB-labeled diffuse plaque load differed between groups ($F(2, 39) = 17.36$, $P < 0.0001$; Tukey multiple comparisons, AD > NC, DS+AD). CN-PiB-labeled load of cored plaques differed between groups ($F(2, 39) = 26.54$, $P < 0.0001$; Tukey multiple comparisons, NCI < AD, DS+AD; AD < DS+AD. *$P < 0.05$; ***$0.0001 < P < 0.001$; ****$P < 0.0001$.