NeuroImage: Clinical 17 (2018) 263–271

Contents lists available at ScienceDirect

NeuroImage: Clinical

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

Neuroimaging and other modalities to assess Alzheimer's disease in Down syndrome☆

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ARTICLE INFO

Keywords:
Biomarkers
Dementia
Diffusion tensor imaging (DTI)
Electroencephalography (EEG)
Magnetic resonance imaging (MRI)
Positron emission tomography (PET)

ABSTRACT

People with Down syndrome (DS) develop Alzheimer's disease (AD) at higher rates and a younger age of onset compared to the general population. As the average lifespan of people with DS is increasing, AD is becoming an important health concern in this group. Neuroimaging is becoming an increasingly useful tool in understanding the pathogenesis of dementia development in relation to clinical symptoms. Furthermore, neuroimaging has the potential to play a role in AD diagnosis and monitoring of therapeutics. This review describes major recent findings from in vivo neuroimaging studies analysing DS and AD via ligand-based positron emission tomography (PET), [18F] fluorodeoxyglucose (FDG)-PET, structural magnetic resonance imaging (sMRI), and diffusion tensor imaging (DTI). Electroencephalography (EEG) and retinal imaging are also discussed as emerging modalities. The review is organized by neuroimaging method and assesses the relationship between cognitive decline and neuroimaging changes. We find that amyloid accumulation seen on PET occurs prior to dementia onset, possibly as a precursor to the atrophy and white matter changes seen in MRI studies. Future PET studies relating tau distribution to clinical symptoms will provide further insight into the role this protein plays in dementia development. Brain activity changes demonstrated by EEG and metabolic changes seen via FDG-PET may also follow predictable patterns that can help track dementia progression. Finally, newer approaches such as retinal imaging will hopefully overcome some of the limitations of neuroimaging and allow for detection of dementia at an earlier stage.

1. Introduction

Neuroimaging has important research and clinical implications in people with Down syndrome (DS) and Alzheimer's disease (AD). Correlating brain changes with clinical presentation can help uncover the mechanisms of dementia development. Clinically, neuroimaging of biomarkers can be used to track the development of AD in DS, allowing for deep phenotyping and analysis of therapeutic efficacy. Furthermore, neuroimaging can be used along with clinical symptoms to help confirm a diagnosis of AD in people with DS. After discussing relevant background information regarding DS and AD, this review provides an overview of clinical neuroimaging studies in the field from the past 10 years. The review is organized by in vivo neuroimaging methods, including ligand-based positron emission tomography (PET), [18F] fluorodeoxyglucose (FDG)-PET, structural magnetic resonance imaging (sMRI), diffusion tensor imaging (DTI), electroencephalography (EEG), and retinal imaging. Correlation of imaging changes to cognitive decline is considered, and a discussion of the limitations and feasibility of neuroimaging is included. This review is aimed at clinicians, psychologists, researchers, and those with an interest in DS and/or AD.

2. Background

2.1. Down syndrome overview

In order to appreciate the neuroimaging findings in people with DS

Abbreviations: Aβ, amyloid beta; AD, Alzheimer's disease; APP, amyloid precursor protein; DS, Down syndrome; DTI, diffusion tensor imaging; EEG, electroencephalography; FDG, fluordexoyglucose; NFT, neurofibrillary tangles; PET, positron emission tomography; sMRI, structural magnetic resonance imaging

☆ The authors have no conflict of interest to declare.

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http://dx.doi.org/10.1016/j.nicl.2017.10.022
Received 18 August 2017; Received in revised form 18 October 2017; Accepted 23 October 2017

and AD, it is important to understand the pathogenesis of DS and its link to AD. DS is a genetic abnormality resulting from an extra copy of chromosome 21, which manifests as intellectual disability and an array of physical characteristics. The vast majority of cases are due to a trisomy of chromosome 21, while 5% are due to Robertsonian Translocation or mosaicism (Wilson et al., 2014). This results in an increased dosage of the gene products on chromosome 21, which can disrupt a variety of pathways, including those involved with brain development, metabolism, and neuronal networks (Bouman and Hennekam, 2015). In regards to epidemiology, DS is one of the most common intellectual disabilities, occurring in 1/750 live births (Antonarakis et al., 2004). The risk of having a child with DS is linked to maternal age, with an 11/1000 chance in women over 40 (Puri and Morris, 2015). As our understanding of DS has increased, the lifespan of individuals with DS in developed countries has improved dramatically, as the average person with DS now lives into their 50s (Zigman and Lott, 2007). With this increase, it is important that we understand the aging process in DS and provide appropriate support throughout the lifespan.

2.2. Structural brain abnormalities in Down syndrome

Neurodevelopmental abnormalities in DS result in characteristic brain features. People with DS are brachycephalic and have a reduced overall brain size, with a specific reduction in the volume of the frontal and temporal lobes and the cerebellum (Newton, 2015). Within the temporal lobe, the superior temporal gyrus is reduced, while the parahippocampal gyrus can be increased compared to the general population. Recent findings (Lee et al., 2016) suggest that surface area reductions rather than a decrease in cortical thickness are responsible for the reduced cortical volume in certain areas. Furthermore, structural imaging findings (Annus et al., 2017) have found that the DS brain has a thicker frontal and occipitoparietal cortex, a thinner motor cortex and temporal pole, a smaller hippocampus and a larger putamen. Additionally, people with DS tend to show accelerated aging in their brains, demonstrating an adjusted brain-predicted age difference increase of 7.69 years (Cole et al., 2017). It has been demonstrated (Beacher et al., 2010) that the frontal, temporal and parietal lobes show greater age-related reduction than the general population. Understanding these structural differences is important in order to have a framework for how pathologies like dementia alter the DS brain.

2.3. Dementia and Down syndrome

AD is becoming an important health concern in people living longer with DS. People with DS are at an increased risk of developing dementia compared to the general population, and the onset occurs at a relatively younger age (Wilson et al., 2014). The prevalence of dementia in people with DS is about 3.4% in their 30s, 10.3% in their 40s, and 40% in those over 50 (Holland et al., 1998). Dementia can be difficult to diagnose in this population for a number of reasons. Individuals with DS may have a low baseline cognitive function, which can negatively affect their performance on cognitive tests designed for the general population that do not take into account the pre-existing intellectual deficits. People with DS also vary considerably in their intellectual ability, and this heterogeneity makes it difficult to establish reliable cut off scores on cognitive tests. For these reasons, DS-specific neuropsychological tests that take into account the spectrum of DS are needed in order to diagnose dementia in this population. In addition to the need for specialized cognitive tests, another challenge in diagnosis is that AD has a different initial presentation in DS compared to the general population, with changes in personality and executive function often manifesting before memory impairment (Wilson et al., 2014). One possible explanation for this is that the frontal lobe in DS is underdeveloped and thus more vulnerable to the effects of amyloid (Holland et al., 2000), but further research in this area is needed (Fonseca et al., 2016). An additional issue in diagnosing AD in people with DS is that they may struggle with communication, so there is often increased reliance on informant reports for diagnosis. Finally, DS is often associated with sensory, neurologic and psychiatric comorbidities which complicate the diagnosis of AD (Newton et al., 2015). For all these reasons, neuroimaging may be helpful as a complementary method of establishing a diagnosis and monitoring AD in this population.

2.4. Pathogenesis: The amyloid cascade hypothesis and other potential mechanisms

The amyloid cascade hypothesis is a major theory for the development of AD. Amyloid beta (Aβ) is a product of one of the pathways of amyloid precursor protein (APP) proteolysis, where APP is cleaved by beta-secretase 1 and gamma-secretase (Querfurth and LaFerla, 2010). Aβ peptides can vary slightly in length, and the Aβ42 form is particularly prone to aggregation, arranging into beta sheets that are responsible for amyloid plaques (Yan and Wang, 2007). In addition to the fibrillar form, there are also oligomer forms of Aβ42 that may have an even greater detrimental impact on neurons (Wilson et al., 2014). The risk of AD is higher in people with DS compared to people with non-DS intellectual disabilities (Strydom et al., 2013), and this is thought to be due to the presence of APP on human chromosome 21 (Goldgaber et al., 1987). The trisomy of chromosome 21 in people with DS therefore leads to increased dosage of APP and accumulation of insoluble, neurotoxic Aβ peptides.

Another biomarker for AD is tau, which correlates more closely with cognitive decline (Wolfe, 2009). Tau is a protein that allows for axonal transport of vesicles and organelles by associating with microtubules (Wilson et al., 2014). In AD, tau can no longer associate with microtubules because it is hyperphosphorylated and, as a result, neurotoxic neurofibrillary tangles (NFTs) are formed. Dual-specificity tyrosine-phosphorylation-regulated kinase 1A is located on chromosome 21, and excess of this kinase in DS could contribute to higher levels of hyperphosphorylated neurotoxic tau (Liu et al., 2008). On the other hand, animal studies suggest that Aβ pathology drives tau pathology, providing support for the amyloid cascade hypothesis as the key mechanism of AD in DS (Götz et al., 2001). On a molecular level, some findings suggest that amyloid influences the hyperphosphorylation of tau, promoting the presence of this neurotoxic form (De Felice et al., 2008). Regardless of the principle mechanism of tau pathogenesis, tau clearly plays a key role in neuronal degeneration.

An additional proposed mechanism in AD development is neuroinflammation. Amyloid plaques cause recruitment of microglia and interact with receptors on these cells, leading to production of pro-inflammatory cytokines and reactive oxygen species that are thought to be neurotoxic (Zotova et al., 2010). Because this is a downstream effect of amyloid, involvement of neuroinflammation is consistent with the amyloid cascade hypothesis of AD in DS. However, there is evidence of people with DS showing increased baseline expression of IL-1, an inflammatory cytokine, and chromosome 21 gene product S100B, a protein that is elevated in reactive astrocytes (Wilcock and Griffin, 2013). This suggests that neuroinflammation may also be working in parallel with the amyloid cascade to increase predisposition to AD.

In addition to these major theories, there are other genes on chromosome 21 that could play a role in premature brain aging, such as SOD-1 and SLC5A3 (Beacher et al., 2010). Mitochondrial dysfunction in neurons and astrocytes could also be involved, either independently or via altered metabolism of APP (Busciglio et al., 2002; Tiano and Busciglio, 2011). In sum, there are likely several mechanisms happening simultaneously to contribute to AD development in people with DS, but the amyloid cascade hypothesis is the most widely accepted theory for this population. While not all with DS eventually develop AD, these genetic factors certainly place them at risk.

3. Methodology

To ensure that no other reviews exist on this exact topic, a thorough search of Cochrane Library was performed. This review summarizes recent findings from our lab as well as literature on neuroimaging in DS and AD from the past 10 years. To identify articles about neuroimaging in Down syndrome and dementia, a literature search on PUBMED was performed using the keywords Alzheimer's disease OR dementia AND MRI AND Down syndrome with the limiters of English, full text, and published in the past 10 years. A MEDLINE search was then performed using the keywords in a different order (Down syndrome AND Alzheimer's disease OR dementia AND MRI) with the same limiters. The same steps were taken with the keywords Alzheimer's disease OR dementia AND PET AND Down syndrome. Finally, an additional search was made in this way using “neuroimaging” instead of “PET.” Sources were also gained from the references of the selected literature. Additionally, the books “Intellectual Disability and Dementia,” edited by Karen Watchman, and “Down Syndrome: Current Perspectives,” edited by Richard W Newton, Shiela Puri and Liz Marder, were used to gather relevant background information and sources. Articles were chosen for studies that involved DS subjects to assess in vivo neuroimaging changes and their relationship with cognitive decline and dementia status.

4. Results: Neuroimaging trends in Down syndrome with dementia

In this section, we present our findings from our literature review of major neuroimaging studies in the field from the past 10 years. We also discuss studies using emerging modalities such as EEG and retinal imaging.

4.1. PET

We review recent findings using in vivo PET to assess amyloid accumulation in people with DS (Table 1). We also include a discussion of the current amyloid ligands available, and the potential for ligand-based tau studies using PET in this population.

4.1.1. Amyloid ligands

In order to appreciate PET ligand-based findings, it is important to include a discussion of the current amyloid ligands available. Pittsburgh compound B (PiB) is used to assess amyloid accumulation in AD. PiB specifically binds to amyloid arranged in beta sheets in classic plaques, cerebrovascular amyloid angiopathy, and, to a lesser extent, diffuse plaques (Cohen et al., 2012; LeVine et al., 2017; Lockhart et al., 2007). One limitation of PiB is that it must be manufactured on-site due to its short half-life, and thus fluoride-based compounds can be a useful alternative (Cohen et al., 2012; Sabbagh et al., 2011). While the current amyloid ligands available are useful tools for detecting AD, one drawback is their limited ability to detect non-neuritic amyloid plaques that may occur in a prodromal or early stage of dementia (Cairns et al., 2009; Ikonomovic et al., 2008; Iwatsubo et al., 1995; Lemere et al., 1996). Even among those with late-stage AD, there may be some PiB-refractory cases due to molecular variants of Aβ (Rosen et al., 2010). Thus, it is important to consider these caveats when interpreting in vivo PET results.

4.1.2. Amyloid distribution based on PET

It has been known for several decades that Aβ accumulation is nearly universal in people with DS over age 40, as demonstrated by post-mortem studies (Mann et al., 1984). More recent methods have used PET to visualize Aβ plaques in vivo with radioligands, and this method has been shown to be safe and ethical in people with DS (Landt et al., 2011). While even those with DS without clinical symptoms of AD show amyloid binding, some of these studies demonstrate that binding is increased with clinically diagnosed dementia status (Annus et al., 2016; Sabbagh et al., 2015). Findings regarding the relationship between amyloid binding and cognitive performance, however, have been inconsistent (Annus et al., 2016; Cole et al., 2017; Hartley et al., 2014; Nelson et al., 2011; Rafii et al., 2015). Nonetheless, regardless of cognitive decline or dementia status, it has been consistently demonstrated in PET studies that amyloid increases with age in this population (Annus et al., 2016; Hartley et al., 2014; Jennings et al., 2015; Lao et al., 2016, 2017; Nelson et al., 2011; Rafii et al., 2015; Sabbagh et al., 2015). While causal relationships cannot be determined from these findings, this predisposition of Aβ accumulation prior to dementia onset is consistent with the amyloid cascade hypothesis.

The progression of amyloid accumulation seems to be unique in DS individuals compared to sporadic AD. Recent studies have demonstrated that the first area of accumulation is the striatum (Annus et al., 2016; Handen et al., 2012; Lao et al., 2016, 2017). Annus et al. (2016) found that amyloid accumulation began in the striatum, starting around age 40, followed by the rostral prefrontal-cingulo-parietal regions, then caudal frontal, rostral temporal, primary sensorimotor and occipital regions, and lastly the mediotemporal regions and remainder of the basal ganglia. This may contrast with amyloid accumulation patterns in sporadic AD in the general population, where an early striatal-only phase has not been demonstrated (Thal et al., 2002). On the other hand, early striatal binding is seen in familial autosomal dominant AD (Klunk et al., 2007), leading Annus et al. (2016) to hypothesize that this early stage may be unique to amyloid overproduction. Further research on the significance of early striatal binding may help elucidate the mechanism of dementia development in DS individuals.

In sum, PET findings analysing amyloid suggest that amyloid accumulation, beginning in the striatum, is a precursor to the development of dementia. While those with dementia show increased levels of amyloid, there is no clear association between amount of amyloid and performance on cognitive tests. This suggests that while amyloid accumulation may be a necessary step in the progression to dementia, there are likely downstream mechanisms more directly influencing cognitive decline.

4.1.3. Tau distribution based on PET

Tau is a microtubule-associated protein that becomes hyperphosphorylated in AD, leading to the formation of NFTs (Bouman and Hennekam, 2015). In the general population, tau pathology is a more accurate marker for cognitive decline in AD than amyloid pathology (Brier et al., 2016). This relationship has been demonstrated in post-mortem pathology of DS brains, correlating NFTs to cognitive decline (Margallo-Lana et al., 2007). Certain markers like [18F]FDDNP PET have been used to analyse both amyloid plaques and NFTs in this population (Nelson et al., 2011), but there have not been any studies in individuals with DS using PET to analyse tau distribution alone. Future studies in this area may provide valuable insight into the relationship between neuropathological changes and cognitive dysfunction in this population. For example, AV1451 is a tracer increasingly being used to study tau in AD that should prove useful (Golla et al., 2017). It is possible that in vivo tau imaging will correlate more closely with atrophy and cognitive measures compared to amyloid, providing a missing link between amyloid overproduction and clinically detectable dementia.

4.1.4. PET assessment of metabolic activity

FDG-PET is a useful neuroimaging tool in assessing neuronal activity based on glucose metabolism. Changes in FDG have been shown to be associated with cognitive function in people with DS (Haier et al., 2008; Matthews et al., 2016; Rafii et al., 2015). Interestingly, even non-demented DS individuals can demonstrate hypometabolism of the posterior cingulate-precuneus, a region that is also hypometabolic in AD in the general population (Matthews et al., 2016; Minoshima et al., 1997). It has also been demonstrated that those with DS and AD have

Table 1
Summary of ligand-based PET findings in DS and AD.

Authors	Final # of participants	Ligand; reference region	Results	Scanning feasibility issues
Landt et al. (2011)	5 with DS/AD, 4 with DS only, 14 healthy controls without DS	PiB; Cerebellum	Only people with DS older than 45 had significant binding in regions of interest, whether or not they had dementia.	1/11 (9.1%) DS participants who agreed to undergo scanning dropped out due to anxiety provoked by elevation of scanning table.
Nelson et al. (2011)	19 with DS, 10 with AD, 10 controls	[18F]FDDNP; Cerebellum	Higher binding in DS (in parietal, medial temporal, lateral temporal, and frontal lobes and posterior cingulate gyrus), comparable or higher than AD group in all regions. Binding had positive association with age and behavioural dysfunction in several regions.	None reported.
Handen et al. (2012)	7 with DS and no dementia	PiB; Cerebellum	The two subjects with PiB binding showed early striatal accumulation.	1/8 (12.5%) participants was unable to complete PET imaging (reason not provided).
Hartley et al. (2014)	63 with DS and no dementia	PiB; Subcortical white matter and cerebellum	Positive correlation between binding and age. No relationship between binding and cognitive measures when controlling for age (except for negative correlation with Rivermead Picture Recognition score when binding considered as continuous variable).	None for PET. In 9/63 scans (14.3%), T1 MRI failed due to motion artefact; An additional 2/54 (3.7%) did not have T2 acquisition.
Jennings et al. (2015)	39 with DS, 2 of which had dementia	Florbetaben; Cerebellum	Uptake was correlated with age and was seen in people without AD.	None reported.
Rafii et al. (2015)	12 with DS and no dementia	Florbetapir, Cerebellum	Amyloid load was associated with hippocampal atrophy. There was an inverse relationship between regional binding and glucose metabolism. No relationship between amyloid load and cognitive measures.	None reported.
Sabbagh et al. (2015)	5 with DS and AD, 12 with DS only, 9 normal controls	Florbetapir; Pons	DS/AD had the highest uptake, followed by DS only. Age-related increases in binding were greater in DS group.	1/5 (20%) DS/AD+ subjects had severe impairment and was too agitated to obtain quality MRI/PET; 1/12 (8.3%) DS/AD- withdrew after PET and did not complete MRI (reason not provided).
Annus et al. (2016)	49 with DS (10 of which had dementia and 6 had cognitive decline)	PiB; Cerebellum	Binding begins in striatum around age 40, and was associated with dementia and cognitive decline.	None reported (most fell asleep during scan).
Cole et al. (2017)	46 with DS (9 of which had dementia and 6 with cognitive decline), 30 controls	PiB; Cerebellum	PiB was associated with brain aging. No relationship between PiB and cognitive score directly, but within the PiB positive group there was a relationship between brain age and cognitive score.	None reported.
Lao et al. (2016)	68 with DS and no dementia	PiB, Cerebellum	Positive correlation between binding and age, particularly in the striatum.	1/72 (1.4%) excluded for being unable to complete PET scan; 1/72 (1.4%) excluded for no TI MRI scan (reasons not provided).
Lao et al. (2017)	52 with DS and no dementia	PiB; Cerebellum	Binding occurred first in the striatum, and rate of change in uptake was correlated to pre-existing amyloid. This happened before evidence of dementia or atrophy.	None reported.

Abbreviations: AD, Alzheimer's disease; DS, Down syndrome; FDDNP, 2-(1-{6-[(2-[fluorine-18]fluoroethyl)(methyl)amino]-2-naphthyl}-ethylidene)malononitrile; PiB, Pittsburgh compound B.

reduced activity in the posterior cingulate relative to individuals with DS but not AD (Sabbagh et al., 2015). While the relationship between amyloid accumulation and these metabolic changes is not fully understood, a small pilot study found an inverse relationship between amyloid accumulation and glucose metabolism (Rafii et al., 2015). On the other hand, one study (Haier et al., 2008) found that some DS participants without clinical signs of dementia demonstrated a higher cerebral glucose metabolic rate in areas of decreased grey matter volume (temporal cortex, hippocampus, thalamus, caudate, and frontal lobe), and that this combination of brain changes in these areas correlated to dementia indicator ratings. It is possible that at an early stage dementia development, metabolic activity is increased in these regions as a compensatory mechanism, similar to some studies in early sporadic AD showing increased metabolism in certain regions (Bookheimer et al., 2000). Interestingly, the neuronal metabolite profile is also different in DS with dementia relative to DS alone, providing further support that metabolic changes are associated with the development of dementia in this population (Lin et al., 2016). Thus, FDG PET and metabolite analysis may serve as useful detection tools for dementia. Future studies analysing the chronologic relationship between metabolic changes and cognitive performance would provide important insight on the development of clinical dementia in DS.

4.2. MRI

In this section, we review recent MRI-based findings regarding AD in DS (Table 2). We discuss studies that used sMRI to assess atrophy and studies that used DTI to analyse white matter damage.

4.2.1. Structural MRI

Structural MRI imaging has elucidated the specific brain regions impacted by dementia in DS. These grey matter changes can be detectable before signs of clinical dementia (Matthews et al., 2016; Rafii et al., 2015). Nonetheless, grey matter volume reductions seen by sMRI likely occur after amyloid accumulation, as non-demented PiB positive subjects with DS do not always show signs of atrophy (Lao et al., 2017). Individuals with DS and AD eventually show decreased volume of the hippocampus, amygdala, caudate, posterior cingulate, parietal, temporal, frontal regions and putamen, as well as increased cerebrospinal fluid (Beacher et al., 2009; Sabbagh et al., 2015). It was recently demonstrated that those with DS and amyloid binding show posterior-dominant cortical thinning and atrophy of hippocampus, thalamus, and striatum, which is similar to what is seen in AD in the general population (Annus et al., 2017). Thus, atrophy seems to be dependent on the presence of amyloid and is exacerbated in those with dementia, consistent with the theory that amyloid may drive atrophy and disease progression.

4.2.2. Diffusion tensor imaging for white matter analysis

DTI is an MRI based method to assess the white matter of the brain. Studies have found that those with DS have reduced white matter integrity, especially in the frontal tracts, and that decreased white matter integrity correlates with cognitive dysfunction (Fenoll et al., 2017; Powell et al., 2014). People with DS and dementia have been shown to have decreased white matter integrity compared to non-demented DS subjects (Powell et al., 2014). Another study found increased white matter damage in PiB positive subjects with DS, but this effect was seen predominantly in the posterior tracts (Wilson, 2016). This is similar to white matter dysfunction patterns seen in AD in the general population (Medina and Gaviria, 2008). Interestingly, another recent study (Fenoll et al., 2017) using DTI suggested that white matter degeneration was not accelerated in non-demented DS subjects relative to normal aging controls. Fenoll et al. suggests this finding could be due to limited sensitivity of DTI in the pre-dementia stage or because accelerated white matter damage may not occur until a later stage in dementia. Due to the limited number of studies and conflicting results, further research using DTI is necessary to determine the relationship between white matter changes and AD in people with DS. It is possible that amyloid accumulation exacerbates white matter damage in an already vulnerable DS brain, but future studies are necessary to explain how this happens mechanistically and relates to clinical symptoms.

4.3. Electroencephalogram (EEG)

Although not as widely used as PET or MRI, EEG is another potential method of assessing AD in people with DS (Table 3). Even non-demented adults with DS show decreased amplitude of alpha waves, which is similar to what is seen in AD (Babiloni et al., 2010). Furthermore, adults with DS and dementia show decreased frequency of theta-1 waves compared to those with DS who do not have dementia (Salem et al., 2015). Salem et al. also found that theta-1 frequency was negatively correlated with scores on a dementia screening questionnaire, suggesting that increased brain wave abnormality may serve as a marker of dementia progression. Additionally, dementia in DS can be associated with senile myoclonic epilepsy, in which EEG changes may follow a predictable pattern, beginning with diffuse abnormalities during sleep at dementia onset followed by increased risk of myoclonic epilepsy and finally non-epileptic myoclonus as the dementia progresses (d'Orsi and Specchio, 2014). Future EEG studies in this population may complement other neuroimaging methods in understanding and tracking dementia.

4.4. Retinal imaging

Another emerging neuroimaging approach to studying dementia development is retinal imaging via optical coherence tomography (OCT). As the optic nerve shares an embryonic origin with the brain and is part of the central nervous system, the eye is susceptible to the same neurodegenerative pathology such as amyloid plaques. In people with AD in the general population, OCT has shown decreased retinal thickness, and decreased macular volume is correlated with cognitive decline (Iseri et al., 2006). It has also been demonstrated that Aβ accumulation occurs in the lenses of people with DS (Moncaster et al., 2010), as well as the retina (Rafii et al., 2015). Similar to PET amyloid studies, it is unclear if there is a direct association between retina amyloid accumulation and cognitive decline in DS (Rafii et al., 2015). Nonetheless, this method is less invasive than MRI and PET, and has the potential to detect AD at an earlier stage (Berisha et al., 2007).

5. Limitations & feasibility of neuroimaging

Neuroimaging has several limitations and thus should be used in conjunction with cognitive and clinical assessments, as well as other biological measures like plasma amyloid. One issue with neuroimaging is that changes may not be detectable until the disease has progressed significantly. For example, radioligands such as PiB and florbetapir may not be able to adequately detect diffuse Aβ plaques that occur early on in the disease process, potentially limiting their usefulness as prodromal biomarkers. Another issue is that the DS brain has significant differences from typical brains, which is important to keep in mind when considering neuroimaging data. In order to distinguish brain changes due to dementia from anomalies associated with DS, longitudinal studies are needed. Furthermore, it is difficult to assess trends via meta-analysis on neuroimaging results, as the studies are heterogeneous with respect to imaging method, study design, and cognitive performance measure. Finally, neuroimaging is costlier and more time-consuming than other clinical tests, such as psychiatric assessments or plasma amyloid analysis, limiting its feasibility as a widespread diagnostic tool. Nonetheless, the relationship between neuroimaging changes and cognitive function can be highly informative, especially as technology in this field improves.

It is also important to note certain limitations with respect to the

Table 2
Summary of MRI findings in DS and AD.

Authors	Final # of participants	Method	Results	Scanning feasibility issues
Beacher et al. (2009)	19 with DS and AD, 39 with DS only	T1 MRI with volumetric analysis	Smaller hippocampus, caudate, right amygdala and putamen, and greater CSF in people with DS and AD compared to DS alone.	None reported.
Powell et al. (2014)	10 non-demented with DS, 10 with DS and dementia, 10 age-matched controls	Fractional anisotropy analysis from DTI	People with DS have decreased white matter integrity, particularly in the frontal tracts. Cognitive dysfunction is associated with white matter damage. Those with dementia and DS showed increased damage compared to those with DS alone.	4 out of 34 (11.8%) initial DS participants excluded due to fear of scan or motion.
Rafii et al. (2015)	12 with DS and no dementia	T1 MRI with volumetric analysis	Amyloid load was associated with hippocampal atrophy. Grey matter changes can be detected before clinical dementia onset.	None reported.
Sabbagh et al. (2015)	5 with DS and AD, 12 non-demented with DS, 9 normal controls	T1 MRI with volumetric analysis	Those with AD and DS show increased atrophy of the posterior cingulate, parietal, temporal and frontal regions compared to those with DS only.	1/5 (20%) DS/AD+ subjects had severe impairment and was too agitated to obtain quality MRI/PET; 1/12 (8.3%) DS/AD- withdrew after PET and did not complete MRI (reason not provided).
Matthews et al. (2016)	12 non-demented with DS	T1 MRI with volumetric analysis	MRI can demonstrate a varying degree of AD atrophy in non-demented DS subjects, and this has some correlation with cognitive measures and amyloid burden.	1/12 (8.3%) excluded from structural MRI analysis due to blur.
Wilson (2016)	13 PiB negative with DS, 10 PiB positive with DS, 18 controls	Fractional anisotropy analysis from DTI	The PiB positive DS group showed decreased white matter integrity, particularly in the posterior tracts, compared to the other groups.	Lower IQ or a diagnosis of dementia was correlated with movement artefacts.
Annus et al. (2017)	46 with DS (19 PiB positive, 27 PiB negative), 30 age-matched controls	T1 MRI with volumetric analysis	Posterior-dominant cortical thinning and atrophy of hippocampus, thalamus, and striatum in those with DS and amyloid.	3 out of 49 (6.1%) who underwent scanning were excluded due to motion artefact.
Fenoll et al. (2017)	45 non-demented with DS, 45 matched controls	Fractional anisotropy analysis from DTI	People with DS have decreased white matter integrity compared to controls, especially in frontal-subcortical circuits, but age-related white matter changes are not accelerated in DS.	18 out of 63 (28.6%) who underwent scanning were excluded due to motion artefact.
Lao et al. (2017)	52 with DS and no dementia	T1 MRI with volumetric analysis	Amyloid accumulation occurs prior to dementia onset or grey matter volume reduction.	None reported.

Abbreviations: AD, Alzheimer's disease; CSF, cerebrospinal fluid; DS, Down syndrome; MRI, magnetic resonance imaging; PiB, Pittsburgh compound B.

Table 3
Summary of EEG findings in DS and AD.

Authors	# of participants	Method	Findings
Babiloni et al. (2010)	45 DS subjects, 45 age-matched cognitively normal subjects	Eyes-closed resting EEG data collected, with EOG.	Central, parietal, occipital, and temporal cortex had alpha and beta rhythms with lower amplitude in DS, while delta rhythms were higher in amplitude in DS.
d'Orsi et al. (2014)	12 with DS/AD/myoclonic epilepsy, over the age of 40	Long-term EEG monitoring during sleep and wake, with EMG and EKG.	3 stages of epilepsy were found: diffuse abnormalities during sleep with dementia onset, myoclonic epilepsy, and finally non-epileptic myoclonus with severe dementia.
Salem et al. (2015)	21 with DS and dementia, 16 with DS and no dementia	EEG during wake resting state, with EOG and EKG.	Decreased theta band frequencies in several regions of the brain are correlated with cognitive deterioration based on the Dementia Screening Questionnaire in Intellectual Disability.

Abbreviations: AD, Alzheimer's disease; DS, Down syndrome; EEG, electroencephalography; EKG, electrocardiography; EMG, electromyography; EOG, electrooculography.

studies considered. Many of these studies, particularly those using PET, did not have participants with DS who also had a diagnosis of AD, which limits the conclusions that can be drawn between neuroimaging findings and dementia. This could also suggest a feasibility issue, so it is important to consider the practicality of using neuroimaging in this population for research and clinical purposes. Both low IQ and dementia status have been associated with motion artefacts, and this is particularly important for DTI and functional scans (Wilson, 2016). None of the studies discussed used anxiolytics to address this issue, despite the fact that they are sometimes used in the general population prior to scans. There is controversy over the ethicality of using sedatives in the DS population for this purpose, and additionally, these drugs can affect the results obtained from functional scans. The authors of this review therefore recommend establishing a strong relationship with participants and their caregivers and allowing participants the opportunity to familiarise with the process of scanning in order to achieve the best outcomes.

6. Conclusions

Despite certain limitations, these recent neuroimaging findings can help us begin to understand the mechanism of dementia in individuals with DS. Aβ quantification and distribution analysis using PET has revealed a distinct pattern of amyloid accumulation, which may suggest something unique about the pathogenesis of dementia in DS. This accumulation occurs in non-demented individuals with DS and is likely a precursor to the grey matter atrophy and white matter integrity loss seen in later stages of AD. From a clinical perspective, these discoveries can potentially aid our screening and diagnosis of dementia in DS individuals. Monitoring these sequential changes, in conjunction with neurocognitive tests and other biomarkers, may contribute to a more comprehensive clinical picture and allow clinicians to more accurately track dementia progression in this population.

Neuroimaging findings will also have important implications in regards to therapeutics. For example, one implication of this research is the identification of a “therapeutic window” where clinicians can intervene in high risk patients prior to disease progression. As changes detected on certain neuroimaging methods such as ligand-based PET and MRI may occur too late for effective intervention, alternative methods such as retinal imaging, EEG, and FDG-PET may prove particularly useful for this purpose. Early abnormalities detected via these modalities could provide an opportunity to administer potential treatments before the disease manifests clinically. In addition to identifying a therapeutic window, neuroimaging can help inform novel therapeutic targets. This is an area where research is greatly needed, as there are currently no preventative treatments for AD. AD drugs to-date are limited in efficacy and are aimed at treating symptoms rather than the underlying neurodegeneration (Castro et al., 2016). Finally, another potential application of neuroimaging is to objectively monitor the efficacy of future therapeutics. For all these reasons, neuroimaging and other modalities discussed will likely have a valuable impact on our treatment of AD.

While the clinical utility of this field is evident, there are several areas that require future research. For example, elucidating the relevance of early striatal accumulation to cognitive decline could inform new cognitive screening measures (Sabbagh and Edgin, 2015). Additionally, as tau correlates more strongly with cognitive decline than Aβ (Brier et al., 2016), future studies with PET using tau ligand may provide important insight. Tau ligands that have been applied in the general population, such as AV1451 (Johnson et al., 2015), are starting to be utilized for the DS population. Understanding how specific cognitive deficits are related to patterns of tau accumulation may help explain the pathogenesis underlying the unique presentation of dementia in DS. Furthermore, since there has not been a clear association between amyloid distribution and atrophy, it will be useful to determine if tau distribution follows the same pattern as brain atrophy and serves as a link between the two processes. Another important area of future research is the use of neuroimaging to analyse additional markers of AD, such as glial cell markers, in people with DS (Wilcock and Griffin, 2013). Finally, future DTI studies may help clarify the impact of amyloid and tau accumulation on the white matter of the DS brain, for example in the striatum. In general, high powered studies that take a prospective longitudinal approach will be critical in increasing our understanding of these mechanisms and identifying biomarkers for tracking dementia development in DS (Caraci et al., 2017). This research will ultimately have great significance for the quality of life of the increasing number of individuals with DS living into their 50′s and beyond, and well as for AD prevention in the general population.

Funding acknowledgements

This work was supported by a scholarship from the Clinical Neuroscience Training Program of Perelman School of Medicine to Natalie Neale. This organization had no role in the study design, data analysis and interpretation, writing, or decision to submit for publication.

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