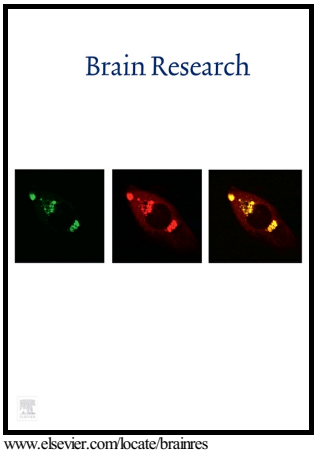


www.elsevier.com/locate/brainres

Brain imaging evidence of early involvement of subcortical regions in familial and sporadic Alzheimer's disease

Vasileios Tentolouris-Piperas, Natalie S. Ryan, David L. Thomas, Kirsi M. Kinnunen

PII: S0006-8993(16)30751-X
DOI: http://dx.doi.org/10.1016/j.brainres.2016.11.011
Reference: BRES45181

To appear in: *Brain Research*

Received date: 21 September 2016
Revised date: 8 November 2016
Accepted date: 9 November 2016

Cite this article as: Vasileios Tentolouris-Piperas, Natalie S. Ryan, David L. Thomas and Kirsi M. Kinnunen, Brain imaging evidence of early involvement o subcortical regions in familial and sporadic Alzheimer's disease, *Brain Research* http://dx.doi.org/10.1016/j.brainres.2016.11.011

Brain imaging evidence of early involvement of subcortical regions in familial and sporadic Alzheimer's disease

Vasileios Tentolouris-Piperas[a], Natalie S. Ryan[a], David L. Thomas[a,b], Kirsi M. Kinnunen[a1]

[a]Dementia Research Centre, UCL Institute of Neurology, University College London, Queen Square, London, UK

[b]Neuroradiological Academic Unit, Department of Brain Repair and Rehabilitation, UCL Institute of Neurology, University College London, Queen Square, London, UK

[*]**Corresponding author.** Dr. Kirsi Kinnunen. UCL Division of Psychiatry, 6th Floor (Wing A), Maple House, 149 Tottenham Court Road, London W1T 7NF, UK

Phone: +44 (0) 20 7679 9123. E-mail: k.kinnunen@ucl.ac.uk

Abstract

Recent brain imaging studies have found changes in subcortical regions in presymptomatic autosomal dominant Alzheimer's disease (ADAD). These regions are also affected in sporadic Alzheimer's disease (sAD), but whether such changes are seen in early-stage disease is still uncertain. In this review, we discuss imaging studies published in the past 12 years that have found evidence of subcortical involvement in early-stage ADAD and/or sAD. Several papers have reported amyloid deposition in the striatum of presymptomatic ADAD mutation carriers, prior to amyloid deposition elsewhere. Altered caudate volume has also been implicated in early-stage ADAD, but findings have been variable. Less is known about subcortical involvement in sAD: the thalamus and striatum have been found to be atrophied in symptomatic patients, but their involvement in the preclinical phase remains unclear, in part due to the difficulties of studying this

[1] Present address: UCL Division of Psychiatry, 6th Floor (Wing A), Maple House, 149 Tottenham Court Road, London W1T 7NF, UK

stage in sporadic disease. Longitudinal imaging studies comparing ADAD mutation carriers with individuals at high-risk for sAD may be needed to elucidate the significance of subcortical involvement in different AD clinical stages.

Keywords: Alzheimer's disease, MRI, PET, subcortical, thalamus, striatum

Abbreviations

Aβ, Amyloid-beta; AD, Alzheimer's disease; ADAD, Autosomal dominant Alzheimer's disease ; aMCI, Amnestic mild cognitive impairment; ApoE, Apolipoprotein E; CERAD, Consortium to establish a registry for Alzheimer's disease; DIAN, Dominantly inherited Alzheimer Network; esMC, Early symptomatic mutation carriers; FDG-PET, Fluorodeoxyglucose positron emission tomography; HC, Healthy controls; IWG, International working group; MC, Mutation carriers; MCI-C, Mild cognitive impairment converters; MCI-NC, Mild cognitive impairment non-converters; MRI, Magnetic resonance imaging; naMCI, Non-amnestic mild cognitive impairment; NC, Non carriers; NFT, Neurofibrillary tangles; NIA-AA, National institute on aging and Alzheimer's Association; PiB-PET, Pittsburgh compound B positron emission tomography; pMC, Presymptomatic mutation carriers; ROI, Regions of interest; sAD, Sporadic Alzheimer's disease; sMC, Symptomatic mutation carriers

1. Introduction

Alzheimer's disease (AD) is the most common cause of dementia in all age groups (Knapp, et al., 2007) and it is estimated that over 36 million people are living with dementia worldwide (Prince, et al., 2013). Being such a common cause of dementia, AD has thus become a matter of high importance for public health and the global economy. There is currently no disease-modifying treatment for AD, but research is ongoing to find reliable markers to improve diagnosis and to use as outcome measures in clinical trials of potential new treatments.

The hallmark pathological features of AD are neuronal loss, neuritic plaques of amyloid-beta (Aβ), and neurofibrillary tangles (NFTs) of hyperphosphorylated tau (Hyman, et al., 2012). These are quantified by criteria put forward by Braak and Braak, Thal, and the 'Consortium to Establish a Registry for AD' (CERAD) (Braak, et al., 2006,Mirra, et al., 1991,Thal, et al., 2002) for the neuropathological diagnosis of AD. Typical imaging features of AD include atrophy of the medial temporal lobe, precuneus, ventrolateral temporal, lateral parietal, and posterior cingulate cortices, the amygdala, and the anterior hippocampus. Furthermore, hypometabolism and amyloid deposition in these regions can be detected using fluorodeoxyglucose and Pittsburgh compound B positron emission tomography (FDG-PET and PiB-PET) respectively (Johnson, et al., 2012). Current diagnostic and classification criteria by the International Working Group (IWG) and the National Institute on Aging and Alzheimer's Association (NIA-AA) support the inclusion of imaging markers from both structural MRI and PET images (Cummings, et al., 2013,Dubois, et al., 2014,McKhann, et al., 2011). Clinical diagnosis of AD can be challenging, particularly in the early stages, and there is overlap between the phenotypes of AD and other neurodegenerative diseases. There is thus a great need for specific imaging markers that can detect AD pathology in vivo as early as possible. In this review, we discuss studies that have used neuroimaging techniques to study structural and functional alterations in subcortical regions of interest (ROIs) in sporadic or autosomal dominantly inherited AD (sAD or ADAD) providing information about the potential utility of such markers in future AD research including clinical trials.

2. Exploring beyond the hippocampus

While presymptomatic intervention trials are already underway, the search continues for the best imaging biomarkers in the early stages of AD. Hippocampal atrophy derived from MRI is currently used in AD therapeutic trials as an outcome measure, and most imaging studies in sAD and ADAD have focused on the 'AD signature' regions (Dickerson, et al., 2011): the medial temporal lobe, inferolateral temporal regions, and medial parietal and frontal cortices. However, amyloid imaging studies using PiB-PET in ADAD mutation carriers (MC) have identified subcortical deposition in the striatum during presymptomatic and early disease, to a greater extent than the signature cortical regions (Klunk, et al., 2007,Villemagne, et al., 2009). Although these subcortical structures have previously received relatively little attention in studies of AD, interest in these regions has grown over the recent years, with a number of related studies published.

The thalamus and basal ganglia exhibit AD pathology (Braak and Braak, 1990,Braak and Braak, 1991), but historically these subcortical structures have not tended to be used as ROIs in imaging studies of AD patients. The role of structural and functional abnormalities in these regions is widely recognized in motor disorders (Rothwell, 2011), but there is also evidence to support their involvement in cognitive functions, including memory (Liljeholm and O'Doherty, 2012,Packard and Knowlton, 2002,White, 2009). Brain networks involving the thalamus – as well as limbic regions – may play a more important role in AD than was previously thought (Aggleton, et al., 2016).

Here, we review studies of preclinical/presymptomatic or early/mildly symptomatic stages of sAD or ADAD published since 2004, reporting on changes identified using neuroimaging techniques in five subcortical ROIs: thalamus, caudate, putamen, nucleus accumbens, and globus pallidus. Studies of atypical or mixed AD, as defined by (Dubois, et al., 2010), have not been included. ADAD is the main focus of this review, owing to the certainty with which preclinical disease can be studied in carriers of mutations in the *APP*, *PSEN1* and *PSEN2* genes, as opposed to the sporadic

form of AD. Findings in these ROIs during the early stages of sAD are also included, in an effort to illustrate what has been done so far, and to motivate and inform future research.

Although early-onset AD accounts for only a small percentage of all AD (Campion, et al., 1999), and its autosomal dominant forms are even rarer, ADAD – unlike sAD – can be studied presymptomatically in individuals destined to develop AD. Reliable presymptomatic diagnosis based on genetics can provide unique insights into the changes during the earliest disease stages, when sporadic disease cannot yet be diagnosed with certainty. Studies of early-stage sAD also face uncertainty in predicting conversion rates from amnestic MCI (aMCI) to AD. Amnestic MCI is thought to be a much stronger risk factor of conversion to AD than non-amnestic MCI (naMCI), but conversion rates in the clinical setting are still relatively low (Tifratene, et al., 2015). For these reasons, this review will focus mostly on studies of ADAD, while also discussing the possible implications of the findings in ADAD for increased understanding of early-stage sAD.

3. Method of systematic literature review

The literature search was performed using PubMed (US National Library of Medicine) and OvidSP Embase, on 11/11/2015. We searched for original research papers published (in English) between 01/01/2004 and the search date. The following keywords were used: Alzheimer*, imaging, mri, fmri, pet, spect, diffusion, subcortical, thalamus, basal ganglia, striat*, putamen, globus pallidus, caudate, nucleus accumbens, early, asymptomatic, presymptomatic, preclinical, mci, amci, mild, prodromal. The reference lists of the papers thus found were also searched for potential publications of interest. Based on title and abstract, we then excluded studies of atypical or mixed AD, AD with significant co-morbidities, other forms of dementia, and studies without appropriate control groups. For selection into the final set, we reviewed the studies' methods and results, selecting only those that investigated our ROIs in presymptomatic or early symptomatic ADAD (Clinical Dementia Rating ≤ 1; (Morris, 1993) or in preclinical or early-stage/mild sAD (CDR ≤ 1 or

Mini Mental State Examination score ≥ 20; Folstein et al., 1975). Figure 1 illustrates the article selection procedure.

4. Imaging findings in autosomal dominant AD

4.1 PiB-PET

The results of the literature search on relevant studies in ADAD are presented in Table 1. A number of studies have demonstrated amyloid deposition in subcortical regions in ADAD mutation carriers (Benzinger, et al., 2013,Klunk, et al., 2007,Knight, et al., 2011,Shi, et al., 2015,Villemagne, et al., 2009). Amyloid deposition has been reported in most of the subcortical ROIs that are the focus of this review, particularly in the caudate, putamen and globus pallidus. Importantly, amyloid deposits in these regions were often greater than deposits observed elsewhere in the brain. (Klunk, et al., 2007) and (Villemagne, et al., 2009) were the first to demonstrate striatal amyloid deposition in presymptomatic ADAD MC (Figure 2). Similar findings were subsequently reported by (Knight, et al., 2011); however, the pattern of deposition in different individuals was more heterogeneous, perhaps reflecting the larger variety of different *PSEN1* mutations represented in the cohort. In an initial longitudinal analysis of a large ADAD cohort from the Dominantly Inherited Alzheimer Network (DIAN), (Benzinger, et al., 2013) found increased PiB retention in all subcortical regions investigated (including the thalamus and corpus striatum) in presymptomatic MCs, before hippocampal involvement, but not before cortical amyloid deposits (Figure 3).

Table 1. Results in ADAD. s/pMC: symptomatic/presymptomatic mutation carriers (where available, average years from expected onset is shown in parentheses), sAD: sporadic AD, HC: healthy controls, MD: mean diffusivity.

Author	Modality	Cohort type	Main relevant findings
(Klunk, et al., 2007)	PiB-PET	PSEN1 pMC (C410Y), sMC (A426P), sAD, HC	Increased amyloid deposition in the striatum in pMC compared to HC.
(Villemagne, et al., 2009)	PiB-PET, FDG-PET	PSEN1, APP pMC + sMC, sAD, HC	High PiB uptake in the striatum of all MC. Some of the pMC also had thalamic and cortical PiB uptake, but to a lesser degree. Lower global and regional FDG uptake in various regions; no common patterns among groups.
(Knight, et al., 2011)	PiB-PET	Mixed PSEN1 pMC (-7.2 years), sMC, sAD, HC	Increased PiB retention in cortical and subcortical areas in pMC (with pons as the reference point). Heterogeneous patterns of uptake.
(Scholl, et al., 2011)	FDG-PET, PiB-PET	PSEN1 (H163Y) pMC, sAD, HC	Reduced glucose metabolism in thalami of pMC, especially on the right. For one MC, PiB-PET was performed after disease onset. This showed an otherwise similar pattern of uptake as in sAD controls, but with greater uptake in the striatum.
(Scholl, et al., 2012)	FDG-PET, PiB-PET, MRI	APParc (E693G), PSEN1(H163Y), APPswe pMC, sMC, sAD, HC	Low PiB retention in APParc carriers and non-carriers. Retention in a symptomatic PSEN1 carrier, similar to sAD, but higher uptake in striatum. APPswe carrier with MCI had higher uptake in striatum, thalamus and hippocampus than sAD.
(Benzinger, et al., 2013)	PiB-PET, FDG-PET, MRI	Mixed PSEN1, PSEN2, APP MC, HC	Increased amyloid uptake in accumbens, caudate, putamen and cortical areas earlier than in hippocampus. Subcortical areas did not exhibit reduced glucose metabolism, unlike the hippocampus. Significant atrophy in all regions except for the caudate and pallidum.
(Fortea, et al., 2010)	MRI, DWI	PSEN1 pMC (-9.9 years) + sMC, HC	Increased caudate size bilaterally in pMC, decreased size in sMC compared with HC. Decreased MD in caudate of pMC compared with HC, but increased in sMC.
(Lee, et al., 2013)	MRI	Mixed PSEN1, APP pMC (-15.5 years), early-stage sMC, demented sMC, HC	Significantly lower thalamus, caudate and putamen volumes in pMC compared with controls; for early-stage sMC reduced thalamus volume only.
(Ryan, et al., 2013)	MRI, DTI	PSEN1 pMC (-5.6 years) + sMC, HC	Caudate and thalamus atrophy pMC compared with HC; volume loss in all ROIs in sMC compared with HC, with greatest losses in thalamus and bilateral striatum; decreased MD in pMC and increased MD in sMC compared with HC.
(McDade, et al., 2014)	fMRI - ASL	PSEN1 and APP pMC, sMC, HC	Relative to HC, decreased perfusion in the caudate and inferior striatum in MCs analyzed as one group, controlling for CDR.
(Shi, et al., 2015)	PiB-PET, FDG-PET	PSEN2, sMC	Cortical and striatal amyloid deposits in 2/3 early-stage sMC.
(Sala-Llonch, et al., 2015)	MRI	PSEN1 pMC (-16.2 years) + sMC, HC	pMC: Trend of reduced volume of left caudate compared to HC. sMC: Reduced thalamus, putamen, amygdala and nucleus accumbens volumes bilaterally, compared to HC. Longitudinally: Volumetric reductions in right caudate and right putamen volumes for pMC; in the thalamus, nucleus accumbens and putamen for sMC.

4.2 FDG-PET

Evidence relating to reduced glucose metabolism from FDG-PET studies is less consistent. (Scholl, et al., 2011) found lower thalamic metabolism in six carriers of the p.His163Tyr *PSEN1* mutation than controls at baseline, with further reductions over a two-year follow-up. Interestingly, although (Benzinger, et al., 2013) reported subcortical amyloid deposition presymptomatically, there was no concurrent hypometabolism (which was observed in the cortical regions).

4.3 Structural MRI and variability in caudate volumes

Structural MRI studies in ADAD have reported particularly variable findings in the caudate. Using T1-weighted MRI volumetry, (Fortea, et al., 2010) observed significantly increased caudate volume bilaterally in their group of six pMC (mean-adjusted -9.9 years from estimated symptom onset) compared to mutation non-carriers (NC). By contrast, early symptomatic MC (esMC) showed decreased caudate volumes relative to NC. On diffusion imaging, mean diffusivity in the caudate of the pMC was slightly decreased relative to NC values, whereas – conversely – the esMC had increased mean diffusivity. (Lee, et al., 2013) showed the opposite picture using volumetric MRI: volume loss in the caudate and putamen of pMC correlated positively with relative age before the diagnosis of dementia. This volume loss was not evident in the esMC. The pMC studied by Lee et al., however, were on average further from expected symptom onset (-15.5 years) than those studied by Fortea et al. (-9.9 years). In fact, the esMC (-10.4 years) in the study by Lee et al. were, on average, at a similar time from predicted age at symptom onset as the pMC in the study by Fortea and colleagues. However, a more recent study from the latter group (Sala-Llonch, et al., 2015), did not find any differences in caudate volume between

controls and either sMC or pMC, attributing the discrepancy between their studies to differences in the mean relative age of the mutation carriers (the sMC group was closer to symptom onset in the 2015 study) and/or to differences in the *PSEN1* mutations included in each study.

(Ryan, et al., 2013) demonstrated reduced volumes of the left thalamus and bilateral caudate in a group of pMC on average -5.5 years from expected onset compared with NC using ROI analysis, a finding that was more pronounced in sMCs. In the same study, the automated image analysis technique voxel-based morphemetry (VBM) was also used to provide whole-brain assessments of group differences. This demonstrated grey matter volume loss in bilateral hippocampus and posterior cortical areas in the SMC group compared to controls but showed that the most significant volume loss was in bilateral thalamic and striatal regions (Figure 4). Widespread loss of white matter volume was also seen in the SMC group. In a study of the DIAN cohort (Benzinger, et al., 2013) found volumetric reductions for the MC relative to NC in all other subcortical regions studied, but not in the caudate or globus pallidus (Figure 3). All MC – far presymptomatic and those nearer and beyond symptom onset – were analyzed as one group.

Apart from differences in image segmentation techniques between studies, participant group stratification, statistical analysis methods, small sample sizes, the different mutations involved, and age differences could contribute to the differing results, which have been particularly contradictory for the caudate. With the caudate located directly adjacent to the lateral ventricles, CSF artifacts/partial volume effects may partly explain some of the unexpected and variable results involving this structure.

These surprising and contradictory results have been discussed previously (Ryan and Fox, 2013,Vishnu, 2013). Atrophy has been hypothesized to manifest relatively late in the pathogenesis of AD, which is why observing subcortical volume changes at such early disease stages raises important questions. For example, the changes could potentially reflect glial involvement and immune-mediated processes. Apart from neuronal loss, the decreased volumes observed in these regions could be due to synaptic and dendritic changes or reduced axons and/or glia. Moreover, initial effect triggering mechanisms (such as inflammation or amyloid accumulation) that cause an increase in a region's size, could later result in more pronounced atrophy.

There is not yet enough evidence to strongly support any of these hypotheses, but they are interesting nonetheless. From the evidence so far, it appears that presymptomatic and early symptomatic mutation carriers exhibit both caudate atrophy and/or increased volume compared to age-matched controls at different points in early-stage disease. Volumes in key cortical regions for AD have been suggested to follow an inverted U-shape pattern over time, as the disease progresses from preclinical through to symptomatic phases. This may also be the case for subcortical structures (Fortea, et al., 2010,Sala-Llonch, et al., 2015).

While the thalamo-striatal region could undergo dynamic changes during disease progression, drawing firm conclusions from the studies so far is complicated by differences in published study designs and inevitable variability in the compositions of the participant groups. Most previous MRI findings are from cross-sectional studies with mostly very small samples. Individual participants grouped together can differ markedly in both their estimated years from symptom onset and samples in different studies have different compositions of the various ADAD mutations. To further complicate matters, different methods to calculate years from symptom onset

have been used in these studies. Well-designed longitudinal studies could mitigate some of the confounding factors in the cross-sectional designs, and provide clearer answers. Results from the longitudinal analysis of the DIAN cohort will be interesting in this regard.

Conflicting results may also very well be due to the small sample sizes. In addition, some of the findings could be specific to a particular mutation, which studies with participants carrying different mutations would not detect. Conversely, findings from studies focusing on one type of mutation may not generalize to other mutations. A well-designed longitudinal study with large numbers of carriers of different mutations and tracking regional volumes could provide answers to the caudate controversy and evaluate the hypothesis that regional atrophy patterns are evolving dynamically over time.

Diffusion MRI may be able to shed some light on the finer structural abnormalities underlying the volumetric changes observed on MRI. However, the interpretation of changes observed in diffusion measures is still difficult because of the relative immaturity of diffusion imaging technology and limitations of the most commonly used implementations. Two studies so far fulfilled the search criteria, (Fortea, et al., 2010,Ryan, et al., 2013), with similar findings: increased mean diffusivity in the caudate of sMC compared with controls but interestingly also reduced mean diffusivity in pMC relative to controls. In the thalamus, higher fractional anisotropy was observed for pMC compared with non-carriers (Ryan, et al., 2013). Conclusions from these studies must remain speculative, but diffusion MRI appears to be a promising method to study subcortical structures during early-stage ADAD.

4.4 Relevance of ADAD findings and genetic heterogeneity

The main message arising from the ADAD literature review is that early striatal involvement – in presymptomatic stages and before other regions – does appear to occur in the form of amyloid deposition, at least for some mutations. Striatal deposits in presymptomatic mutation carriers were more common, and were greater than deposits in other regions of the brain, when present. The pattern of deposition seems to differ from that seen in symptomatic sAD patients. However, most of the ADAD studies published so far have been on *PSEN1* carriers, or have involved mixed groups of carriers of various mutations. Imaging findings may also be gene- or mutation-specific (Kinnunen, et al., 2013,Scahill, et al., 2013). In the (Scholl, et al., 2012) study for example, no significant amyloid deposits were found for carriers of the Arctic *APP* (p.Glu693Gly) mutation, while the opposite was true for Swedish *APP* (p.Lys670Asn;Met671Leu) and *PSEN1* (p.His163Tyr) mutation carriers. However, the sample size was extremely small for these mutations (N=1 for each). The (Fleisher, et al., 2012) study of the Colombian *PSEN1* p.Glu280Ala kindred, found no striatal deposits. Imaging in this study was performed using the Florbetapir (18F) compound, binding to beta-amyloid like PiB. Finally, the (Shi, et al., 2015) case series of four *PSEN2* mutation carriers discovered striatal deposits in only some of the individuals investigated. Striatal amyloid deposition does not seem to be present in all cases of *PSEN1* ADAD, nor does it seem to be exclusive to *PSEN1* mutations. It seems that mutations in *APP* and *PSEN2* can also lead to a similar picture. It is clear that more and larger quantitative, longitudinal studies are needed to shed light on the similarities and differences among the different genetic causes of ADAD.

Amyloid imaging studies of individuals with Down syndrome provide interesting complementary evidence. These individuals have three copies of chromosome 21,

and very often develop AD early in their life (Hartley, et al., 2015) due to overexpression of the *APP* gene that resides on chromosome 21. Like in ADAD, in cases of Down syndrome early amyloid deposits have been discovered in striatal regions (Annus, et al., 2015,Handen, et al., 2012,Lao, et al., 2015,Price, et al., 2011). It is an attractive theory to postulate that the development of dementia in ADAD and Down syndrome relies on some shared steps to the protein accumulation and propagation, and that subcortical regions may therefore be the first to show observable deposits of amyloid in both forms of dementia. Longitudinal results from the Neurodegeneration in Aging Down Syndrome (NiAD) and Down Alzheimer Barcelona Neuroimaging Initiative (DABNI; Fortea, et al., 2016) studies will be of great interest here.

In summary, presymptomatic imaging changes in ADAD seem to occur in subcortical regions, especially in the caudate and thalamus. The evidence reviewed here points to early accumulation of amyloid and regional atrophy, with dynamic changes possible. Large-scale longitudinal investigations of ADAD, particularly the DIAN study, can help to determine how these regions change structurally and functionally during the long disease process, from early presymptomatic to mild and then late symptomatic stages.

5. Imaging findings in sporadic AD

It is difficult to study sAD in its early stages due to the vast heterogeneity, the close relationship with advancing age, and the difficulty of reliably identifying patients who will develop clinical AD dementia while they are still very mildly or mildly affected. Many studies not only use different terminology, but also use different definitions and classifications for MCI and AD, and varying Clinical Dementia Rating or Mini Mental State Examination cut-off points. Another important factor is Apolipoprotein E (ApoE) status; some studies use it in an effort to study AD during preclinical stages, but others perform no such group stratification. These differences have contributed to a much hazier picture of subcortical involvement in preclinical and mild sAD than in ADAD. Despite these important difficulties, an effort is made here to group the various findings according to imaging modality (Table 2).

Table 2. Results in sporadic AD. HC: healthy controls, aMCI: amnestic mild cognitive impairment, MCI-C/NC: MCI converters/non-converters, sAD: sporadic AD.

Author	Modality	Cohort type	Main relevant findings
(Klunk, et al., 2004)	PiB-PET, FDG-PET	Early sAD, HC	Increased striatal deposition (PiB-PET) in early-stage sAD compared with HC. FDG-PET did not focus on our ROIs.
(Reiman, et al., 2009)	PiB-PET	Asymptomatic, w/ sAD family history, genotyped for ApoE status	Striatal deposition in cognitively normal homozygote carriers of APOE4 allele(s) compared with non-carriers, but not earlier than in other regions.
(Koivunen, et al., 2011)	PiB-PET	MCI-C, MCI-NC, HC	Increased striatal deposition in MCI to dementia converters, but not different from other regions.
(Koivunen, et al., 2012)	PiB-PET	aMCI-C, aMCI-NC	Increased amyloid deposition in the caudate and putamen for aMCI converters compared with controls.
(Bruck, et al., 2013)	PiB-PET, FDG-PET, MRI	MCI-C, MCI-NC, HC	Significantly increased amyloid deposition in MCI converters vs. non-converters and controls.
(Nordberg, et al., 2013)	PiB-PET	Early sAD, HC	Increased striatal deposition in early-stage sAD in all subcortical regions studied.
(Morbelli, et al., 2010)	FDG-PET, MRI	aMCI-C, aMCI-NC, HC	Lower grey matter density in bilateral thalami of aMCI converters; no significant differences between groups in thalamus metabolism.
(Dukart, et al., 2013b)	FDG-PET, MRI	MCI-C, MCI-NC, early sAD, HC	In early-stage sAD and MCI converters compared with HC: concurrent bilateral volume loss and reduced glucose metabolism in the thalami bilaterally; reduced glucose metabolism also in the right caudate.
(Chen, et al., 2013)	Resting fMRI, MRI	Early sAD, HC	Abnormal insular region connectivity in early-stage sAD compared with HC, including with the putamen and globus pallidus.
(Cai, et al., 2015)	Resting fMRI, connectivity	Early aMCI, late aMCI, HC	In both early and late aMCI compared with HC: decreased functional connectivity in some thalamic networks; other thalamic networks showed increased connectivity. Patients with late aMCI showed more abnormal functional connectivity of the thalamus than those with early aMCI.
(Chetelat, et al., 2005)	MRI	MCI-C, MCI-NC, no HC	Both converters and non-converters showed left thalamus volume loss during an 18-month follow-up.
(Liu, et al., 2010)	MRI	sAD, MCI-C, MCI-NC, HC	Reduced caudate volume in MCI converters compared with non-converters.
(Madsen, et al., 2010)	MRI (3D)	MCI-C, MCI-NC, early sAD	More caudate atrophy at baseline in MCI converters compared with non-converters. Caudate atrophy in the sAD group was more pronounced than in the MCI groups. Reduced volume of right caudate was associated with conversion from MCI to AD.
(Cho, et al., 2014)	MRI (shape)	Early sAD, HC	At baseline, lower volumes in the putamen bilaterally and in the right caudate for early-stage sAD relative to HC. Atrophy progression over time was observed in these regions.

(Tang, et al., 2014)	MRI (shape)	Early sAD, MCI-C, MCI-NC	Shape changes in basal ganglia structures (caudate, putamen, globus pallidus) in all MCI and early sAD compared with controls. Shape differences between MCI-C and MCI-NC only in the hippocampus, amygdala and lateral ventricles.
(Tang, et al., 2015)	MRI (shape)	MCI-C, MCI-NC, sAD, HC	A model-based approach to study shape diffeomorphometry patterns of 14 regions, including the right thalamus, right caudate, and bilateral putamen. The combined model incorporating these subcortical ROIs was superior to single structure approaches in predicting conversion from MCI to AD.
(H.A. Yi, et al., 2015)	MRI	MCI-C, MCI-NC, sAD, HC	All structures apart from globus pallidus showed decreased volume in all MCI groups compared with HC. The volumes were further reduced in sAD. MCI to AD conversion was associated with smaller hippocampal and nucleus accumbens volumes. Severity of cognitive symptoms was associated with subcortical volume losses.
(Leh, et al., 2015)	MRI (VBM, shape, cortical thickness)	aMCI, HC	Reduced putamen volumes in aMCI and significant shape differences between aMCI and HC in the thalamus and striatum bilaterally (without but no volumetric differences).
(Hirao, et al., 2005)	SPECT	MCI-C, MCI-NC, HC	Significantly reduced regional cerebral blood flow (rCBF) in the right caudate of MCI-NC compared to HC. No findings in our ROIs for converters.
(Trollor, et al., 2006)	SPECT memory task	Early sAD, NC	Decreased rCBF in the right thalamus of early-stage sAD patients compared with NC, but this was not specific to the memory task.

5.1 PiB-PET

Striatal and thalamic amyloid deposits are known to exist in most sporadic AD patients post-mortem (Braak and Braak, 1990,Brilliant, et al., 1997,Thal, et al., 2002), and have also been observed *in vivo* in PET studies of sAD cohorts (Price, et al., 2005). As always, the difficulty resides in identifying if these deposits occur before other abnormalities. The first human PiB-PET study in early-stage sAD (Klunk, et al., 2004) found striatal deposits. However, the sAD participants represented various levels of dementia severity, but were grouped together for comparison with healthy controls. Since then, a number of studies have been

conducted (Bruck, et al., 2013,Koivunen, et al., 2012,Koivunen, et al., 2011,Nordberg, et al., 2013,Reiman, et al., 2009), finding amyloid deposits in the striatum or the caudate, but not earlier than in other, more typical AD regions. It appears that the thalamo-striatal ROIs do show amyloid deposition in early-stage AD, but given the evidence, it is unclear whether other regions develop deposits earlier in disease. However, these results are not directly comparable to those from ADAD, as naturally there are no studies investigating truly presymptomatic sAD stages.

5.2 FDG-PET and SPECT

Very few FDG-PET studies met the inclusion criteria and investigated subcortical ROIs during early-stage sAD. Of those that did, (Dukart, et al., 2013b) and ,Morbelli, et al., 2010), looked at the thalamus and caudate as regions of particular interest. While (Dukart, et al., 2013b) reported hypometabolism in the thalamus and caudate in early sAD and in MCI converters compared with healthy controls, an earlier study from the same group postulated that this pattern may be due to changes related to aging (Dukart, et al., 2013a). We additionally found two SPECT studies that had investigated our ROIs. (Trollor, et al., 2006) demonstrated reduced regional cerebral blood flow (rCBF) in the thalamus during early-stage sAD. (Hirao, et al., 2005) studied rCBF of the caudate, but found no reductions in MCI converters.

5.3 Structural and functional MRI

As in ADAD, the thalamo-striatal regions seem to undergo early atrophic changes in sAD, but the evidence so far is inconclusive. Loss of caudate volume is the most common finding in MCI converters (Liu, et al., 2010,Madsen, et al., 2010), with

losses of normal caudate asymmetry as the disease progresses (Madsen, et al., 2010). (Dukart, et al., 2013b) reported thalamic volume losses in AD converters, while (Chetelat, et al., 2005) found this in both converters and non-converters alike. (Zhao, et al., 2015) reported decreased putamen volume in sAD relative to both MCI and HC, but found no significant losses of caudate or thalamic volume in either sAD or MCI. The MCI group in this study included both converters and non-converters.

A number of recent studies have used shape measurement techniques (Cho, et al., 2014,Tang, et al., 2014,Tang, et al., 2015). For example, (Leh, et al., 2015) found significant shape alterations in aMCI in the thalamus and striatal regions, which perhaps could be used as complementary measures to distinguish between aMCI to AD converters and non-converters.

It is important to note that structural changes, including some of those discussed in the current review, are found in other forms of dementia, and are not exclusive to AD (L.Y. Yi, et al., 2015). This, again, adds to the difficulty of finding imaging biomarkers that could help to reliably identify early-stage sAD.

As far as functional MRI studies are concerned, resting-state fMRI findings on our ROIs include abnormal insula-putamen and insula-globus pallidus connectivity in early-stage sAD compared with healthy controls (Chen, et al., 2013), and decreased connectivity in thalamic networks in both early and late aMC relative to healthy controls (Cai, et al., 2015).

5.4 Relevance of sAD findings

The sAD literature identified using the current search terms and inclusion/exclusion criteria indicates that the ROIs for this review are affected in the early stages of sAD, but perhaps not as centrally involved as they are in ADAD. In addition, the pattern of early-stage amyloid accumulation and regional atrophy does not seem to be any more focused on the striatum than on other, more typical AD regions. Again, the strongest evidence regarding the early disease stages pertains to amyloid deposition, consistent with the proposed staging of biomarker progression in AD (Jack, et al., 2013). Interestingly, it was suggested in 2008 that reduced thalamus and putamen volumes may contribute to cognitive decline in sAD (de Jong et al., 2008). Although firm conclusions cannot be drawn based on the studies reviewed here, the aMCI findings by (Leh, et al., 2015) imply that further study of subcortical regions in sAD could be worthwhile. This notion was recently further reinforced in a review by (Aggleton, et al., 2016), suggesting particular involvement of the anterior "limbic thalamus" in early-stage AD. Specifically, they postulated that the participation of cognitively relevant thalamic nuclei in multiple networks could underpin the changes observed in many of the studies they reviewed. Whether the thalamo-striatal changes in sAD are a downstream effect of medial temporal degeneration, or develop before the medial temporal lobe changes remains an open question.

When attempting to investigate pre-clinical and early sAD, it is also important to consider changes associated with healthy aging. However, in any aging study, no matter how strict the exclusion criteria, it is impossible to determine early on which

participants will eventually develop AD. In a study by (Oh, et al., 2014), putamen volume was positively associated with cognitive performance in both PIB+ and PIB- individuals, whereas hippocampal volume was positively associated with cognitive performance in PIB+ individuals only. Interestingly, (Fjell, et al., 2010) found the strongest relationships between CSF Aβ1-42 levels and atrophy (more pronounced in individuals with low levels of Aβ1-42) in areas including the caudate and thalamus. If these regions, then considered to be “not especially vulnerable to AD pathology”, do indeed play a role in early-stage sAD, some of the individuals in the low Aβ1-42 subgroup might have been on an AD trajectory.

New longitudinal studies of sAD, implementing the recently updated diagnostic criteria and disease classification by two international working groups (IWG and NIA-AA, could provide a clearer picture of the progression of subcortical changes through different disease stages.

6. Limitations

A range of papers has been published in both ADAD and sAD reporting on the thalamus, caudate, putamen, nucleus accumbens, and globus pallidus. However, the reporting of negative results is unfortunately rare. It is possible that some studies with interest in these subcortical regions have been conducted without finding significant results, but such negative results may not be mentioned in the title, abstracts, or methods sections (included in our initial selection of relevant studies). This may have introduced a bias into the evaluation of the results described in this review.

Another important factor to consider is the various imaging techniques and image processing methods used in the publications reviewed, a factor that becomes integral to extrapolating useful conclusions, especially when the number of studies published is still relatively low.

7. Conclusion

To summarize, the literature seems to suggest that subcortical regions may be involved in the early stages of AD. The most conclusive among the findings was the evidence of amyloid deposition in the striatum in ADAD presymptomatically, before deposition is observed in other regions. Some evidence also exists to suggest volumetric abnormalities and changes in glucose metabolism, but these findings have been less consistent. The same conclusions cannot yet be drawn for sAD. For some time, it has been known that the thalamo-striatal regions show AD pathology post mortem. It also seems that these regions are involved in aMCI and early-stage

sAD. They do not, however, seem to stand out from other brain regions, at least at the point of the disease process that current imaging methods supporting *in vivo* diagnosis of sAD allow. Furthermore, it is not yet safe to say whether these subcortical regions are more relevant to ADAD and sAD than other forms of dementia, or, in fact are seen across different neurodegenerative diseases. The review of the literature nevertheless indicates that there could be merit in further investigating these regions, rather than solely focusing on the AD signature medial and inferolateral temporal and parietal and frontal cortical areas. Well-designed imaging studies of the thalamus and corpus striatum could provide useful complementary measures of early-stage neurodegeneration in AD.

Disclosure statement

The authors have no conflicts of interest to disclose.

Acknowledgements

The study was undertaken at UCLH/UCL who received a proportion of funding from the Department of Health's NIHR Biomedical Research Centres funding scheme. The Dementia Research Centre (DRC) is supported by Alzheimer's Research UK (ARUK), Brain Research Trust and The Wolfson Foundation. The DRC is also an ARUK coordinating centre, and has received equipment funded by ARUK and the Brain Research Trust. KK was supported by a grant from ARUK (ARUK-PCRF2014B-1). NSR is supported by a Brain Exit Fellowship. DT is supported by the UCL Leonard Wolfson Experimental Neurology Centre (PR/ylr/18575).

References

Aggleton, J.P., Pralus, A., Nelson, A.J.D., Hornberger, M. 2016. Thalamic pathology and memory loss in early Alzheimer's disease: moving the focus from the medial temporal lobe to Papez circuit. Brain : a journal of neurology. doi:10.1093/brain/aww083.

Annus, T., Wilson, L.R., Hong, Y.T., Acosta-Cabronero, J., Fryer, T.D., Cardenas-Blanco, A., Smith, R., Boros, I., Coles, J.P., Aigbirhio, F.I., Menon, D.K., Zaman, S.H., Nestor, P.J., Holland, A.J. 2015. The pattern of amyloid accumulation in the brains of adults with Down syndrome. Alzheimer's & dementia : the journal of the Alzheimer's Association. doi:10.1016/j.jalz.2015.07.490.

Benzinger, T.L., Blazey, T., Jack, C.R., Jr., Koeppe, R.A., Su, Y., Xiong, C., Raichle, M.E., Snyder, A.Z., Ances, B.M., Bateman, R.J., Cairns, N.J., Fagan, A.M., Goate, A., Marcus, D.S., Aisen, P.S., Christensen, J.J., Ercole, L., Hornbeck, R.C., Farrar, A.M., Aldea, P., Jasielec, M.S., Owen, C.J., Xie, X., Mayeux, R., Brickman, A., McDade, E., Klunk, W., Mathis, C.A., Ringman, J., Thompson, P.M., Ghetti, B., Saykin, A.J., Sperling, R.A., Johnson, K.A., Salloway, S., Correia, S., Schofield, P.R., Masters, C.L., Rowe, C., Villemagne, V.L., Martins, R., Ourselin, S., Rossor, M.N., Fox, N.C., Cash, D.M., Weiner, M.W., Holtzman, D.M., Buckles, V.D., Moulder, K., Morris, J.C. 2013. Regional variability of imaging biomarkers in autosomal dominant Alzheimer's disease. Proceedings of the National Academy of Sciences of the United States of America 110(47), E4502-9. doi:10.1073/pnas.1317918110.

Braak, H., Alafuzoff, I., Arzberger, T., Kretzschmar, H., Del Tredici, K. 2006. Staging of Alzheimer disease-associated neurofibrillary pathology using paraffin sections and immunocytochemistry. Acta neuropathologica 112(4), 389-404. doi:10.1007/s00401-006-0127-z.

Braak, H., Braak, E. 1990. Alzheimer's disease: striatal amyloid deposits and neurofibrillary changes. J Neuropathol Exp Neurol 49(3), 215-24.

Braak, H., Braak, E. 1991. Alzheimer's disease affects limbic nuclei of the thalamus. Acta neuropathologica 81(3), 261-8.

Brilliant, M.J., Elble, R.J., Ghobrial, M., Struble, R.G. 1997. The distribution of amyloid beta protein deposition in the corpus striatum of patients with Alzheimer's disease. Neuropathology and applied neurobiology 23(4), 322-5.

Bruck, A., Virta, J.R., Koivunen, J., Koikkalainen, J., Scheinin, N.M., Helenius, H., Nagren, K., Helin, S., Parkkola, R., Viitanen, M., Rinne, J.O. 2013. PIB, [18F]FDG and MR imaging in patients with mild cognitive impairment. European journal of nuclear medicine and molecular imaging 40(10), 1567-72. doi:http://dx.doi.org/10.1007/s00259-013-2478-8.

Cai, S., Huang, L., Zou, J., Jing, L., Zhai, B., Ji, G., von Deneen, K.M., Ren, J., Ren, A. 2015. Changes in thalamic connectivity in the early and late stages of amnestic mild cognitive impairment: a resting-state functional magnetic resonance study from ADNI. PloS one 10(2), e0115573. doi:10.1371/journal.pone.0115573.

Campion, D., Dumanchin, C., Hannequin, D., Dubois, B., Belliard, S., Puel, M., Thomas-Anterion, C., Michon, A., Martin, C., Charbonnier, F., Raux, G., Camuzat, A., Penet, C., Mesnage, V., Martinez, M., Clerget-Darpoux, F., Brice, A., Frebourg, T. 1999. Early-onset autosomal dominant Alzheimer disease: prevalence, genetic heterogeneity, and mutation spectrum. American journal of human genetics 65(3), 664-70. doi:10.1086/302553.

Chen, G., Zhang, H.Y., Xie, C., Chen, G., Zhang, Z.J., Teng, G.J., Li, S.J. 2013. Modular reorganization of brain resting state networks and its independent validation in Alzheimer's disease patients. Frontiers in human neuroscience 7, 456. doi:10.3389/fnhum.2013.00456.

Chetelat, G., Landeau, B., Eustache, F., Mezenge, F., Viader, F., de la Sayette, V., Desgranges, B., Baron, J.C. 2005. Using voxel-based morphometry to map the structural changes associated with rapid conversion in MCI: a longitudinal MRI study. NeuroImage 27(4), 934-46. doi:10.1016/j.neuroimage.2005.05.015.

Cho, H., Kim, J.H., Kim, C., Ye, B.S., Kim, H.J., Yoon, C.W., Noh, Y., Kim, G.H., Kim, Y.J., Kim, J.H., Kim, C.H., Kang, S.J., Chin, J., Kim, S.T., Lee, K.H., Na, D.L., Seong, J.K., Seo, S.W. 2014. Shape changes of the basal ganglia and thalamus in Alzheimer's disease: a three-year longitudinal study. Journal of Alzheimer's disease : JAD 40(2), 285-95. doi:10.3233/jad-132072.

Cummings, J.L., Dubois, B., Molinuevo, J.L., Scheltens, P. 2013. International Work Group criteria for the diagnosis of Alzheimer disease. The Medical clinics of North America 97(3), 363-8. doi:10.1016/j.mcna.2013.01.001.

Dickerson, B.C., Stoub, T.R., Shah, R.C., Sperling, R.A., Killiany, R.J., Albert, M.S., Hyman, B.T., Blacker, D., Detoledo-Morrell, L. 2011. Alzheimer-signature MRI biomarker predicts AD dementia in cognitively normal adults. Neurology 76(16), 1395-402. doi:10.1212/WNL.0b013e3182166e96.

Dubois, B., Feldman, H.H., Jacova, C., Cummings, J.L., Dekosky, S.T., Barberger-Gateau, P., Delacourte, A., Frisoni, G., Fox, N.C., Galasko, D., Gauthier, S., Hampel, H., Jicha, G.A., Meguro, K., O'Brien, J., Pasquier, F., Robert, P., Rossor, M., Salloway, S., Sarazin, M., de Souza, L.C., Stern, Y., Visser, P.J., Scheltens, P. 2010. Revising the definition of Alzheimer's disease: a new lexicon. The Lancet Neurology 9(11), 1118-27. doi:10.1016/s1474-4422(10)70223-4.

Dubois, B., Feldman, H.H., Jacova, C., Hampel, H., Molinuevo, J.L., Blennow, K., DeKosky, S.T., Gauthier, S., Selkoe, D., Bateman, R., Cappa, S., Crutch, S., Engelborghs, S., Frisoni, G.B., Fox, N.C., Galasko, D., Habert, M.O., Jicha, G.A., Nordberg, A., Pasquier, F., Rabinovici, G., Robert, P., Rowe, C., Salloway, S., Sarazin, M., Epelbaum, S., de Souza, L.C., Vellas, B., Visser, P.J., Schneider, L., Stern, Y., Scheltens, P., Cummings, J.L. 2014. Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. The Lancet Neurology 13(6), 614-29. doi:10.1016/s1474-4422(14)70090-0.

Dukart, J., Kherif, F., Mueller, K., Adaszewski, S., Schroeter, M.L., Frackowiak, R.S., Draganski, B. 2013a. Generative FDG-PET and MRI model of aging and disease progression in Alzheimer's disease. PLoS computational biology 9(4), e1002987. doi:10.1371/journal.pcbi.1002987.

Dukart, J., Mueller, K., Villringer, A., Kherif, F., Draganski, B., Frackowiak, R., Schroeter, M.L. 2013b. Relationship between imaging biomarkers, age, progression and symptom severity in Alzheimer's disease. NeuroImage: Clinical 3, 84-94. doi:http://dx.doi.org/10.1016/j.nicl.2013.07.005.

Fjell, A.M., Walhovd, K.B., Fennema-Notestine, C., McEvoy, L.K., Hagler, D.J., Holland, D., Blennow, K., Brewer, J.B., Dale, A.M. 2010. Brain atrophy in healthy aging is related to CSF levels of Abeta1-42. Cerebral cortex (New York, NY : 1991) 20(9), 2069-79. doi:10.1093/cercor/bhp279.

Fleisher, A.S., Chen, K., Quiroz, Y.T., Jakimovich, L.J., Gomez, M.G., Langois, C.M., Langbaum, J.B., Ayutyanont, N., Roontiva, A., Thiyyagura, P., Lee, W., Mo, H., Lopez, L., Moreno, S., Acosta-Baena, N., Giraldo, M., Garcia, G., Reiman, R.A., Huentelman, M.J., Kosik, K.S., Tariot, P.N., Lopera, F., Reiman, E.M. 2012. Florbetapir PET analysis of amyloid-beta deposition in the presenilin 1 E280A autosomal dominant Alzheimer's disease kindred: a cross-sectional study. The Lancet Neurology 11(12), 1057-65. doi:10.1016/s1474-4422(12)70227-2.

Fortea, J., Carmona-Iragui, M., Fernandez, S., Benejam, B., Videla, L., Alcolea, D., Vilaplana, E., Clarimón, J., Videla, S., Blesa, R., Lleo, A. 2016. DOWN ALZHEIMER BARCELONA NEUROIMAGING INITIATIVE (DABNI): A PROSPECTIVE LONGITUDINAL BIOMARKER COHORT TO STUDY ALZHEIMER'S DISEASE IN DOWN SYNDROME. Alzheimer's & Dementia: The Journal of the Alzheimer's Association 12(7), P380-P1. doi:10.1016/j.jalz.2016.06.713.

Fortea, J., Sala-Llonch, R., Bartres-Faz, D., Bosch, B., Llado, A., Bargallo, N., Molinuevo, J.L., Sanchez-Valle, R. 2010. Increased cortical thickness and caudate volume precede atrophy in PSEN1 mutation carriers. Journal of Alzheimer's disease : JAD 22(3), 909-22. doi:10.3233/jad-2010-100678.

Handen, B.L., Cohen, A.D., Channamalappa, U., Bulova, P., Cannon, S.A., Cohen, W.I., Mathis, C.A., Price, J.C., Klunk, W.E. 2012. Imaging brain amyloid in nondemented young adults with Down syndrome using Pittsburgh compound B. Alzheimer's & dementia : the journal of the Alzheimer's Association 8(6), 496-501. doi:10.1016/j.jalz.2011.09.229.

Hartley, D., Blumenthal, T., Carrillo, M., DiPaolo, G., Esralew, L., Gardiner, K., Granholm, A.C., Iqbal, K., Krams, M., Lemere, C., Lott, I., Mobley, W., Ness, S., Nixon, R., Potter, H., Reeves, R., Sabbagh, M., Silverman, W., Tycko, B., Whitten, M., Wisniewski, T. 2015. Down syndrome and Alzheimer's disease: Common pathways, common goals. Alzheimer's & dementia : the journal of the Alzheimer's Association 11(6), 700-9. doi:10.1016/j.jalz.2014.10.007.

Hirao, K., Ohnishi, T., Hirata, Y., Yamashita, F., Mori, T., Moriguchi, Y., Matsuda, H., Nemoto, K., Imabayashi, E., Yamada, M., Iwamoto, T., Arima, K., Asada, T. 2005. The prediction of rapid conversion to Alzheimer's disease in mild

cognitive impairment using regional cerebral blood flow SPECT. NeuroImage 28(4), 1014-21. doi:10.1016/j.neuroimage.2005.06.066.

Hyman, B.T., Phelps, C.H., Beach, T.G., Bigio, E.H., Cairns, N.J., Carrillo, M.C., Dickson, D.W., Duyckaerts, C., Frosch, M.P., Masliah, E., Mirra, S.S., Nelson, P.T., Schneider, J.A., Thal, D.R., Thies, B., Trojanowski, J.Q., Vinters, H.V., Montine, T.J. 2012. National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease. Alzheimer's & dementia : the journal of the Alzheimer's Association 8(1), 1-13. doi:10.1016/j.jalz.2011.10.007.

Jack, C.R., Jr., Knopman, D.S., Jagust, W.J., Petersen, R.C., Weiner, M.W., Aisen, P.S., Shaw, L.M., Vemuri, P., Wiste, H.J., Weigand, S.D., Lesnick, T.G., Pankratz, V.S., Donohue, M.C., Trojanowski, J.Q. 2013. Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. The Lancet Neurology 12(2), 207-16. doi:10.1016/s1474-4422(12)70291-0.

Johnson, K.A., Fox, N.C., Sperling, R.A., Klunk, W.E. 2012. Brain imaging in Alzheimer disease. Cold Spring Harb Perspect Med 2(4), a006213. doi:10.1101/cshperspect.a006213.

Kinnunen, K., Ryan, N., Cash, D., Leite, A.B., Finnegan, S., Cardoso, M., Leung, K., Modat, M., Benzinger, T., Jack, C., Marcus, D., Raichle, M., Thompson, P., Ringman, J., Ghetti, B., Salloway, S., Sperling, R., Schofield, P., Masters, C., Mayeux, R., Martins, R., Weiner, M., Bateman, R., Goate, A., Fagan, A., Cairns, N., Buckles, V., Morris, J., Rossor, M., Ourselin, S., Fox, N. 2013. Are early atrophy patterns in autosomal dominant familial Alzheimer's disease gene-dependent? Alzheimer's and Dementia 1), P251-P2. doi:http://dx.doi.org/10.1016/j.jalz.2013.05.494.

Klunk, W.E., Engler, H., Nordberg, A., Wang, Y., Blomqvist, G., Holt, D.P., Bergstrom, M., Savitcheva, I., Huang, G.F., Estrada, S., Ausen, B., Debnath, M.L., Barletta, J., Price, J.C., Sandell, J., Lopresti, B.J., Wall, A., Koivisto, P., Antoni, G., Mathis, C.A., Langstrom, B. 2004. Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. Annals of neurology 55(3), 306-19. doi:10.1002/ana.20009.

Klunk, W.E., Price, J.C., Mathis, C.A., Tsopelas, N.D., Lopresti, B.J., Ziolko, S.K., Bi, W., Hoge, J.A., Cohen, A.D., Ikonomovic, M.D., Saxton, J.A., Snitz, B.E.,

Pollen, D.A., Moonis, M., Lippa, C.F., Swearer, J.M., Johnson, K.A., Rentz, D.M., Fischman, A.J., Aizenstein, H.J., DeKosky, S.T. 2007. Amyloid deposition begins in the striatum of presenilin-1 mutation carriers from two unrelated pedigrees. The Journal of neuroscience : the official journal of the Society for Neuroscience 27(23), 6174-84. doi:10.1523/jneurosci.0730-07.2007.

Knapp, M., Prince, M., Albanese, E., Banerjee, S., Dhanasiri, S., Fernandez, J., L, Ferri, C., McCrone, P., Snell, T., Stewart, R. 2007. Dementia UK.

Knight, W.D., Okello, A.A., Ryan, N.S., Turkheimer, F.E., Rodriguez Martinez de Llano, S., Edison, P., Douglas, J., Fox, N.C., Brooks, D.J., Rossor, M.N. 2011. Carbon-11-Pittsburgh compound B positron emission tomography imaging of amyloid deposition in presenilin 1 mutation carriers. Brain : a journal of neurology 134(Pt 1), 293-300. doi:10.1093/brain/awq310.

Koivunen, J., Karrasch, M., Scheinin, N.M., Aalto, S., Vahlberg, T., Nagren, K., Helin, S., Viitanen, M., Rinne, J.O. 2012. Cognitive decline and amyloid accumulation in patients with mild cognitive impairment. Dementia and geriatric cognitive disorders 34(1), 31-7. doi:10.1159/000341580.

Koivunen, J., Scheinin, N., Virta, J.R., Aalto, S., Vahlberg, T., Nagren, K., Helin, S., Parkkola, R., Viitanen, M., Rinne, J.O. 2011. Amyloid PET imaging in patients with mild cognitive impairment: a 2-year follow-up study. Neurology 76(12), 1085-90. doi:10.1212/WNL.0b013e318212015e.

Lao, P.J., Betthauser, T.J., Hillmer, A.T., Price, J.C., Klunk, W.E., Mihaila, I., Higgins, A.T., Bulova, P.D., Hartley, S.L., Hardison, R., Tumuluru, R.V., Murali, D., Mathis, C.A., Cohen, A.D., Barnhart, T.E., Devenny, D.A., Mailick, M.R., Johnson, S.C., Handen, B.L., Christian, B.T. 2015. The effects of normal aging on amyloid-beta deposition in nondemented adults with Down syndrome as imaged by carbon 11-labeled Pittsburgh compound B. Alzheimer's & dementia : the journal of the Alzheimer's Association. doi:10.1016/j.jalz.2015.05.013.

Lee, G.J., Lu, P.H., Medina, L.D., Rodriguez-Agudelo, Y., Melchor, S., Coppola, G., Braskie, M.N., Hua, X., Apostolova, L.G., Leow, A.D., Thompson, P.M., Ringman, J.M. 2013. Regional brain volume differences in symptomatic and presymptomatic carriers of familial Alzheimer's disease mutations. Journal of

neurology, neurosurgery, and psychiatry 84(2), 154-62. doi:10.1136/jnnp-2011-302087.

Leh, S.E., Kalin, A.M., Schroeder, C., Park, M.T., Chakravarty, M.M., Freund, P., Gietl, A.F., Riese, F., Kollias, S., Hock, C., Michels, L. 2015. Volumetric and Shape Analysis of the Thalamus and Striatum in Amnestic Mild Cognitive Impairment. Journal of Alzheimer's disease : JAD 49(1), 237-49. doi:10.3233/jad-150080.

Liljeholm, M., O'Doherty, J.P. 2012. Contributions of the striatum to learning, motivation, and performance: an associative account. Trends in cognitive sciences 16(9), 467-75. doi:10.1016/j.tics.2012.07.007.

Liu, Y., Paajanen, T., Zhang, Y., Westman, E., Wahlund, L.O., Simmons, A., Tunnard, C., Sobow, T., Mecocci, P., Tsolaki, M., Vellas, B., Muehlboeck, S., Evans, A., Spenger, C., Lovestone, S., Soininen, H. 2010. Analysis of regional MRI volumes and thicknesses as predictors of conversion from mild cognitive impairment to Alzheimer's disease. Neurobiology of aging 31(8), 1375-85. doi:10.1016/j.neurobiolaging.2010.01.022.

Madsen, S.K., Ho, A.J., Hua, X., Saharan, P.S., Toga, A.W., Jack, C.R., Jr., Weiner, M.W., Thompson, P.M. 2010. 3D maps localize caudate nucleus atrophy in 400 Alzheimer's disease, mild cognitive impairment, and healthy elderly subjects. Neurobiology of aging 31(8), 1312-25. doi:10.1016/j.neurobiolaging.2010.05.002.

McDade, E., Kim, A., James, J., Minhas, D., Ikonomovic, S., Lopez, O., Snitz, B., Price, J., Becker, J., Mathis, C., Klunk, W. 2014. Early striatal perfusion deficits in autosomal dominant Alzheimer disease detected with arterial spin labeled MRI. Neurology 1).

McKhann, G.M., Knopman, D.S., Chertkow, H., Hyman, B.T., Jack, C.R., Jr., Kawas, C.H., Klunk, W.E., Koroshetz, W.J., Manly, J.J., Mayeux, R., Mohs, R.C., Morris, J.C., Rossor, M.N., Scheltens, P., Carrillo, M.C., Thies, B., Weintraub, S., Phelps, C.H. 2011. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's & dementia : the journal of the Alzheimer's Association 7(3), 263-9. doi:10.1016/j.jalz.2011.03.005.

Mirra, S.S., Heyman, A., McKeel, D., Sumi, S.M., Crain, B.J., Brownlee, L.M., Vogel, F.S., Hughes, J.P., van Belle, G., Berg, L. 1991. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part II. Standardization of the neuropathologic assessment of Alzheimer's disease. Neurology 41(4), 479-86.

Morbelli, S., Piccardo, A., Villavecchia, G., Dessi, B., Brugnolo, A., Piccini, A., Caroli, A., Frisoni, G., Rodriguez, G., Nobili, F. 2010. Mapping brain morphological and functional conversion patterns in amnestic MCI: A voxel-based MRI and FDG-PET study. European journal of nuclear medicine and molecular imaging 37(1), 36-45. doi:http://dx.doi.org/10.1007/s00259-009-1218-6.

Morris, J.C. 1993. The Clinical Dementia Rating (CDR): current version and scoring rules. Neurology 43(11), 2412-4.

Nordberg, A., Carter, S.F., Rinne, J., Drzezga, A., Brooks, D.J., Vandenberghe, R., Perani, D., Forsberg, A., Langstrom, B., Scheinin, N., Karrasch, M., Nagren, K., Grimmer, T., Miederer, I., Edison, P., Okello, A., Van Laere, K., Nelissen, N., Vandenbulcke, M., Garibotto, V., Almkvist, O., Kalbe, E., Hinz, R., Herholz, K. 2013. A European multicentre PET study of fibrillar amyloid in Alzheimer's disease. European journal of nuclear medicine and molecular imaging 40(1), 104-14. doi:10.1007/s00259-012-2237-2.

Oh, H., Madison, C., Villeneuve, S., Markley, C., Jagust, W.J. 2014. Association of gray matter atrophy with age, beta-amyloid, and cognition in aging. Cerebral cortex (New York, NY : 1991) 24(6), 1609-18. doi:10.1093/cercor/bht017.

Packard, M.G., Knowlton, B.J. 2002. Learning and memory functions of the Basal Ganglia. Annual review of neuroscience 25, 563-93. doi:10.1146/annurev.neuro.25.112701.142937.

Price, C.C., Jefferson, A.L., Merino, J.G., Heilman, K.M., Libon, D.J. 2005. Subcortical vascular dementia: integrating neuropsychological and neuroradiologic data. Neurology 65(3), 376-82. doi:10.1212/01.wnl.0000168877.06011.15.

Price, J.C., Christian, B.T., Klunk, W.E., Cohen, A.D., Hartley, S.L., Seltzer, M.M., Johnson, S.C., Murali, D., Bulova, P.D., Tumuluru, R., Lopresti, B.L., C, A.M., Handen, B.L. 2011. Assessing amyloid load in non-demented young adults with down's syndrome. Neuropsychopharmacology : official publication of the

American College of Neuropsychopharmacology 36, S154. doi:http://dx.doi.org/10.1038/npp.2011.291.

Prince, M., Bryce, R., Albanese, E., Wimo, A., Ribeiro, W., Ferri, C.P. 2013. The global prevalence of dementia: a systematic review and metaanalysis. Alzheimer's & dementia : the journal of the Alzheimer's Association 9(1), 63-75.e2. doi:10.1016/j.jalz.2012.11.007.

Reiman, E.M., Chen, K., Liu, X., Bandy, D., Yu, M., Lee, W., Ayutyanont, N., Keppler, J., Reeder, S.A., Langbaum, J.B., Alexander, G.E., Klunk, W.E., Mathis, C.A., Price, J.C., Aizenstein, H.J., DeKosky, S.T., Caselli, R.J. 2009. Fibrillar amyloid-beta burden in cognitively normal people at 3 levels of genetic risk for Alzheimer's disease. Proceedings of the National Academy of Sciences of the United States of America 106(16), 6820-5. doi:10.1073/pnas.0900345106.

Rothwell, J.C. 2011. The motor functions of the basal ganglia. Journal of integrative neuroscience 10(3), 303-15. doi:10.1142/s0219635211002798.

Ryan, N.S., Fox, N.C. 2013. Reply: Implications of presymptomatic change in thalamus and caudate in Alzheimer's disease. Brain : a journal of neurology 136(11), e259. doi:http://dx.doi.org/10.1093/brain/awt168.

Ryan, N.S., Keihaninejad, S., Shakespeare, T.J., Lehmann, M., Crutch, S.J., Malone, I.B., Thornton, J.S., Mancini, L., Hyare, H., Yousry, T., Ridgway, G.R., Zhang, H., Modat, M., Alexander, D.C., Rossor, M.N., Ourselin, S., Fox, N.C. 2013. Magnetic resonance imaging evidence for presymptomatic change in thalamus and caudate in familial Alzheimer's disease. Brain : a journal of neurology 136(Pt 5), 1399-414. doi:10.1093/brain/awt065.

Sala-Llonch, R., Llado, A., Fortea, J., Bosch, B., Antonell, A., Balasa, M., Bargallo, N., Bartres-Faz, D., Molinuevo, J.L., Sanchez-Valle, R. 2015. Evolving brain structural changes in PSEN1 mutation carriers. Neurobiology of aging 36(3), 1261-70. doi:10.1016/j.neurobiolaging.2014.12.022.

Scahill, R.I., Ridgway, G.R., Bartlett, J.W., Barnes, J., Ryan, N.S., Mead, S., Beck, J., Clarkson, M.J., Crutch, S.J., Schott, J.M., Ourselin, S., Warren, J.D., Hardy, J., Rossor, M.N., Fox, N.C. 2013. Genetic influences on atrophy patterns in familial Alzheimer's disease: a comparison of APP and PSEN1 mutations. J Alzheimers Dis 35(1), 199-212. doi:10.3233/jad-121255.

Scholl, M., Almkvist, O., Axelman, K., Stefanova, E., Wall, A., Westman, E., Langstrom, B., Lannfelt, L., Graff, C., Nordberg, A. 2011. Glucose metabolism and PIB binding in carriers of a His163Tyr presenilin 1 mutation. Neurobiology of aging 32(8), 1388-99. doi:10.1016/j.neurobiolaging.2009.08.016.

Scholl, M., Wall, A., Thordardottir, S., Ferreira, D., Bogdanovic, N., Langstrom, B., Almkvist, O., Graff, C., Nordberg, A. 2012. Low PiB PET retention in presence of pathologic CSF biomarkers in Arctic APP mutation carriers. Neurology 79(3), 229-36. doi:10.1212/WNL.0b013e31825fdf18.

Shi, Z., Wang, Y., Liu, S., Liu, M., Liu, S., Zhou, Y., Wang, J., Cai, L., Huo, Y.R., Gao, S., Ji, Y. 2015. Clinical and neuroimaging characterization of Chinese dementia patients with PSEN1 and PSEN2 mutations. Dementia and geriatric cognitive disorders 39(1-2), 32-40. doi:10.1159/000366272.

Tang, X., Holland, D., Dale, A.M., Younes, L., Miller, M.I. 2014. Shape abnormalities of subcortical and ventricular structures in mild cognitive impairment and Alzheimer's disease: detecting, quantifying, and predicting. Human brain mapping 35(8), 3701-25. doi:10.1002/hbm.22431.

Tang, X., Holland, D., Dale, A.M., Younes, L., Miller, M.I. 2015. Baseline shape diffeomorphometry patterns of subcortical and ventricular structures in predicting conversion of mild cognitive impairment to Alzheimer's disease. Journal of Alzheimer's disease : JAD 44(2), 599-611. doi:10.3233/jad-141605.

Thal, D.R., Rub, U., Orantes, M., Braak, H. 2002. Phases of A beta-deposition in the human brain and its relevance for the development of AD. Neurology 58(12), 1791-800.

Tifratene, K., Robert, P., Metelkina, A., Pradier, C., Dartigues, J.F. 2015. Progression of mild cognitive impairment to dementia due to AD in clinical settings. Neurology 85(4), 331-8. doi:10.1212/wnl.0000000000001788.

Trollor, J.N., Sachdev, P.S., Haindl, W., Brodaty, H., Wen, W., Walker, B.M. 2006. A high-resolution single photon emission computed tomography study of verbal recognition memory in Alzheimer's disease. Dementia and geriatric cognitive disorders 21(4), 267-74. doi:10.1159/000091433.

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

mutation types. Archives of neurology 66(12), 1537-44. doi:10.1001/archneurol.2009.285.

Vishnu, V.Y. 2013. Implications of presymptomatic change in thalamus and caudate in Alzheimer's disease. Brain : a journal of neurology 136(11), e258. doi:http://dx.doi.org/10.1093/brain/awt167.

White, N.M. 2009. Some highlights of research on the effects of caudate nucleus lesions over the past 200 years. Behavioural brain research 199(1), 3-23. doi:10.1016/j.bbr.2008.12.003.

Yi, H.A., Moller, C., Dieleman, N., Bouwman, F.H., Barkhof, F., Scheltens, P., van der Flier, W.M., Vrenken, H. 2015. Relation between subcortical grey matter atrophy and conversion from mild cognitive impairment to Alzheimer's disease. Journal of neurology, neurosurgery, and psychiatry. doi:10.1136/jnnp-2014-309105.

Yi, L.Y., Liang, X., Liu, D.M., Sun, B., Ying, S., Yang, D.B., Li, Q.B., Jiang, C.L., Han, Y. 2015. Disrupted Topological Organization of Resting-State Functional Brain Network in Subcortical Vascular Mild Cognitive Impairment. CNS neuroscience & therapeutics 21(10), 846-54. doi:10.1111/cns.12424.

Zhao, H., Li, X., Wu, W., Li, Z., Qian, L., Li, S., Zhang, B., Xu, Y. 2015. Atrophic Patterns of the Frontal-Subcortical Circuits in Patients with Mild Cognitive Impairment and Alzheimer's Disease. PloS one 10(6), e0130017. doi:10.1371/journal.pone.0130017.

Captions

Figure 1. Flow diagram of article selection following literature search.

Figure 2. Presence of striatal amyloid deposits in five cognitively normal PS1C410Y mutation carriers, and their absence in the non-carrier cousin (CY-C(35). Reprinted from Klunk et al., Amyloid deposition begins in the striatum of presenilin-1 mutation carriers from two unrelated pedigrees, The Journal of neuroscience, 2007, 27(23), 6174-84.

Figure 3. Subcortical amyloid deposits (PiB-PET) and volumetric losses (MRI) in ADAD mutation carriers from the DIAN cohort. Reprinted from Benzinger et al., Regional variability of imaging biomarkers in autosomal dominant Alzheimer's disease, PNAS, 2013, 110(47), E4502-9.

Figure 4. Voxel-based morphometry results showing (top) grey matter volume loss and (bottom) white matter volume loss in symptomatic ADAD mutation carriers compared to controls. Reprinted from Ryan et al., Magnetic resonance imaging evidence for presymptomatic change in thalamus and caudate in familial Alzheimer's disease, Brain, 2013, 136(Pt 5), 1399-414, by permission of Oxford University Press.

Highlights

- Subcortical regions may play an important role in AD development.
- The most consistent finding was striatal amyloid deposition in presymptomatic ADAD.
- Thalamo-striatal regions may also be involved in early-stage sAD.
- Targeted research will show if measures from these regions are useful in AD models.

Fig. 1

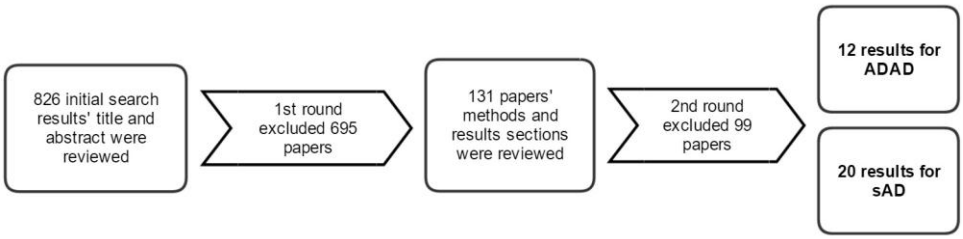

826 initial search results' title and abstract were reviewed
1st round excluded 695 papers
131 papers' methods and results sections were reviewed
2nd round excluded 99 papers
12 results for ADAD
20 results for sAD

Fig. 2

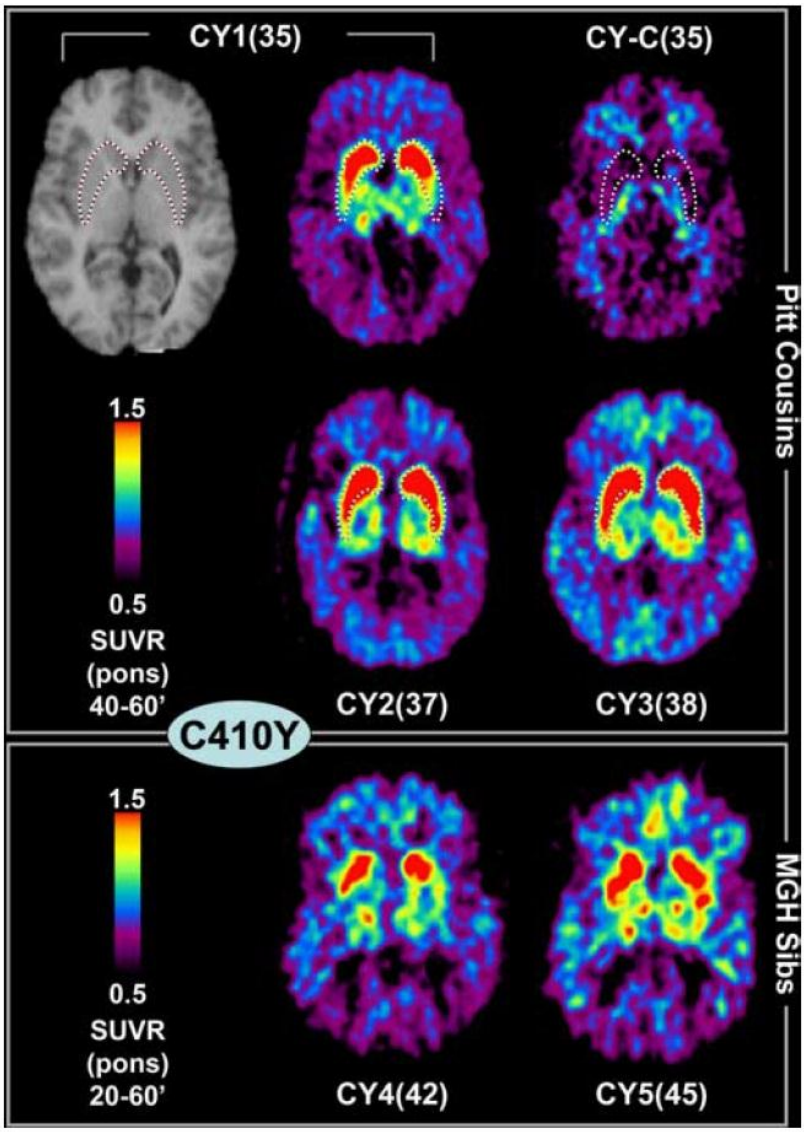

CY1(35)
CY-C(35)
1.5
0.5
SUVR
(pons)
40-60'
CY2(37)
CY3(38)
Pitt Cousins
C410Y
1.5
0.5
SUVR
(pons)
20-60'
CY4(42)
CY5(45)
MGH Sibs

Fig. 3

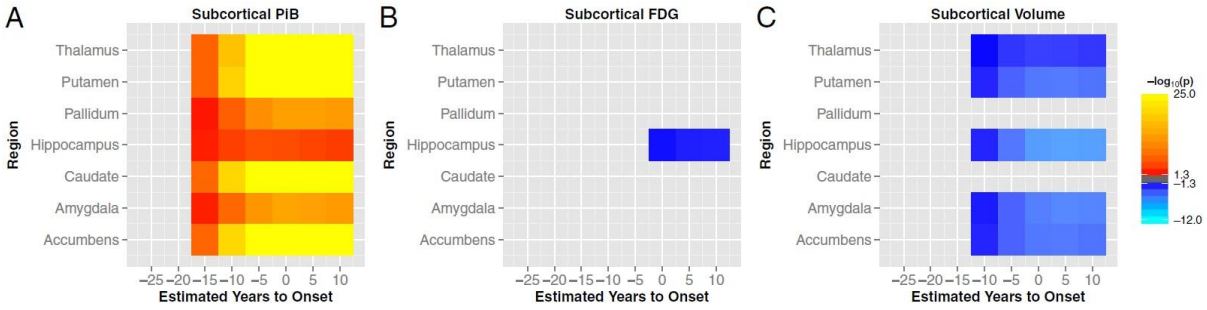
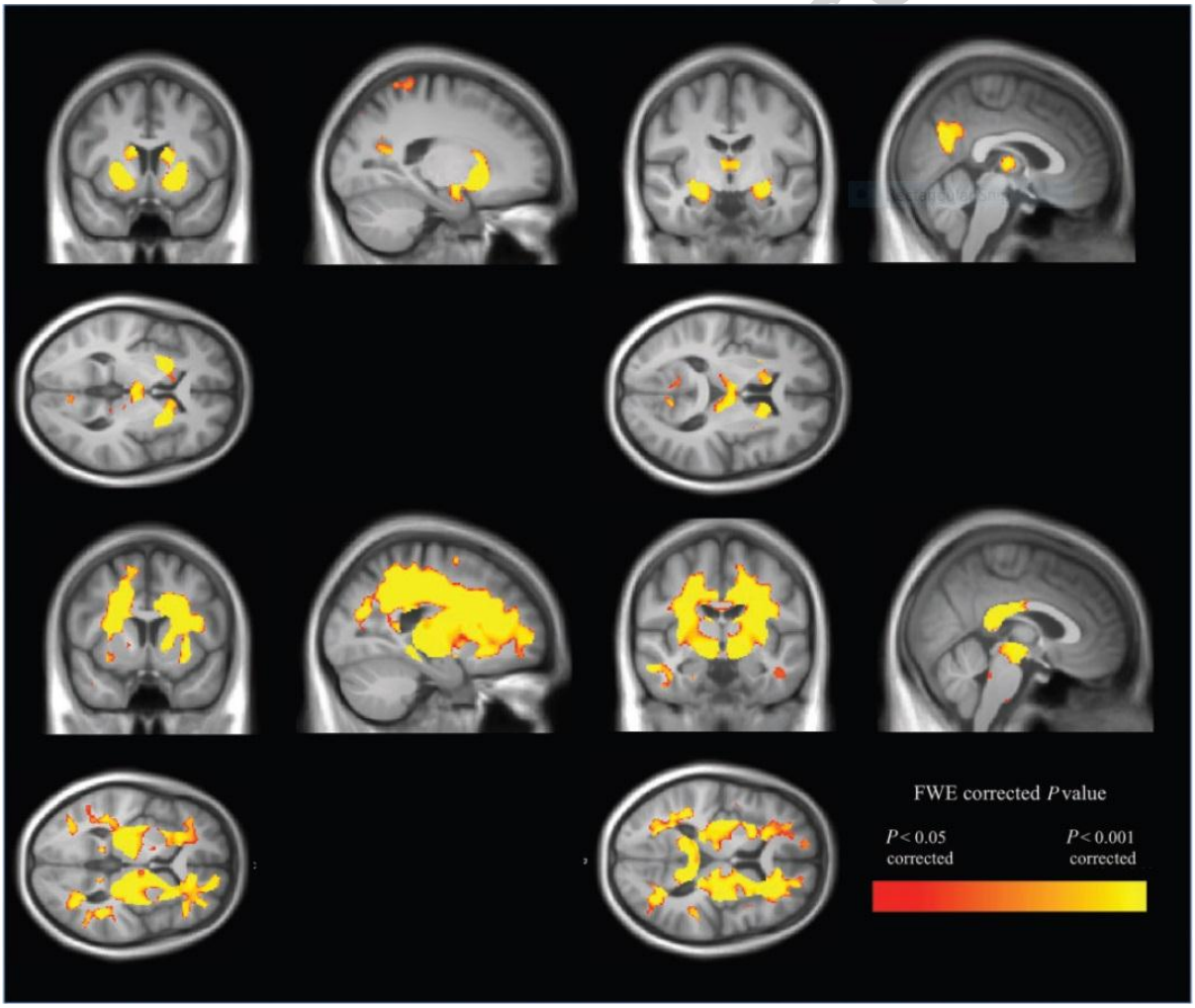

A
Subcortical PiB
B
Subcortical FDG
C
Subcortical Volume
Region
Thalamus
Putamen
Pallidum
Hippocampus
Caudate
Amygdala
Accumbens
−25 −20 −15 −10 −5 0 5 10
Estimated Years to Onset
−log10(p)
25.0
1.3
−1.3
−12.0

Fig. 4


FWE corrected P value
P < 0.05
corrected
P < 0.001
corrected