Suspected non-Alzheimer disease pathophysiology – concept and controversy

Article *in* Nature Reviews Neurology · January 2016

DOI: 10.1038/nrneurol.2015.251

OPINION

Suspected non-Alzheimer disease pathophysiology — concept and controversy

Clifford R. Jack Jr, David S. Knopman, Gaël Chételat, Dennis Dickson, Anne M. Fagan, Giovanni B. Frisoni, William Jagust, Elizabeth C. Mormino, Ronald C. Petersen, Reisa A. Sperling, Wiesje M. van der Flier, Victor L. Villemagne, Pieter J. Visser and Stephanie J. B. Vos

Abstract | Suspected non-Alzheimer disease pathophysiology (SNAP) is a biomarker-based concept that applies to individuals with normal levels of amyloid-β biomarkers in the brain, but in whom biomarkers of neurodegeneration are abnormal. The term SNAP has been applied to clinically normal individuals (who do not meet criteria for either mild cognitive impairment or dementia) and to individuals with mild cognitive impairment, but is applicable to any amyloid-negative, neurodegeneration-positive individual regardless of clinical status, except when the pathology underlying neurodegeneration can be reliably inferred from the clinical presentation. SNAP is present in ~23% of clinically normal individuals aged >65 years and in ~25% of mildly cognitively impaired individuals. *APOE*ε4* is underrepresented in individuals with SNAP compared with amyloid-positive individuals. Clinically normal and mildly impaired individuals with SNAP have worse clinical and/or cognitive outcomes than individuals with normal levels of neurodegeneration and amyloid-β biomarkers. In this Perspectives article, we describe the available data on SNAP and address topical controversies in the field.

Suspected non-Alzheimer disease (AD) pathophysiology (SNAP) is a biomarker-based concept denoting AD-like neurodegeneration in individuals without excessive amyloid-β (Aβ) deposition. SNAP was first described in a study[1] in which the National Institute on Ageing–Alzheimer disease Association (NIA–AA) criteria of preclinical AD[2] were examined.

The NIA–AA criteria rely on biomarkers to classify individuals as either Aβ-positive or Aβ-negative, and as neurodegeneration-positive or neurodegeneration-negative[2–5]. Five biomarkers are used in the NIA–AA classification. Biomarkers of fibrillary Aβ deposition include high ligand retention on amyloid-PET and low levels of $A\beta_{42}$ in the cerebrospinal fluid (CSF). The biomarkers of AD-related neurodegeneration include high levels of tau in the CSF, signature topographic patterns characteristic of AD-associated brain hypometabolism as assessed by ^{18}F-FDG–PET, and atrophy as assessed by structural MRI[5,6] (FIG. 1). The NIA–AA classification also introduced a new concept of preclinical AD, in which clinically normal individuals with biomarker evidence of AD pathology were hypothesized to be on the trajectory towards symptomatic AD[2]. Of note, cognitive performance inevitably declines with ageing; thus, the definition of what constitutes 'normal' cognitive performance in the context of an ageing population is not straightforward. In this article, we therefore use the term 'clinically normal' rather than 'cognitively normal' to describe an elderly individual who does not meet criteria for either mild cognitive impairment or dementia.

The NIA–AA preclinical AD workgroup that proposed the concept of preclinical AD operated under the assumption that the term 'AD' referred to the pathological condition and that clinical symptoms resulting from the pathological condition are not required in the definition of AD[2]. The NIA–AA staging framework for preclinical AD[2] is based on biomarker combinations and cognition: stage 1 refers to amyloidosis without neurodegeneration (A^+N^-), stage 2 refers to amyloidosis plus neurodegeneration (A^+N^+) and stage 3 refers to amyloidosis plus neurodegeneration (A^+N^+) plus subtle cognitive deficit(s) (BOX 1).

In the study in which SNAP was first described, 450 clinically normal individuals aged >70 years were classified using amyloid plaque density assessed by PET, brain metabolism assessed by ^{18}F-FDG–PET and hippocampal volume assessed by MRI[1] (see Supplementary information S1 (table)). Of this sample, 31% of participants were at NIA–AA preclinical AD stages 1–3; 43% had neither amyloidosis nor neurodegeneration (A^-N^-) and were classified as being at stage 0 (REF. 1). 23% of participants had neurodegeneration without amyloidosis (A^-N^+). The term SNAP was used to convey the notion that the latter group did not represent preclinical AD, but rather had biomarker evidence of non-AD neurodegenerative processes[1] (FIG. 2). The proportion of *APOE*ε4* carriers in the SNAP group was 13%, much lower than that in individuals with preclinical AD (~40%), and half that in individuals at stage 0 (24%). This observation supported the view that SNAP was not simply the result of measurement or classification errors, but rather had a biological basis.

Controversies followed the publication of the SNAP concept[1,7]. In this article, we discuss the available data supporting the concept of SNAP, the course of cognitive decline in individuals with SNAP, pathophysiological basis of SNAP, as well as the controversies in the field.

SNAP and cognitive status

Clinically normal individuals

Most studies in which the SNAP concept was used have not been focused on SNAP as a primary aim, but were designed to evaluate diagnostic criteria of AD that incorporate biomarkers. Different methods were used to classify the participants in these studies (see Supplementary information S1 (table)). Some studies used imaging alone[1,8–11], others CSF biomarkers alone[12–14], others CSF biomarkers combined with imaging[15].

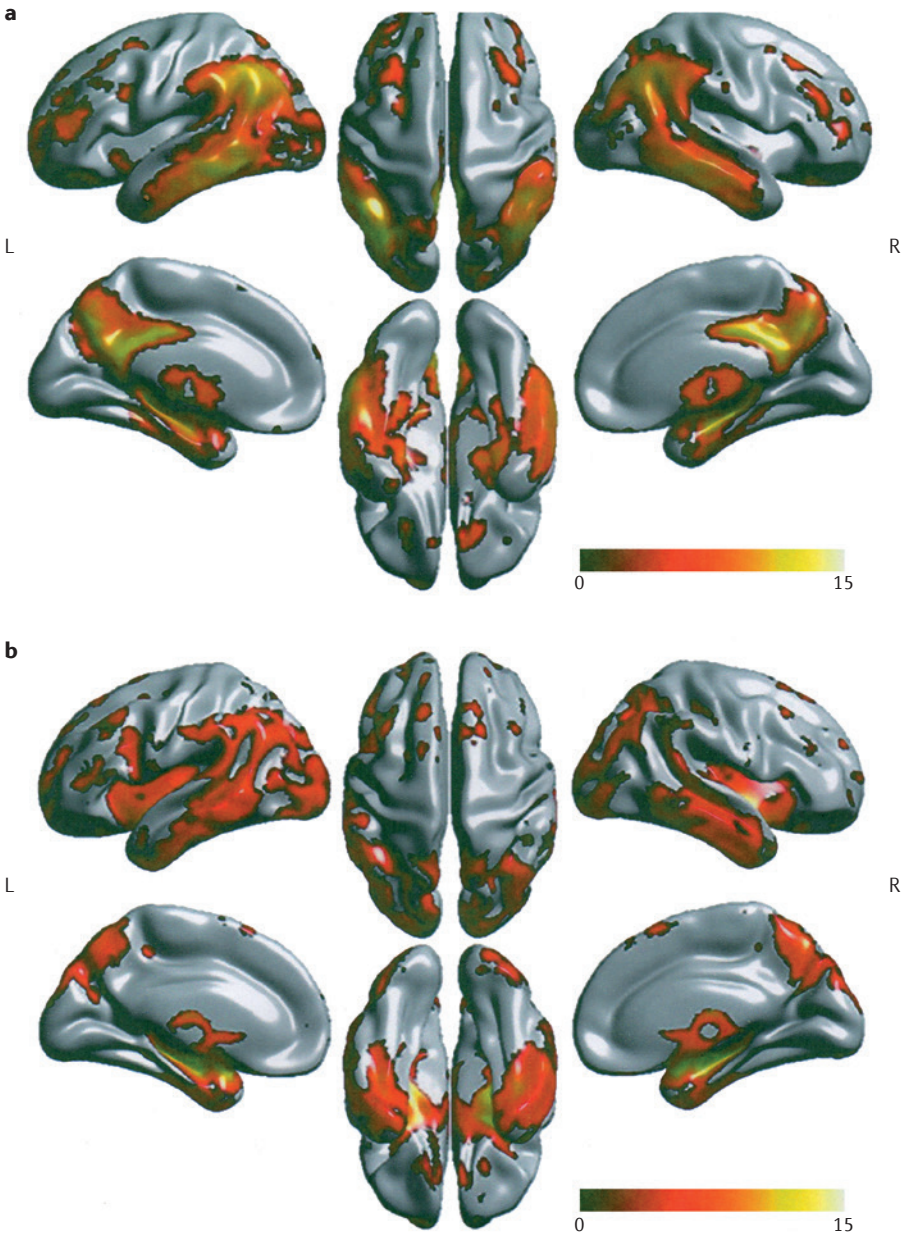

Figure 1 | **Signature patterns of AD.** Individuals with AD dementia ($n = 50$) were age-matched and sex-matched with cognitively normal elderly individuals ($n = 50$). **a** | ^{18}F-FDG–PET maps (FWE threshold set at $P < 0.001$) illustrate decreased FDG uptake in the basal temporal, lateral temporal–parietal, lateral prefrontal, and posterior cingulate–precuneus areas in individuals with AD dementia compared with clinically normal elderly individuals. This spatial pattern constitutes an 'AD-signature' in FDG PET. **b** | Structural MRI maps (FWE threshold set at $P < 0.05$) illustrate grey matter loss in the medial, basal and lateral temporal, lateral parietal, occipital, insula, and precuneus areas in individuals with AD dementia compared with clinically normal elderly individuals. This spatial pattern constitutes an 'AD-signature' in structural MRI. All voxel-based comparison images were generated with SPM5. 3D displays were generated by Brain Net Viewer[95]. The colour bar scale indicates the *t*-test differences between the groups. AD, Alzheimer disease; FEW, family-wise error;L, left; R, right; SPM5, statistical parametric mapping. Permission obtained from Elsevier Ltd © Jack, C.R. Jr & Holtzman D. M. *Neuron* **18**, 1347–1358 (2013).

The proportion of individuals with SNAP among clinically normal participants aged >65 years was very consistent across these studies, many of which, perhaps coincidently, reported exactly 23% (see Supplementary information S1 (table)). Compared with other concepts used in the field of cognitive ageing, this consistency is unusual and supports the legitimacy of the SNAP concept.

Clinical and/or cognitive outcomes have been described in several of these cohorts (see Supplementary information S1 (table); FIG. 3). Average follow-up times ranged from 1.3 to 6 years. Although progression rates vary by study, a common pattern for the risk of clinical progression to mild impairment or dementia or cognitive decline overall is apparent. This risk is greatest for preclinical AD stage 3, next for preclinical AD stage 2, next for preclinical AD stage 1 or SNAP, and is the lowest for preclinical AD stage 0. The risk of cognitive decline seems to be greater for preclinical AD stage 1 than for SNAP when CSF biomarkers alone are used, but not when imaging is used (see Supplementary information S1 (table); FIG. 3). This observation could indicate that some neurodegeneration biomarkers are more sensitive than others at predicting imminent cognitive decline[15]. It could also simply reflect a confounding interaction between the biomarkers selected for use in individual cohorts and the characteristics of those cohorts. Each research group tends to use one set of biomarkers and the inherent predisposition to clinical progression is undoubtedly not equal among different cohorts.

Several studies examined the cognitive profiles of clinically normal individuals classified according to biomarkers of Aβ accumulation and neurodegeneration at baseline[8,9,12,14] (see Supplementary information S1 (table)). Overall, no significant differences in cognitive performance were observed between the SNAP group and the A^-N^- or A^+N^- groups. Therefore, the consensus at this time is that SNAP does not have a distinct cognitive phenotype among clinically normal individuals.

Studies in which imaging was used to classify clinically normal individuals into different biomarker-based groups indicated that men are more likely to have SNAP than women, which does not seem to be the case when CSF is used for classification into amyloid pathology and neurodegeneration categories (see Supplementary information S1 (table)). Individuals with SNAP also tend to be older than those at preclinical AD

Box 1 | **Terminology for classification**

- A^-N^-: NIA–AA preclinical stage 0
- A^+N^-: NIA–AA preclinical stage 1
- A^+N^+: NIA–AA preclinical stages 2 and 3
- A^-N^+: SNAP

A, amyloidosis; N, neurodegeneration; NIA–AA, National Institute on Ageing–Alzheimer disease Association; SNAP, suspected non-Alzheimer disease pathophysiology.

stages 0 or 1. All studies indicate that *APOE*ε4* is markedly less common in SNAP than in preclinical AD (A^+N^- and A^+N^+). Some studies indicate that *APOE*ε4* is less common in SNAP than in the A^-N^- reference group[1,8,9]. These observations are logical given that *APOE*ε4* is a major risk factor for Aβ pathology[16,17].

Clinical and imaging features of cerebrovascular disease and Lewy body disease[18] were assessed among 430 clinically normal individuals classified in preclinical AD and SNAP categories[19]. Some of these features were more prevalent in individuals with SNAP than in A^-N^- individuals, but were not different between individuals with SNAP and A^+N^+ individuals. These results could be interpreted to indicate that neither subclinical cerebrovascular disease nor Lewy body disease are likely to be the substrates of the neurodegeneration observed in SNAP; however, the fact that these features were more prevalent in the SNAP than in the A^-N^-group argues against this conclusion. An alternative interpretation would attribute the findings to age differences among biomarker groups. The frequency of cerebrovascular disease and Lewy body disease increases with ageing and individuals with SNAP were older than A^-N^- individuals, but had about the same age as A^+N^+ individuals.

One study that examined the changes in the frequency of biomarker-based groups with age[20] found that the frequency of SNAP was 0 in the 50–60 years age range and then increased monotonically, reaching 24% by 89 years of age. Therefore, the frequency of SNAP in the population is not static, but increases with ageing after age 60 years.

The characteristics of clinically normal individuals aged >70 years who were documented to become newly amyloid-positive by serial imaging of amyloid plaques by PET were assessed[21]. 42% of the individuals who met the criteria of incident amyloid positivity had SNAP at baseline and later transitioned to A^+N^+. As SNAP represents one or more of the non-AD processes that are common in the elderly, the researchers concluded that frequently finding elderly individuals with SNAP at baseline who later develop evidence of Aβ pathology entirely logical[21]. As Aβ accumulates slowly (over decades)[22–24], individuals with SNAP who became Aβ-positive over a short interval undoubtedly had Aβ values close to the threshold of detection at baseline.

Cognitively impaired individuals

SNAP is a biomarker-based concept that is independent of any particular level of cognitive impairment. As in the studies of clinically normal individuals, studies of individuals with mild cognitive impairment (MCI) used several different classification methods (Supplementary information S1 (table)). The proportions of individuals with SNAP within the MCI group reported in these studies were more variable than those reported within clinically normal individuals. This difference is likely to be due to several factors, including smaller sample sizes, differences in recruitment methods — and hence the characteristics of participants in the different study populations — and the inherent heterogeneity of MCI. SNAP was found in 17% of participants in the Alzheimer disease Disease Neuroimaging Initiative[25], 17% of those in the study by Caroli *et al.*[26], 20% of those in the study by Prestia *et al.*[27], 29% of those in the study by Vos *et al.*[28], 29% of those in the Mayo Clinic Study of Ageing[25], and 35% of those in the study by Duara *et al.*[29] In the Alzheimer disease Disease Neuroimaging Initiative[30], 7% of participants who were clinically diagnosed as having AD dementia met the criteria of SNAP.

The rates of clinical progression to dementia among individuals with MCI and SNAP have been assessed, with average follow-up times ranging from 1 to 2.5 years in different cohorts (see Supplementary information S1 (table)). In the study by Prestia *et al.*[27], 47% of individuals with MCI and SNAP progressed to dementia compared with 100% of the A^+N^+, 27% of the A^+N^- and 5% of the A^-N^- groups. In the Mayo Clinic Study of Ageing[25], 21% of individuals with MCI and SNAP progressed to dementia compared with 16% of the A^+N^+, 0% of the A^+N^- and 8% of the A^-N^- groups. In the Alzheimer disease Disease Neuroimaging Initiative[25], 40% of individuals with MCI and SNAP progressed to dementia, compared with 42% of the A^+N^+, 0% of the A^+N^- and 11% of the A^-N^- groups.

Caroli *et al.*[26] found that progressive cognitive deterioration in individuals with MCI and SNAP was more frequent than in A^-N^- and A^+N^- individuals with MCI, but less frequent than in A^+N^+ individuals with MCI. Of the 19 patients with SNAP and MCI at baseline who progressed to dementia, seven developed clinically defined non-AD dementias and the remaining 12 developed clinically defined AD dementia. Neurodegeneration was defined as either hippocampal atrophy or hypometabolism (assessed with ^{18}F-FDG–PET) in AD-like neocortical areas. Caroli *et al.*[26] suggested that these two different sources of biomarker information about neurodegeneration might indicate that two different subgroups exist within SNAP.

Vos *et al.*[28] assessed features of individuals classified as mildly impaired (for simplicity, referred to as MCI here) according to International Working Group[31,32] and NIA–AA criteria[3]. The proportion of *APOE*ε4* carriers among individuals with MCI and SNAP was roughly half that among A^+N^+ individuals with MCI (32% and 62%, respectively). The rate of progression to clinically defined AD dementia at last follow-up was 21% among individuals with SNAP and MCI, 4% among A^-N^- individuals with MCI and 59% among A^+N^+ individuals with MCI. The rate of progression to clinically defined non-AD dementia at last follow-up was 10% among individuals with SNAP and among A^-N^- individuals with MCI, whereas it was 3% among A^+N^+ individuals with MCI.

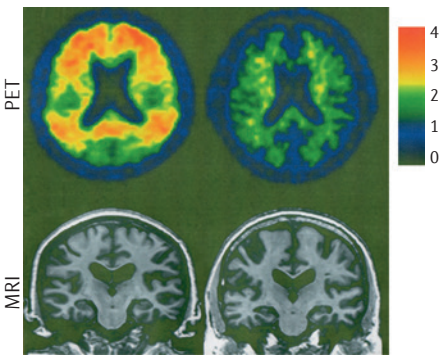

Figure 2 | **Imaging differences between preclinical AD stage 1 and SNAP.** Left-hand column, clinically normal 75 year-old-woman with abnormal amyloid-β levels as seen by PET and normal brain structure as seen by MRI, who was diagnosed as having preclinical AD stage 1. Right-hand column, clinically normal 77 year-old-woman with normal amyloid-β levels as seen by PET and visually obvious atrophic hippocampi as seen by MRI, who was diagnosed as having SNAP. AD, Alzheimer disease; SNAP, suspected non-AD pathophysiology. Permission obtained from the Radiological Society of North America © Jack, C.R. Jr *et al. Radiology* **263**, 344–361 (2012).

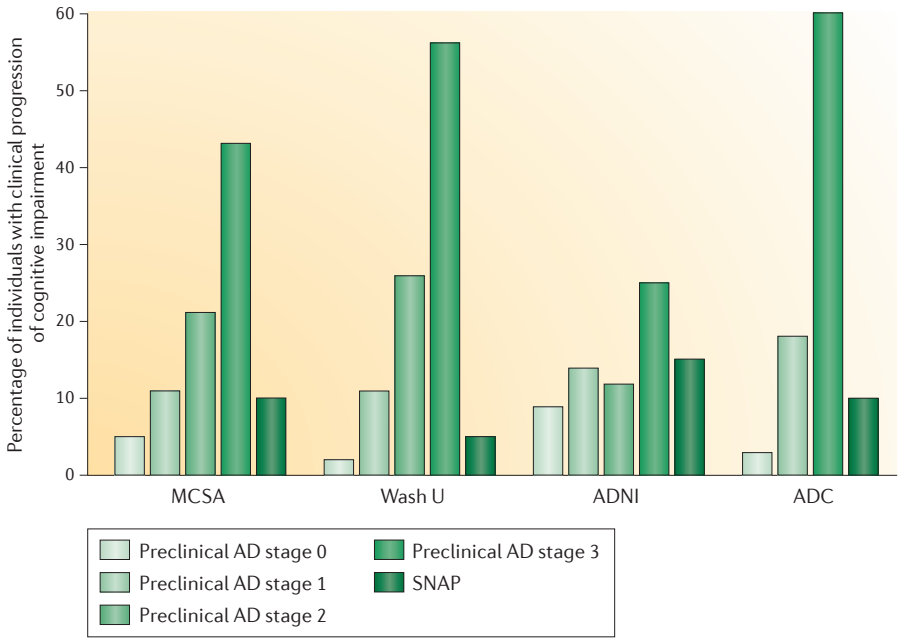

Figure 3 | **Comparisons of clinical outcomes of individuals with preclinical AD and SNAP across different cohorts.** The percentages of individuals within each group who progressed clinically from being clinically normal to having mild cognitive impairment or dementia are shown for four different studies. AD, Alzheimer disease; ADC, Amsterdam Dementia cohort; ADNI, Alzheimer disease Disease Neuroimaging Initiative; MCSA, Mayo Clinic Study on Ageing; SNAP, suspected non-AD pathophysiology; Wash U, Washington University.

Cognitive trajectories in SNAP

Overall, these studies indicate that the risk of cognitive decline and clinical progression to dementia is greater for individuals with MCI and SNAP than the risk of cognitive decline and progression to either MCI or dementia for clinically normal individuals with SNAP (see Supplementary information S1 (table)). The risk profile across biomarker-based groups might also differ between clinically normal and MCI individuals. In individuals with MCI, the risk of cognitive decline is lowest in A^-N^- and A^+N^- individuals, intermediate in those with SNAP, and is highest in A^+N^+ individuals. In clinically normal individuals, the risk of decline is lowest in A^-N^- individuals, intermediate in those with SNAP and in A^+N^- individuals, and is highest in A^+N^+ individuals. One exception is the largest study of individuals with MCI[28], in which the risk of cognitive decline was not different between the SNAP and the A^+N^- MCI groups. The discrepancies in the risk profiles of individuals with MCI reported in different studies might be attributable to the rarity of A^+N^- and A^-N^- individuals with MCI and, therefore, to a lack of power to accurately determine the outcomes of these individuals. Nonetheless, the differences in outcomes observed when the results of the studies are aggregated suggest that a slightly different mix of underlying aetiologies might be present in patients with MCI and SNAP than those present in clinically normal individuals with SNAP.

The number of individuals with MCI and SNAP who progress to what is clinically labelled 'probable or possible AD dementia' might seem unusually high as SNAP is a non-AD state. However, two potentially confounding factors must be considered. The first is the frequency of clinical misdiagnosis of AD dementia. Up to a third of *APOE*ε4* non-carrier individuals clinically diagnosed as having AD dementia by experts are amyloidosis-negative according to PET scans[33], and thus their dementia is likely to result from pathologies other than AD. Given that *APOE*ε4* carriers are underrepresented in the SNAP group relative to the A^+N^- and A^+N^+ MCI groups, some patients who progressed from having SNAP and MCI to 'probable or possible AD dementia' actually had non-AD aetiologies. The second factor is that the levels of Aβ in individuals who progress from having MCI and SNAP to clinical AD dementia are more likely to have been very close to the threshold of abnormality at baseline and, therefore, these individuals were more similar to A^+N^+ individuals than to the rest of the SNAP group[28].

Thresholds and cut-off points

All individuals that took part in the studies discussed above were classified categorically regarding to their positive or negative status for Aβ and neurodegeneration. However, we should note that no uniform agreement exists in the field about how to perform these measurements, nor is there agreement on numeric cut-off points denoting normal and abnormal values[34]. In fact, the precise methods for classifying individuals according to these biomarker characteristics vary considerably among studies from different centres (see Supplementary information S1 (table)). Different assays or platforms used for CSF analyses give different absolute values[35,36]. Similarly, the output of quantitative image analyses is heavily dependent on the implementation of image processing pipelines[6]. Attempts to standardize imaging and CSF measurements are underway[35,37–39], but standardized methods and agreement on cut-off points have not yet been achieved.

We discuss SNAP and preclinical AD stages in terms of discrete binary classifications of amyloidosis and neurodegeneration, but for many individuals the biomarker values lie near cut-off points. Some individuals classified as having SNAP have a level of neurodegeneration just inside the abnormal range (or have conflicting information from different neurodegeneration biomarkers) and thus do not differ greatly from A^-N^- individuals. Similarly, some individuals with SNAP whose degree of amyloidosis is very close to the threshold of abnormality behave clinically more like A^+N^+ individuals than like SNAP individuals with obviously absent amyloidosis[40]. In the studies by Vos *et al.*[12,28], some clinically normal individuals and some individuals with MCI who progressed to clinical AD dementia had indeed CSF Aβ levels very close to the CSF Aβ cut-off point that define the presence of amyloidosis.

Pathological basis of SNAP

In addition to AD[41,42], non-AD pathologies are common with advancing age in impaired and clinically normal elderly people[42–46]. These pathologies include cerebrovascular disease, α-synucleinopathy, argyrophilic grain disease, TDP-43 proteinopathy and hippocampal sclerosis. Ageing alone (that is, the passage of time) is implicated in brain atrophy and cognitive decline, which probably develop as a result of synapse loss[47,48].

Medial temporal tau pathology without amyloidosis might be a major constituent of SNAP[49,50]. The term primary age-related

tauopathy (PART) has been proposed by Crary *et al.*[51] to describe this phenomenon, although not without controversy[7,52,53]. Autopsy studies indicate that medial temporal tau pathology (often without amyloidosis, particularly at young ages) is present in 25% of the population by age 25 years, 50% by age 50 years, and in most individuals aged >75 years[49,50,54,55]. Therefore, PART has been argued to be an ageing process separate from AD, the latter requiring amyloidosis[51,56–58]. As pointed out by Crary *et al.*[51], SNAP and PART share some highly salient features: both are common in clinically normal elderly people; *APOE*ε4* is underrepresented in both; both increase in prevalence with ageing; and medial temporal lobe pathology features prominently in both. The first autopsy studies in individuals classified antemortem as having SNAP were performed at Washington University[12]. Three of the four individuals with SNAP who were studied had low probability of having AD and the fourth did not have AD[58,59]. Medial temporal tau pathology without amyloidosis (that is, meeting the criteria of PART[51]) was detected postmortem in two of the four individuals. More recent autopsy data from the Mayo Clinic also indicates that individuals in whom imaging findings meet the criteria of a SNAP diagnosis in life uniformly have non-AD diagnoses at autopsy[60].

In summary, a variety of non-AD processes are likely to contribute to neurodegeneration in individuals who meet the criteria of SNAP. Developmental factors might also play a part. This lack of specificity could be interpreted as undermining the utility of the SNAP concept; however, many examples of useful constructs with different aetiologies exist in medicine and biology. For example, neurodegeneration is a pathologic condition and MCI and dementia are clinical conditions with many aetiologies.

Defining a non-AD aetiology

The biomarkers of neurodegeneration that are characteristic of AD — medial temporal lobe atrophy assessed by MRI, hypometabolism in temporal–parietal regions assessed by ^{18}F-FDG–PET, and abnormally elevated levels of total tau in CSF — also define SNAP. Total tau is a nonspecific marker of neuronal injury and neurodegeneration, which is elevated in AD, whereas phosphorylated tau is specific for neurofibrillary tangle pathology of AD[61]. We recognize that this similarity might seem incongruous, but not if one views these processes as independent of Aβ.

The patterns of atrophy and hypometabolism in non-AD conditions often overlap spatially with the patterns seen in AD. This overlap is probably most obvious in the medial temporal lobe. Hippocampal atrophy is a prominent and early feature in typical AD[62], but it is also a prominent feature of hippocampal sclerosis[63–65], TDP-43 pathology[66], argyrophilic grain disease, anoxic–ischaemic injury[67] and in ageing[48] (FIG. 4). Temporoparietal hypometabolism is found in non-AD conditions, such as corticobasal degeneration, primary progressive aphasia[68], and cerebrovascular disease[11]. The AD-like hypometabolism in posterior association areas that is observed in PART can be explained by the fact that these areas are highly connected, both structurally and functionally, to the medial temporal lobe[69–72].

The aetiological nonspecificity of atrophy and hypometabolism observed by MRI and ^{18}F-FDG–PET in areas of the brain associated with AD has given rise to the concept that the brain networks in these areas can be vulnerable to a variety of insults associated with AD, non-AD disorders and ageing[47,48,56,73,74]. The same logic applies to elevated total tau levels in CSF, which are seen in conditions other than AD, including ischaemic cerebrovascular disease, traumatic brain injury, and Creutzfeldt–Jacob disease[75].

'A' for 'amyloid' or for 'AD'?

SNAP was originally coined as an abbreviation for 'suspected non-AD pathophysiology'[1], but the term has also been referred to as an abbreviation for 'suspected non-amyloid pathophysiology' (REF. 26) (even if 'non-amyloid' is known, not suspected, in someone with a negative result in the Aβ biomarker analysis). These semantic differences define two important points of view. One is that biomarker evidence of Aβ pathology alone is not sufficient to define AD pathophysiology. The other perspective is that biomarker evidence of Aβ pathology alone is sufficient to define AD pathophysiology, and thus Aβ negative, neurodegeneration positive individuals (those with SNAP) should be classified as having a 'non-AD' condition. As the co-authors of this article do not unanimously agree on these points of view, we present the arguments on both sides of the issue.

The argument for defining SNAP as 'suspected non-amyloid pathophysiology' has several lines of support. First, the term 'non-amyloid' accurately reports an observation about an individual without the assumptions that A^+N^-, SNAP, both of these conditions, or neither of them represent AD. Second, if preclinical A^+N^- is AD, whereas preclinical SNAP is not, then the likelihood of progression to more advanced stages of clinical and biomarker-defined AD should be greater for preclinical A^+N^- than for SNAP; however, this result was not consistently found in the different studies that examined clinical outcomes (see Supplementary information S1 (table)). Third, the neuropathological definition of AD requires both Aβ and tau pathology[58,59]. Therefore, both Aβ pathology and neurodegeneration should be required as biomarker evidence of AD pathophysiology. A^+N^- does not meet these criteria any more than SNAP. Finally, if the amyloid cascade hypothesis[76] is not correct for late-onset AD (that is, if Aβ deposition is not an upstream driver of the AD pathophysiological cascade that leads to neurodegeneration), then labelling A^+N^- as preclinical AD is not more reasonable than doing so with SNAP[77–79].

The argument for defining SNAP as "suspected non-AD pathophysiology" likewise has several lines of support. First, non-AD processes are prevalent in the elderly population, as seen by autopsy studies[42–44,51,80], and these processes should be evidenced by neurodegenerative biomarker abnormalities. 'Suspected non-AD pathophysiology' seems the only logical label when SNAP is due to one or more of these non-AD processes. Second, medial temporal tau pathology without excessive Aβ accumulation is explicitly defined as an ageing phenomenon separate from AD in the most recent pathological criteria for AD assessment[58,59] and in the position paper in which the diagnostic criteria for PART are defined[51]. As PART is one of the contributing aetiologies to SNAP, labelling SNAP 'non-AD' is appropriate. Finally, if the amyloid cascade hypothesis[76] is correct (that is, if Aβ deposition drives AD-related neurodegeneration in the AD pathological cascade in early-onset and late-onset AD[81–83]) then imaging and/or biomarker evidence of Aβ accumulation without neurodegeneration should be labelled 'AD', whereas SNAP should be labelled "non-AD". Genetics provides strong evidence that Aβ accumulation is an upstream driver of the AD pathological cascade. Mutations that increase Aβ production or aggregation inevitably lead to clinical and pathological AD[84] in young individuals, and a mutation that decreases $A\beta_{42}$ production protects against development of clinical AD and cognitive decline in the elderly[85]. By contrast, genetically determined tauopathies do not lead to clinical or pathological AD[86].

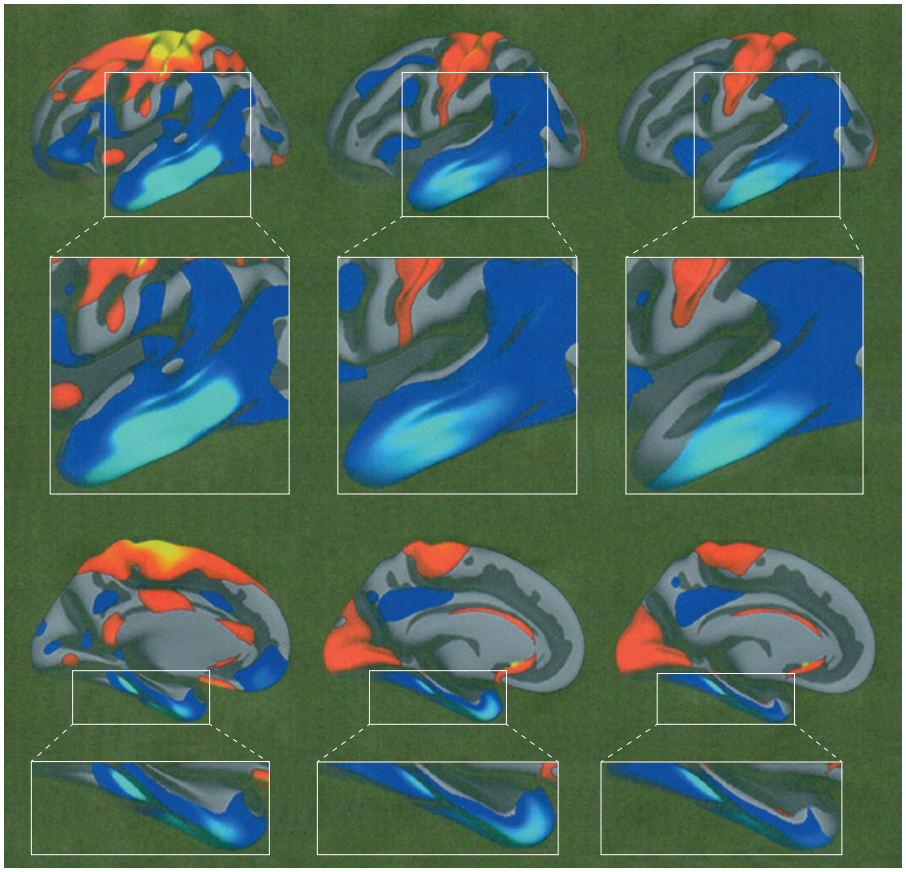

Figure 4 | **Topographic atrophy patterns.** Patterns of atrophy rates in individuals from the Alzheimer's Neuroimaging Initiative, diagnosed as clinically normal, or with MCI or AD dementia. Left column, maps of atrophy rates from serial MRI in clinically normal elderly individuals who were amyloid-β-negative (as assessed by measurement of amyloid-β_{42} levels in the CSF) and *APOE*ε4*-negative. Middle and right columns, similar maps from individuals with MCI and AD dementia, respectively. The top-row images are left lateral surface views. The bottom-row images are left medial surface views. Atrophy rates are scaled within each group and changes are displayed relative to within-group means. A common topographic pattern of standardized rates of change is present in the lateral and medial temporal lobe across groups. The rates of loss of brain volume in AD-signature regions are not necessarily associated with amyloid-β, nor with *APOE*ε4* carrier status, and therefore cannot be ascribed solely to AD but rather seem to be a feature of normal ageing. AD, Alzheimer disease; MCI, mild cognitive impairment. Permission obtained from the Society for Neuroscience © Fjell, A. M. *et al. J. Neurosci.* **33**, 8237–8242 (2013).

Whether the 'A' in SNAP stands for 'amyloid' or 'AD' is a semantic difference important to conceptual precision. How SNAP is defined also serves to define AD (and vice-versa), particularly in clinically asymptomatic individuals in whom the full pathophysiological cascade of AD has yet to play out and in whom no clinical indicators of underlying pathophysiology are present. Some researchers who believe SNAP should be included as part of the AD spectrum point to the high prevalence of clinically normal individuals with SNAP (23%) as evidence that the amyloid-centric models of AD and the concept of preclinical AD (as now defined[2,87–89]) are flawed. Viewed from the perspective that SNAP is not AD, however, the SNAP concept is completely consistent with Aβ-centric models of AD biomarkers and the current definition of preclinical AD[2]. From this second perspective, SNAP represents biomarker evidence of the non-AD pathologies that autopsy data indicate are frequent in the elderly[42–44]. Biomarker evidence of non-AD pathologies (that is, SNAP) may or may not precede Aβ accumulation in specific individuals[21,90], but in either instance Aβ seems to act as a biological driver of tauopathy[23,57,91–94]. Use of PET for detecting tau, a novel technique that, for the first time, enables *in vivo* determination of the anatomic distribution of tau pathology[95–97], will shed light on this debate in the future.

Conclusions

SNAP is a biomarker-based concept that fills a gap in the characterization of cognitively normal and impaired individuals (except those individuals with cognitive impairment in whom the underlying pathology can be confidently inferred from the clinical syndrome, such as those with progressive supranuclear palsy, Lewy Body disease, semantic variant primary progressive aphasia, etc.). The findings that SNAP is common in the population and that clinically normal individuals and those with MCI who have SNAP have a greater risk of clinical or cognitive decline than biomarker-negative (A^-N^-) individuals have implications for counselling patients with subjective cognitive complaints or MCI in clinical practice.

Clifford R. Jack Jr is at the Department of Radiology, Mayo Clinic and Foundation.

David S. Knopman and Ronald C. Petersen are at the Department of Neurology, Mayo Clinic and Foundation, 200 First Street SW, Rochester, Minnesota 55905, USA.

Gaël Chételat is at INSERM, Université de Caen, EPHE, CHU de Caen, U1077, Caen, France.

Dennis Dickson is at the Department of Pathology, Mayo Clinic and Foundation, 4500 San Pablo Road South, Jacksonville, Florida 32224, USA.

Anne M. Fagan is at the Department of Neurology, Knight Alzheimer's Disease Research Center, Washington University School of Medicine, 4488 Forest Park Avenue, Suite 101, St Louis, Missouri 63108, USA.

Giovanni B. Frisoni is at the University Hospitals and University of Geneva, Rue Gabrielle-Perret-Gentil 4, 1205 Genève, Switzerland.

William Jagust is at the Helen Wills Neuroscience Institute, University of California Berkeley, 175 Li Ka Shing Center, Berkeley, California 94720, USA.

Elizabeth C. Mormino and Reisa A. Sperling are at the Department of Neurology, Massachusetts General Hospital, Harvard Medical School, 221 Longwood Avenue, Boston, Massachusetts 02115, USA.

Wiesje M. van der Flier is at the Alzheimer Center, Department of Neurology, VU University Medical Center, Neuroscience Campus Amsterdam, PO Box 7057, 1007 MB Amsterdam, Netherlands.

Victor L. Villemagne is at the Department of Molecular Imaging & Therapy, Centre for PET, Austin Health, 145 Studley Road, PO Box 5555 Melbourne, Victoria, Australia 3084.

Pieter J. Visser and Stephanie J. B. Vos are at the Department of Psychiatry and Neuropsychology, Institute of Mental Health and Neuroscience, Maastricht University, PO Box 616 MD Maastricht, Netherlands.

Correspondence to C.R.J.Jr
jack.clifford@mayo.edu

doi:10.1038/nrneurol.2015.251
Published online 18 Jan 2016

1. Jack, C. R. *et al.* An operational approach to NIA-AA crtiteria for preclinical Alzheimer's disease. *Ann. Neurol.* **71**, 765–775 (2012).
2. Sperling, R. A. *et al.* Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement.* **7**, 280–292 (2011).
3. Albert, M. S. *et al.* The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging and Alzheimer's Association Workgroup. *Alzheimers Dement.* **7**, 270–279 (2011).
4. McKhann, G. M. *et al.* The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging and the Alzheimer's Association Workgroup. *Alzheimers Dement.* **7**, 263–269 (2011).
5. Jack, C. R. *et al.* Introduction to the recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement.* **7**, 257–262 (2011).
6. Senjem, M. L. *et al.* Comparison of different methodological implementations of voxel-based morphometry in neurodegenerative disease. *NeuroImage* **26**, 600–608 (2005).
7. Duyckaerts, C. *et al.* PART is part of Alzheimer disease. *Acta Neuropathol.* **129**, 749–756 (2012).
8. Knopman, D. S. *et al.* Short-term clinical outcomes for stages of NIA-AA preclinical Alzheimer disease. *Neurology* **78**, 1576–1582 (2012).
9. Mormino, E. C. *et al.* Synergistic effect of β-amyloid and neurodegeneration on cognitive decline in clinically normal individuals. *JAMA Neurol.* **71**, 1379–1385 (2014).
10. Ivanoiu, A. *et al.* Classification of non-demented patients attending a memory clinic using the new diagnostic criteria for Alzheimer's disease with disease-related biomarkers. *J. Alzheimers Dis.* **43**, 835–847 (2015).
11. Wirth, M. *et al.* Associations between Alzheimer disease biomarkers, neurodegeneration, and cognition in cognitively normal older people. *JAMA Neurol.* **70**, 1512–1519 (2013).
12. Vos, S. J. *et al.* Preclinical Alzheimer's disease and its outcome: a longitudinal cohort study. *Lancet Neurol.* **12**, 957–965 (2013).
13. Roe, C. M. *et al.* Amyloid imaging and CSF biomarkers in predicting cognitive impairment up to 7.5 years later. *Neurology* **80**, 1784–1791 (2013).
14. van Harten, A. C. *et al.* Preclinical AD predicts decline in memory and executive functions in subjective complaints. *Neurology* **81**, 1409–1416 (2013).
15. Toledo, J. B. *et al.* Neuronal injury biomarkers and prognosis in ADNI subjects with normal cognition. *Acta Neuropathol. Commun.* **2**, 26 (2014).
16. Morris, J. C. *et al. APOE* predicts amyloid-beta but not tau Alzheimer pathology in cognitively normal aging. *Ann. Neurol.* **67**, 122–131 (2010).
17. Vemuri, P. *et al.* Effect of apolipoprotein E on biomarkers of amyloid load and neuronal pathology in Alzheimer disease. *Ann. Neurol.* **67**, 308–316 (2010).
18. Lim, S. M. *et al.* The ^{18}F-FDG PET cingulate island sign and comparison to ^{123}I-β-CIT SPECT for diagnosis of dementia with Lewy bodies. *J. Nucl. Med.* **50**, 1638–1645 (2009).
19. Knopman, D. S. *et al.* Brain injury biomarkers are not dependent on β-amyloid in normal elderly. *Ann. Neurol.* **73**, 472–480 (2013).
20. Jack, C. R. *et al.* Age-specific population frequencies of cerebral β-amyloidosis and neurodegeneration among people with normal cognitive function aged 50–89 years: a cross-sectional study. *Lancet Neurol.* **13**, 997–1005 (2014).
21. Jack, C. R. *et al.* Amyloid-first and neurodegeneration-first profiles characterize incident amyloid PET positivity. *Neurology* **81**, 1732–1740 (2013).
22. Villain, N. *et al.* Regional dynamics of amyloid-β deposition in healthy elderly, mild cognitive impairment and Alzheimer's disease: a voxelwise PiB-PET longitudinal study. *Brain* **135**, 2126–2139 (2012).
23. Villemagne, V. L. *et al.* Amyloid β deposition, neurodegeneration, and cognitive decline in sporadic Alzheimer's disease: a prospective cohort study. *Lancet Neurol.* **12**, 357–367 (2013).
24. Jack, C. R. *et al.* Brain β-amyloid load approaches a plateau. *Neurology* **80**, 890–896 (2013).
25. Petersen, R. C. *et al.* Criteria for mild cognitive impairment due to alzheimer's disease in the community. *Ann. Neurol.* **74**, 199–208 (2013).
26. Caroli, A. *et al.* Mild cognitive impairment with suspected nonamyloid pathology (SNAP): prediction of progression. *Neurology* **84**, 508–515 (2015).
27. Prestia, A. *et al.* Prediction of dementia in MCI patients based on core diagnostic markers for Alzheimer disease. *Neurology* **80**, 1048–1056 (2013).
28. Vos, S. J. *et al.* Prevalence and prognosis of Alzheimer's disease at the mild cognitive impairment stage. *Brain* **138**, 1327–1338 (2015).
29. Duara, R. *et al.* Amyloid positron emission tomography with ^{18}F-flutemetamol and structural magnetic resonance imaging in the classification of mild cognitive impairment and Alzheimer's disease. *Alzheimers Dement.* **9**, 295–301 (2013).
30. Lowe, V. J. *et al.* Application of the National Institute on Aging-Alzheimer's Association AD criteria to ADNI. *Neurology* **80**, 2130–2137 (2013).
31. Dubois, B. *et al.* Revising the definition of Alzheimer's disease: a new lexicon. *Lancet Neurol.* **9**, 1118–1127 (2010).
32. Dubois, B. *et al.* Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. *Lancet Neurol.* **13**, 614–629 (2014).
33. Salloway, S. *et al.* Two phase 3 trials of bapineuzumab in mild-to-moderate Alzheimer's disease. *N. Engl. J. Med.* **370**, 322–333 (2014).
34. Villeneuve, S. *et al.* Existing Pittsburgh Compound-B positron emission tomography thresholds are too high: statistical and pathological evaluation. *Brain* **138**, 2020–2033 (2015).
35. Mattsson, N. *et al.* Reference measurement procedures for Alzheimer's disease cerebrospinal fluid biomarkers: definitions and approaches with focus on amyloid β42. *Biomark Med.* **6**, 409–417 (2012).
36. Shaw, L. M. *et al.* Cerebrospinal fluid biomarker signature in Alzheimer's disease neuroimaging initiative subjects. *Ann. Neurol.* **65**, 403–413 (2009).
37. Frisoni, G. B. *et al.* The EADC-ADNI Harmonized Protocol for manual hippocampal segmentation on magnetic resonance: evidence of validity. *Alzheimers Dement.* **11**, 111–125 (2015).
38. Klunk, W. E. *et al.* The Centiloid Project: standardizing quantitative amyloid plaque estimation by PET. *Alzheimers Dement.* **11**, 1–15 (2015).
39. Mattsson, N. *et al.* The Alzheimer's Association external quality control program for cerebrospinal fluid biomarkers. *Alzheimers Dement.* **7**, 386–395 (2011).
40. Zwan, M. *et al.* Concordance between cerebrospinal fluid biomarkers and [^{11}C]PIB PET in a memory clinic cohort. *J. Alzheimers Dis.* **41**, 801–807 (2014).
41. Savva, G. M. *et al.* Age, neuropathology, and dementia. *N. Engl. J. Med.* **360**, 2302–2309 (2009).
42. Nelson, P. T. *et al.* Alzheimer's disease is not 'brain aging': neuropathological, genetic, and epidemiological human studies. *Acta Neuropathol.* **121**, 571–587 (2011).
43. Schneider, J. A., Aggarwal, N. T., Barnes, L., Boyle, P. & Bennett, D. A. The neuropathology of older persons with and without dementia from community versus clinic cohorts. *J. Alzheimers Dis.* **18**, 691–701 (2009).
44. Sonnen, J. A. *et al.* Ecology of the aging human brain. *Arch. Neurol.* **68**, 1049–1056 (2011).
45. Bennett, D. A. *et al.* Neuropathology of older persons without cognitive impairment from two community-based studies. *Neurology* **66**, 1837–1844 (2006).
46. Jicha, G. A. *et al.* Neuropathologic outcome of mild cognitive impairment following progression to clinical dementia. *Arch. Neurol.* **63**, 674–681 (2006).
47. Jagust, W. Vulnerable neural systems and the borderland of brain aging and neurodegeneration. *Neuron* **77**, 219–234 (2013).
48. Fjell, A. M., McEvoy, L., Holland, D., Dale, A. M. & Walhovd, K. B. Brain changes in older adults at very low risk for Alzheimer's disease. *J. Neurosci.* **33**, 8237–8242 (2013).
49. Braak, H., Thal, D. R., Ghebremedhin, E. & Del Tredici, K. Stages of the pathologic process in Alzheimer disease: age categories from 1 to 100 years. *J. Neuropathol. Exp. Neurol.* **70**, 960–969 (2011).
50. Delacourte, A. *et al.* The biochemical pathway of neurofibrillary degeneration in aging and Alzheimer's disease. *Neurology* **52**, 1158–1165 (1999).
51. Crary, J. F. *et al.* Primary age-related tauopathy (PART): a common pathology associated with human aging. *Acta Neuropathol.* **128**, 755–766 (2014).
52. Jack, C. R. Jr. PART and SNAP. *Acta Neuropathol.* **128**, 773–776 (2014).
53. Jellinger, K. A. *et al.* PART, a distinct tauopathy, different from classical sporadic Alzheimer disease. *Acta Neuropathol.* **129**, 757–762 (2015).
54. Duyckaerts, C. & Hauw, J. J. Prevalence, incidence and duration of Braak's stages in the general population: can we know? *Neurobiol. Aging* **18**, 362–369; discussion 89–92 (1997).
55. Duyckaerts, C., Uchihara, T., Seilhean, D., He, Y. & Hauw, J. J. Dissociation of Alzheimer type pathology in a disconnected piece of cortex. *Acta Neuropathol.* **93**, 501–507 (1997).
56. Delacourte, A. *et al.* Tau aggregation in the hippocampal formation: an ageing or a pathological process? *Exp. Gerontol.* **37**, 1291–1296 (2002).
57. Price, J. L. & Morris, J. C. Tangles and plaques in nondemented aging and 'preclinical' Alzheimer's disease. *Ann. Neurol.* **45**, 358–368 (1999).
58. Hyman, B. T. *et al.* National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease. *Alzheimers Dement.* **8**, 1–13 (2012).
59. Montine, T. J. *et al.* National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease: a practical approach. *Acta Neuropathol.* **123**, 1–11 (2012).
60. Murray, M. E. *et al.* The relationship of primary age-related tauopathy (PART) to SNAP: controversy or parallel? Presented at the Alzheimer's Association International Conference (2015).
61. Tapiola, T. *et al.* Cerebrospinal fluid β-amyloid 42 and tau proteins as biomarkers of Alzheimer-type pathologic changes in the brain. *Arch. Neurol.* **66**, 382–389 (2009).
62. Morra, J. H. *et al.* Automated 3D mapping of hippocampal atrophy and its clinical correlates in 400 subjects with Alzheimer's disease, mild cognitive impairment, and elderly controls. *Hum. Brain Mapp.* **30**, 2766–2788 (2009).
63. Jack, C. R. *et al.* Antemortem MRI findings correlate with hippocampal neuropathology in typical aging and dementia. *Neurology* **58**, 750–757 (2002).
64. Nelson, P. T. *et al.* Hippocampal sclerosis of aging, a prevalent and high-morbidity brain disease. *Acta Neuropathol.* **126**, 161–177 (2013).
65. Probst, A., Taylor, K. I. & Tolnay, M. Hippocampal sclerosis dementia: a reappraisal. *Acta Neuropathol.* **114**, 335–345 (2007).
66. Whitwell, J. L. *et al.* Does TDP-43 type confer a distinct pattern of atrophy in frontotemporal lobar degeneration? *Neurology* **75**, 2212–2220 (2010).
67. Di Paola, M. *et al.* Hippocampal atrophy is the critical brain change in patients with hypoxic amnesia. *Hippocampus* **18**, 719–728 (2008).
68. Josephs, K. A. *et al.* Fluorodeoxyglucose F18 positron emission tomography in progressive apraxia of speech and primary progressive aphasia variants. *Arch. Neurol.* **67**, 596–605 (2010).
69. Villain, N. *et al.* Relationships between hippocampal atrophy, white matter disruption, and gray matter hypometabolism in Alzheimer's disease. *J. Neurosci.* **28**, 6174–6181 (2008).
70. Villain, N. *et al.* Sequential relationships between grey matter and white matter atrophy and brain metabolic abnormalities in early Alzheimer's disease. *Brain* **133**, 3301–3314 (2010).
71. Buckner, R. L. *et al.* Cortical hubs revealed by intrinsic functional connectivity: mapping, assessment of stability, and relation to Alzheimer's disease. *J. Neurosci.* **29**, 1860–1873 (2009).
72. Sperling, R. A. *et al.* Amyloid deposition is associated with impaired default network function in older persons without dementia. *Neuron* **63**, 178–188 (2009).
73. Rosenzweig, E. S. & Barnes, C. A. Impact of aging on hippocampal function: plasticity, network dynamics, and cognition. *Prog. Neurobiol.* **69**, 143–179 (2003).
74. Yeoman, M., Scutt, G. & Faragher, R. Insights into CNS ageing from animal models of senescence. *Nat. Rev. Neurosci.* **13**, 435–445 (2012).
75. Tsitsopoulos, P. P. & Marklund, N. Amyloid-β peptides and tau protein as biomarkers in cerebrospinal and interstitial fluid following traumatic brain injury: a review of experimental and clinical studies. *Front. Neurol.* **4**, 79 (2013).
76. Hardy, J. The amyloid hypothesis for Alzheimer's disease: a critical reappraisal. *J. Neurochem.* **110**, 1129–1134 (2009).
77. Chetelat, G. Alzheimer disease: a β-independent processes-rethinking preclinical AD. *Nat. Rev. Neurol.* **9**, 123–124 (2013).

78. Herrup, K. Reimagining Alzheimer's disease — an age-based hypothesis. *J. Neurosci.* **30**, 16755–16762 (2010).
79. Resnick, S. M. Preclinical biomarkers in Alzheimer disease: a sum greater than the parts. *JAMA Neurol.* **71**, 1357–1358 (2014).
80. Kawas, C. H. *et al.* Multiple pathologies are common and related to dementia in the oldest-old: the 90 + Study. *Neurology* **85**, 535–542 (2015).
81. Jack, C. R. *et al.* Serial PIB and MRI in normal, mild cognitive impairment and Alzheimer's disease: implications for sequence of pathological events in Alzheimer's disease. *Brain* **132**, 1355–1365 (2009).
82. Mormino, E. C. *et al.* Episodic memory loss is related to hippocampal-mediated β-amyloid deposition in elderly subjects. *Brain* **132**, 1310–1323 (2009).
83. Perrin, R. J., Fagan, A. M. & Holtzman, D. M. Multimodal techniques for diagnosis and prognosis of Alzheimer's disease. *Nature* **461**, 916–922 (2009).
84. Goate, A. *et al.* Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer's disease. *Nature* **349**, 704–706 (1991).
85. Jonsson, T. *et al.* A mutation in *APP* protects against Alzheimer's disease and age-related cognitive decline. *Nature* **488**, 96–99 (2012).
86. Hutton, M. *et al.* Association of missense and 5′-splice-site mutations in tau with the inherited dementia FTDP-17. *Nature* **393**, 702–705 (1998).
87. Jack, C. R. *et al.* Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. *Lancet Neurol.* **12**, 207–216 (2013).
88. Jack, C. R. *et al.* Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. *Lancet Neurol.* **9**, 119–128 (2010).
89. Jack, C. R. *et al.* Evidence for ordering of Alzheimer disease biomarkers. *Arch. Neurol.* **68**, 1526–1535 (2011).
90. Jack, C. R. Jr, Holtzman, D. M. Biomarker modeling of Alzheimer's disease. *Neuron* **80**, 1347–1358 (2013).
91. Musiek, E. S. & Holtzman, D. M. Origins of Alzheimer's disease: reconciling cerebrospinal fluid biomarker and neuropathology data regarding the temporal sequence of amyloid-beta and tau involvement. *Curr. Opin. Neurol.* **25**, 715–720 (2012).
92. Delacourte, A. *et al.* Nonoverlapping but synergetic tau and APP pathologies in sporadic Alzheimer's disease. *Neurology* **59**, 398–407 (2002).
93. Jack, C. R. *et al.* Rates of β-amyloid accumulation are independent of hippocampal neurodegeneration. *Neurology* **82**, 1605–1612 (2014).
94. Knopman, D. S. *et al.* Selective worsening of brain injury biomarker abnormalities in cognitively normal elderly persons with β-amyloidosis. *JAMA Neurol.* **70**, 1030–1038 (2013).
95. Maruyama, M. *et al.* Imaging of tau pathology in a tauopathy mouse model and in Alzheimer patients compared to normal controls. *Neuron* **79**, 1094–1108 (2013).
96. Chien, D. T. *et al.* Early clinical PET imaging results with the novel PHF-tau radioligand [F-18]-T807. *J. Alzheimers Dis.* **34**, 457–468 (2013).
97. Villemagne, V. L. *et al.* *In vivo* evaluation of a novel tau imaging tracer for Alzheimer's disease. *Eur. J. Nucl. Med. Mol. Imaging* **41**, 816–826 (2014).

Acknowledgements

C.R.J.Jr receives research funding from the NIH and the Alexander Family Alzheimer disease Disease Research Professorship of the Mayo Foundation. D.D. receives research support from the NIH (P50-AG016574; P50-NS072187; P01-AG003949) and CurePSP: Foundation for PSP/CBD and Related Disorders. A.M.F. receives research funding from the the DIAN Pharma Consortium and the Alzheimer disease Association. R.A.S. received research support from the BrightFocus Foundation. W.M.v.d.F. receives research funding from the Netherlands Organization for Scientific Research (NWO), ZonMw, Cardiovasculair Onderzoek Nederland, and European Union (EU) 7th Framework Programme (FP7); all funds are paid to her institution. P.J.V. receives research funding from EU Joint Programme–Neurodegenerative Disease Research (JPND) and ZonMw, and from EU FP7 and Innovative Medicines Initiative joint resources, which are composed of financial contributions from EU FP7 (FP7/2007-2013) and in-kind contributions from the European Federation of Pharmaceutical Industries and Associations (EFPIA). S.J.B.V. receives research support from the Innovative Medicines Initiative Joint Undertaking under EMIF grant agreement n° 115372, resources that are composed of financial contributions from EU FP7 (FP7/2007-2013) and in-kind contributions from EFPIA.

Author contributions

C.R.J.Jr researched data for the article and wrote the article. All authors provided substantial contribution to discussion of content and reviewing/editing of manuscript before submission.

Competing interests statement

C.R.J.Jr has provided consulting services for Eli Lilly. D.S.K. is on a data safety monitoring board for Lundbeck Pharmaceuticals and is participating in clinical trials sponsored by Lilly Pharmaceuticals and TauRx Pharmaceuticals. A.M.F. has provided consulting services for Eli Lilly, Roche, AbbVie, IBL International and Novartis. W.J. is a consultant to Synarc–Bioclinica and to Banner Alzheimer disease Institute–Genentech. R.C.P. is on a data monitoring committee for Pfizer and Janssen Alzheimer Immunotherapy; is a consultant for Merck, Roche, and Genentech; receives royalties from publishing *Mild Cognitive Impairment* (Oxford University Press, 2003). R.A.S. has been a consultant for Janssen Eisai, Lundbeck, Isis, Boehringer Ingelheim, Roche and Genentech; and receives research support from the Fidelity Biosciences, and Janssen. W.M.v.d.F. has provided consulting services for Boehringer Ingelheim and received research funding from Boehringer Ingelheim; all funds are paid to her institution. V.L.V. has provided consulting services for Bayer Healthcare and Novartis, and has received speaker's honouraria from AstraZeneca, GE Healthcare and Piramal Imaging. P.J.V. has provided consulting services for Bristol–Myers Squibb, Élan–Wyeth, Ipsen, and Roche Diagnostics. G.C. and G.B.F. declare no competing interests.

SUPPLEMENTARY INFORMATION
See online article: S1 (table)
ALL LINKS ARE ACTIVE IN THE ONLINE PDF