Neuroimaging in subjective cognitive decline

Verfaillie, S.C.J.

2018

document version
Publisher's PDF, also known as Version of record

SUMMARY AND GENERAL DISCUSSION

The aim of the current thesis was to investigate the earliest neurobiological changes related to Alzheimer's Disease (AD) using amyloid positron emission tomography (PET), structural and functional magnetic resonance imaging (MRI) in patients with Subjective Cognitive Decline (SCD). More specifically, this thesis had three aims: 1) to provide an overview of the of the Subjective Cognitive ImpairmENt Cohort (SCIENCe), 2) to investigate the predictive value of structural MRI for cognitive decline and clinical progression in individuals with subjective cognitive decline (SCD), 3) to investigate the most optimal kinetic model for the quantification of the amyloid tracer [^{18}F]florbetapir, and to investigate associations between amyloid and resting-state fMRI and patterns of cognitive complaints, cognition and spontaneous speech.

Key findings include:

1) The SCIENCe study confirms that SCD is a heterogeneous group, including individuals with preclinical AD and subthreshold psychiatric features, as well as a relatively large group with complaints of undetermined origin.
2) Thinner temporal and parietal cortex in SCD is associated with increased risk of future clinical progression to dementia.
3) In SCD, thinner cortex, especially in the temporal cortex, is associated with a steeper decline of memory
4) Less efficient grey matter network organization in SCD is associated with a steeper decline of language and global cognition.
5) SCD is associated with a pattern of brain connectivity that mirrors early AD-related connectivity failure.
6) [^{18}F]florbetapir binding can be robustly quantified by a reversible two tissue compartmental model.
7) Increased amyloid load-β in SCD is associated with worries but not with severity or specific pattern of cognitive complaints.
8) SCD individuals with abnormal amyloid accumulation use fewer specific words in spontaneous speech.

Summary

Initial baseline findings of the SCIENCe cohort confirmed that SCD is a heterogeneous group, with preclinical AD (25%) and subthreshold psychiatric features (38%) as well as a relatively large group with complaints of undetermined origin (43%) (**chapter 2**). In a retrospective study (**chapter 3**) investigating cortical thickness in relation to clinical progression we found that 16% of individuals with SCD showed clinical progression to mild cognitive impairment (MCI (n=32)), Alzheimer's Disease (AD (n=9)) or non-AD dementia

(n=8) after a follow-up of 3 years. More specifically, lower hippocampal volumes, thinner cortex of the AD-signature regions and various temporal and parietal cortices were associated with an approximate fivefold increased risk of clinical progression to MCI and AD. Subsequently (**chapter 4**), we aimed to investigate associations between regional cortical thickness and rate of decline over time in four cognitive domains. We found that thinner temporal cortex was related to memory decline over time, which seemed particularly driven by SCD patients who developed MCI and AD on follow-up. In addition (**chapter 5**), we found that lower grey matter network values (normalized clustering and path length [gamma and lambda]), indicative of a more randomly organized network, were associated with steeper decline in global cognition and language. Furthermore, in a sample of cognitively normal individuals with a family history of AD (**chapter 6**) we found that SCD was related to altered default mode network (DMN) connectivity in brain regions vulnerable for AD such as the posterior DMN and medial temporal memory system. In addition, higher connectivity between the MTMS and rest of the brain was associated with better baseline immediate memory, attention and global cognition, whereas higher MTMS and pDMN-MTMS connectivity were associated with lower immediate memory over time. In the third part of this thesis we investigated amyloid accumulation. Firstly (**chapter 7**), we aimed to identify the optimal model for quantifying [^{18}F]florbetapir uptake and to assess test-retest (TRT) reliability of corresponding outcome measures in patients with AD and controls. We found that [^{18}F]florbetapir binding can be robustly quantified by a reversible two tissue compartmental model, independent of brain regions of interest or diagnostic label. In a follow-up study on individuals with SCD (**chapter 8**) we aimed to investigate whether amyloid pathology is associated with linguistic parameters derived from spontaneous speech. We found that abnormal amyloid accumulation was associated with fewer specific words, but not with lexical diversity or syntactic complexity or conventional neuropsychological language tests. In the last chapter (**chapter 9**) we aimed to investigate whether amyloid-β load is associated with a specific pattern of cognitive complaints. We found that increased amyloid-β load in all cortical regions was associated with presence of worries, but not with any particular pattern of cognitive complaints or with the severity of complaints, as measured using CCI (informant and self-reported, total scores or individual items) or SCF.

In the following paragraphs these findings will be integrated and placed in the context of the existing literature, followed by a discussion of methodological issues relevant for this thesis. Final paragraphs consist of recommendations for future research and concluding remarks.

Subjective cognitive decline

While SCD portends an increased risk of dementia, a minority (10-15%) of individuals with SCD showed clinical progression to mild cognitive impairment (MCI) or AD dementia

in approximately 2-4 years.[1–3] A vital question remains which individuals with SCD are at increased risk of clinical progression. One difficulty lies in the observation that self-perceived cognitive decline can be caused by a myriad of factors such as preclinical AD, normal aging, depressive symptoms and neuroticism.[4] It is currently difficult to clinically identify preclinical AD in cognitively healthy individuals experiencing memory complaints. In order to investigate the earliest signs related to AD we initiated the Subjective Cognitive ImpairmENt Cohort (SCIENCe) in 2014.

Our first aim was to characterize patients with SCD who visited our memory clinic and we showed that SCD is a heterogeneous label, with preclinical AD (i.e. abnormal amyloid accumulation, 25%) and subthreshold psychiatric features (38%). The largest group of individuals with SCD (43%) had neither evidence of amyloid, nor subthreshold psychiatric symptoms (**chapter 2**). Individuals with preclinical AD were on average older, and had more frequently a family history of dementia, and were more frequently APOE e4 carrier. APOE e4 genotype and age≥60 are part of *SCD plus* criteria, which have been proposed to facilitate and harmonize SCD research.[5] We now provide evidence that these factors are associated with increased risk of preclinical AD in individuals with SCD. In **chapter 2,** we also measured the degree of cognitive complaints, and almost all participants reported cognitive decline compared to five years ago, which seems substantially higher than in the general population,[6] but comparable to another memory clinic study,[7] and could be an explanation for these individuals to actively seek medical evaluation.

In cognitively normal individuals with SCD, biomarkers of AD can already be abnormal, such as increased amyloid deposition on PET or brain atrophy on MRI. However, the sequence of neurodegenerative changes eventually leading to AD may vary amongst individuals, and where to position SCD in these pathological sequences remains to be elucidated. For this reason, it is crucial which (neuroimaging) biomarkers are associated with clinical progression and earliest cognitive changes related to AD.

MRI biomarkers associated with subsequent cognitive decline

In the **second part** of this thesis we investigated associations between baseline MRI measures and incident clinical progression and longitudinal cognitive functioning. So far, memory clinic studies have demonstrated decreased gray matter volumes[8–10] and cortical thinning[11] in medial temporal regions in SCD compared to healthy controls. It has been suggested that regional thinning of the cortical mantle, coined as the AD-signature (consisting of frontal, temporal and parietal cortices), can be predictive for dementia in cognitively normal individuals until one decade before clinical progression.[12] Central in our studies was further investigation of whether such brain variations were related to clinical progression and cognitive functioning over time.

In **chapter 3**, we investigated if thinner cortex of the AD-signature region was predictive for clinical progression to MCI or dementia. After a follow-up of approximately 3 years, 49 (16%) individuals with SCD showed clinical progression to MCI (n=32), AD (n=9) or

non-AD dementia (n=8). These progression rates are comparable to earlies studies based on data from the Amsterdam Dementia Cohort.[2,3,13] We furthermore found that thinner cortex of the AD-signature and mean cortical thickness were both associated with a fivefold increased risk of clinical progression to MCI and dementia (figure 1A). Of these AD-signature subcomponents, temporal and parietal cortices were mostly associated clinical progression. More specifically, the medial temporal cortex showed the strongest predictive value for clinical progression to MCI and dementia, and hippocampal volume did not add any predictive value over this effect. Interestingly, we observed that thinner cortex of the AD-signature was associated with progression to AD dementia as well as non-AD dementia, but not to MCI. This suggests that the predictive value seemed to be non-specific for progression to AD or non-AD, and that AD-signature is likely sensitive for a more general neurodegenerative process.

In two follow-up papers (**chapter 4 & 5**), including individuals with SCD with repeated neuropsychological assessment, we sought to investigate whether thinner cortical lobar thickness is associated with rate of decline over time in the cognitive domains of memory, attention, language and executive functioning. Although individuals with SCD typically complain about their memory, early cognitive decline may also affect other cognitive domains. In **chapter 4**, we showed that language functioning decreased over time across the entire group of individuals with SCD, which illustrates that cognitive complaints could also originate from poorer language performance. In **chapter 7,** we also show that amyloid was related to lower use of specific words during spontaneous speech, whilst conventional neuropsychological tests were still unimpaired (figure 1D). Two recent cross-sectional studies on cognitively intact and mildly cognitively impaired elderly demonstrated that thinner temporal, precuneus and occipital cortex were associated with impaired episodic memory.[14,15] We found that widespread cortical thinning in SCD patients was associated with faster subsequent decline in memory over time, but not related to concurrent cognitive function.

Global brain atrophy is common in AD, but also occurs with normal aging[16,17] and both can evoke cognitive complaints.[18] Others demonstrated that over a period of 10 years, those who remained cognitively intact (i.e. normal aging), showed brain volume decreases in the frontal lobes and superior parietal regions, whereas those who progressed to MCI, showed accelerated volume loss in temporal regions.[19] Our findings also point towards involvement of temporal, frontal and occipital cortical regions (figure 1A) in relation to memory decline (**chapter 4**) and clinical progression (**chapter 3**). Thinner temporal cortex could be an early reflection of AD, especially since some of the individuals with SCD finally progressed to MCI or AD dementia during the course of the study.

Evidence is accumulating that brain changes leading to cognitive decline and dementia are not restricted to specific regions such as the medial temporal lobe, but rather include widespread changes in structure, function and organization of the brain.[20–24] Brain

morphology can be considered as a large-scale network consisting of multiple small regions of grey matter (i.e. nodes) that work in harmony.[25–29] In **chapter 5**, we aimed to investigate whether grey matter networks are related to decline in specific cognitive functioning over time. Our main finding (figure 1B) was that SCD subjects with more randomly organized grey matter networks show steeper decline in language and global cognition over time (**chapter 5**). We found associations with network parameters that are often reported in AD literature, i.e. normalized clustering and path length.[21–24,30] In addition, we found that lower path length values in precuneus and fronto-occipital brain regions were associated with global cognitive decline. Our findings suggest that at very early, preclinical stages, less efficient network organization may prelude subsequent cognitive impairment. There was a relatively large overlap with respect to neuropsychological and structural MRI data between **chapter 4 and 5**. In both chapters we found associations between cortical thickness and grey matter network organization in relation to memory and language decline.

After correction for multiple comparisons, however, associations between cortical thickness and language, and grey matter network organization and memory did not survive more stringent thresholds. While the precise implications and biological relevance of grey matter networks are not yet fully understood, these results provide evidence that network parameters provide additional information over atrophy measures.

In **chapter 6** we took a different approach. In this chapter we sought to investigate whether SCD was associated with functional brain connectivity. In this chapter we investigated SCD in pre-symptomatic individuals with a parental or multiple-sibling family history of AD dementia from the Pre-symptomatic Evaluation of Novel or Experimental Treatments for Alzheimer's Disease (PREVENT-AD) program (Montreal, Quebec, Canada). The primary goal of this program is to test whether serial determination of multi-modal biomarkers of AD may be measured and used in pre-symptomatic persons at high risk of subsequent AD dementia to trace the progression of the disease. Functional brain changes may precede structural abnormalities and clinical symptoms and could therefore serve as a potential early AD biomarker.[31,32] It has been suggested that brain hyperconnectivity in the posterior default mode network (pDMN) compensates for early pathophysiological processes, but later gives way to global brain hypoconnectivity, perhaps resulting from sustained excitotoxicity [33,34]. So far studies have shown altered DMN connectivity in SCD patients compared to AD patients and controls, [9,35,36] but not yet investigated this in cognitively normal individuals at risk for AD. We found that subjects with SCD had increased connectivity between the pDMN and medial temporal memory system (MTMS) if compared to subjects without SCD (figure 1C). Moreover, we found that hyperconnectivity, particularly between the pDMN and MTMS, was related to better concurrent cognitive performance (e.g. compensatory mechanism), but could have a detrimental effect over time. These findings were independent of cortical atrophy, and demonstrate the functional brain connectivity could be considered as an early disease marker in the future.

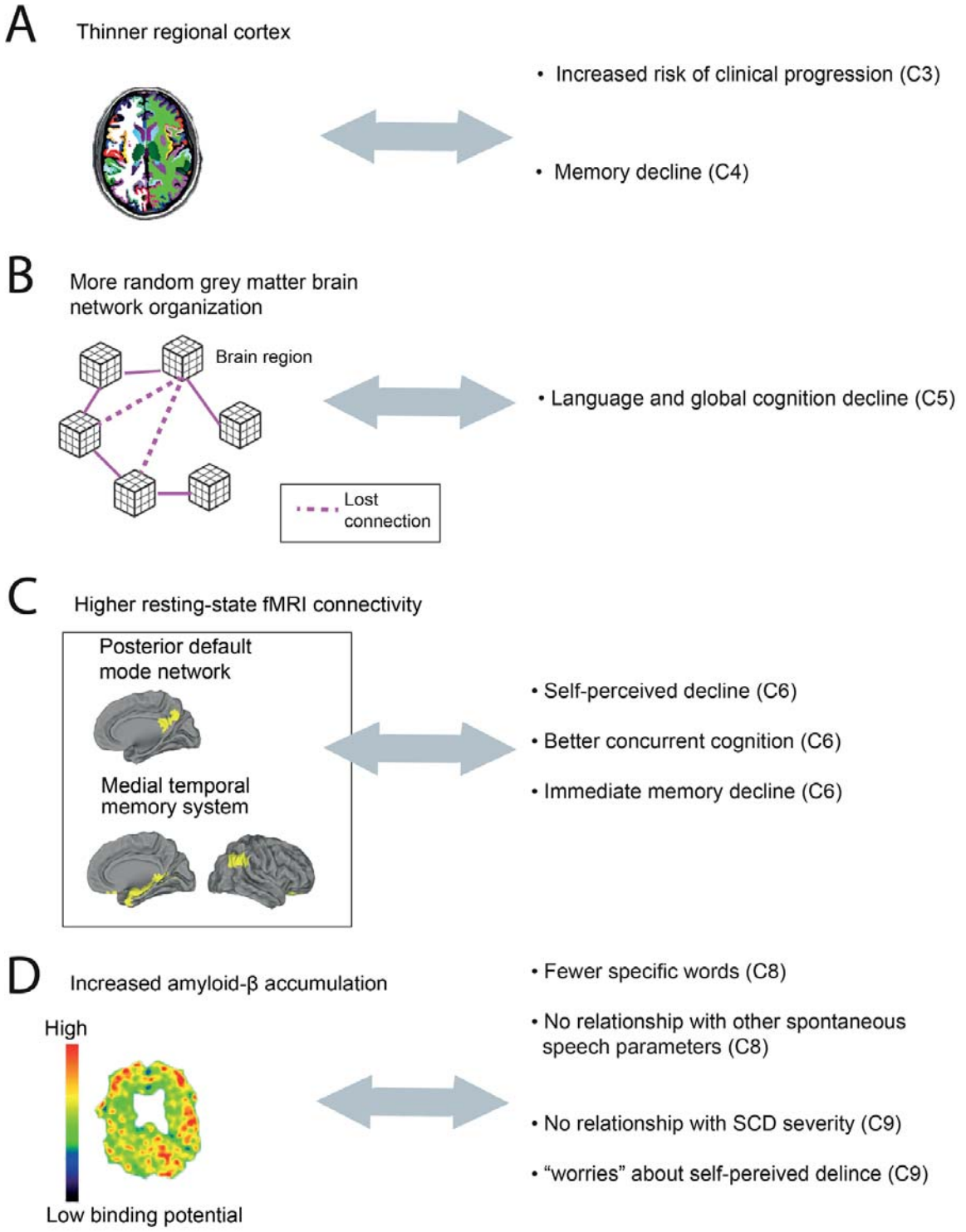

Figure 1. Summary of findings. Thinner cortex in memory clinic patients with subjective cognitive decline (SCD) is associated with increased risk of clinical progression, and steeper decline of memory (A). Less efficient grey matter brain network organization is associated with a steeper decline of language and global cognition (B). SCD in cognitively normal individuals with a family history of AD is associated with altered resting-state fMRI connectivity and cognitive functioning (C). Higher amyloid-β levels are associated with fewer specific words during spontaneous speech, and SCD-related worries (D). Abbreviations. C, Chapter

Amyloid imaging, spontaneous speech and cognitive complaints

In the **third part** of this thesis we investigated associations between amyloid and spontaneous speech and cognitive complaints. Firstly, to more accurately quantify amyloid deposition for subsequent research projects in this thesis, we have investigated various kinetic models in relation to [^{18}F]florbetapir binding (**chapter 7**). A validated tracer kinetic model is important, not only for identification of early (subtle) amyloid accumulation,[37] but also for studying its relation with early cognitive changes related to AD in individuals with SCD. In **chapter 7**, we found that *in vivo* kinetics of [^{18}F]florbetapir binding could best be described by a reversible two tissue compartmental model with fitted blood volume parameter. These results are in line the kinetic model of a widely used first generation amyloid imaging agent ([^{11}C]PiB),[37–39] but also converge with recent findings on [^{18}F] florbetapir quantification.[40] We extend previous findings by showing that this model produced robust and consistent test-retest results, with comparable findings for AD patients and controls. In addition, we found that simplified reference tissue models can be used to quantify amyloid-β load, with substantially less bias if compared to standardized uptake values.

In two follow-up papers (figure 1D) we investigated associations between amyloid and spontaneous speech (**chapter 8**) and cognitive complaints (**chapter 9**) respectively in individuals with SCD from the SCIENCe cohort. Individuals with subjective cognitive decline often experience word-finding problems, but these are difficult to verify with standard neuropsychological language tests and it is unknown whether spontaneous speech deficiencies are related to underlying AD pathology. In **chapter 8**, we aimed to investigate whether preclinical AD in individuals with SCD predisposes for less use of specific words, lexical diversity or syntactic complexity. AD dementia is characterized by gradual deterioration in various cognitive domains, including language.[41] Lexical diversity and the number of content words in spontaneous speech are impaired in AD.[42–46] Moreover, a recent case study showed that increased use of conversational fillers and decreased number of content words can be observed years before onset of dementia.[47] We found that higher amyloid-β load was associated with decreased use of content and concrete words, and to a lesser extent with lexical diversity or syntactic complexity (**chapter 8**). Of note, we did not find any differences between conventional neuropsychological language tests in individuals with and without preclinical AD, suggesting that subtle changes in spontaneous speech occur very early in the AD continuum.

Inconsistent findings have been reported in literature regarding which cognitive complaint questions which can be used to unmask cognitively normal individuals at risk for AD.[48] Therefore, it remains to be elucidated whether amyloid load is associated with a specific pattern of cognitive complaints. In **chapter 9** we used all available questionnaires (total scores and single items or questions) that are used in SCIENCe cohort to assess severity and content of cognitive complaints, and we found that increased amyloid-β load

was associated with worries about the self-perceived cognitive decline, but not with any specific item on cognitive complaints or questionnaire. One explanation is that inquiries about cognitive complaints in a memory clinic setting, could lead to receive false-positive answers, which do not necessarily relate to SCD due preclinical AD. Notwithstanding, these findings suggest that worries about self-perceived cognitive decline is a strong indicator of preclinical AD. These findings are also in line with results described in chapter 6, showing that a dichotomous SCD question can provide an unrefined but effective risk stratification for individuals at risk for AD.

METHODOLOGICAL CONSIDERATIONS

There are a number of methodological considerations. First, we studied patients who visited a memory clinic because they perceived deficits in their cognitive functioning. Cognitive complaints in elderly could be caused by a myriad of factors, including normal aging, preclinical AD, cerebrovascular disease, psychological factors, mood disorders and many more. Others have shown that memory clinic individuals with SCD exhibit additional subclinical depressive symptomatology if compared to SCD in the general population.[48] In this thesis we aimed to investigate the earliest changes related to AD, and the majority of the observed associations between neuroimaging, cognition, and cognitive complaints seemed independent of age, gender, education and (subclinical) depressive symptoms. It is nearly impossible to adjust for all factors that could potentially influence cognitive complaints. In addition, factors influencing cognitive complaints will greatly vary from one individual to another, and very large datasets with refined psychometric measures will be necessary to adjust for human variation. Of note, in most of our chapters we additionally adjusted for common causes of cognitive complaints such as; normal aging (**chapters 3-9**), depressive symptoms (**chapter 5 and 6**), cerebrovascular disease (**chapter 5**) and neuroticism (**chapter 6**). Furthermore, because the majority of research presented in this thesis was performed in a memory clinic setting, it is unclear to which extent our results can be extrapolated to the general population. Others observed increased anxiety and amyloid-β deposition in both community-dwelling as well as memory clinic SCD, whereas subclinical depression and (hippocampal) atrophy was mostly observed in memory clinic SCD.[48] Notwithstanding, our results are highly relevant for cognitively normal individuals with SCD in memory clinics. Moreover, referred SCD patients could be a clinically relevant group for future preventive trials as they self-perceive cognitive decline and actively seek help. Third, because we investigated cognitively normal individuals, we cannot rule out that (subtle) practice effects may have occurred in relation to our cognitive data. We expect that these effects were especially present in “lower-risk” cognitively intact individuals, but that practice effect may have been less apparent in individuals with future progression.

In addition, in our longitudinal studies individuals were tested once each year, where available with parallel versions of the test (**chapter 6**), which reduces the risk for practice effects. Others have demonstrated that preclinical AD could reduce the magnitude of gain from retesting, especially with regard to episodic memory.[49,50] Fourth, ideally one would use repeated neuroimaging measures to investigate brain changes related to AD, and many of our studies made use of a single neuroimaging measure to predict a certain clinical outcome. Therefore, we cannot fully disentangle the brain changes that might have occurred during the time of study. Nonetheless, single neuroimaging measures are commonly used for diagnostic decision making, recruitment for intervention studies, and generally reflect a realistic clinical setting. Fifth, we have used different measures of amyloid-β load in this thesis (radiotracers [^{18}F]florbetapir and [^{18}F]florbetaben, and Aβ1-42 cerebrospinal fluid (CSF) levels), which could have impacted our findings. Notwithstanding, both imaging agents are able to detect beta-sheet fibrillar deposits of amyloid β-protein in plaques,[51,52] and both CSF and PET provide comparable diagnostic accuracies in AD patients, but lower accuracies in cases with less amyloid-β deposition.[53,54] More importantly, for all our clinical PET studies (**chapter 8 and 9**), we used state-of-art quantification techniques to estimate specific binding of [^{18}F]florbetapir. Compared to standardized uptake values reference tissue approaches, parametric methods are less susceptible for perfusion differences, generally show less bias, and thus more accurately reflect amyloid-β load. Finally, in all our longitudinal studies follow-up duration was relatively short, hence it is likely that more individuals with SCD will progress at later times, especially since the earliest brain changes leading to AD probably occur as early as 10-20 years before clinical manifestation of the disease.[31]

IMPLICATIONS AND FUTURE DIRECTIONS

Research presented in this thesis has several implications, and these will be outlined in the next paragraphs.

Clinical implications

For clinicians it is important that SCD is not merely a benign "label". Based on the research of this thesis we emphasize that only a minority of individuals with SCD, however, show clinical progression in the short-term. Notwithstanding, progression rates seem higher in cognitively normal individuals who visit a memory clinics if compared to community-dwelling based cohorts.[55] Therefore, clinicians should pay extra attention to certain patterns of cognitive complaints and subtle cognitive deficits, which may be associated with increased likelihood of progression of disease. On the other side, individuals with "benign SCD" and (persistent) cognitive complaints could be referred to other professionals

for amelioration of symptoms if there is a medical indication by means of therapy (e.g. cognitive behavioral therapy, memory strategies/training, psycho-education) or life-style interventions (current Euro-SCD research project).

In general, clinicians are reluctant to disclose individual biomarker results to patients with SCD, but it can be questioned whether certain neuroimaging biomarker information should be disclosed. It is too early to incorporate findings from resting-state fMRI, grey matter networks, and cortical thickness into clinical practice. Rather, clinicians could use the medial temporal visual rating scale, which has been widely used for approximately two decades, and is still very effective.[56,57] The predictive value of amyloid status is different than other neuroimaging biomarkers. Abnormal amyloid accumulation is a major risk factor for AD, and should to some extent be incorporated in clinical care and scientific research. One of the first studies investigating amyloid imaging disclosure showed that disclosing this information to cognitively normal individuals did not evoke any psychological harm based on pre- and post-disclosure counseling.[58] Nonetheless, one should be careful with disclosing amyloid positivity, because long-term effects (>10 years) are not yet clear, especially in relatively older individuals. AD pathogenesis may take 20 years, and longitudinal prospective studies covering the entire spectrum from normal until dementia are still ongoing. With respect to short-term effects, this thesis has provided evidence that amyloid can affect cognitive functions and cognition-related worries in individuals with SCD. On the other side, the high negative predictive value of a normal amyloid scan could potentially re-assure individuals with SCD. However, at baseline, there could be borderline amyloid positive cases who may become abnormal over the years. It has also been recently suggested that amyloid thresholds might be too high.[59] For this reason, it remains important to accurately determine and quantify amyloid load. In addition, in the present thesis we have not investigated tau pathology in SCD, while this is an important component in AD pathophysiology as well in preclinical stages. Initial findings are showing that tau pathology is associated with amyloid pathology and memory performance.[60,61] Current research of the LUNAR study is therefore investigating tau pathology in conjunction with amyloid imaging in SCD, with repeated PET scans over time.

Subjective cognitive decline research

The last few years important papers have been published in the field of SCD. Two clinico-methodological landmark studies introduced 1) SCD as a conceptual framework to study preclinical AD 2) criteria to implement SCD in research studies.[5,62] These two studies harmonize the various ways to investigate SCD, and support a common nomenclature to enhance the understanding of several SCD characteristics. There is still ongoing debate about which cognitive complaint items could be most effective to unmask preclinical AD in asymptomatic individuals. In this thesis we have shown cognitive complaints questions,

of various subjective cognitive decline questionnaires, are not associated with amyloid-β load. Partially in line with literature, we did find evidence for worries about to self-perceived decline were associated with amyloid-β.[1]

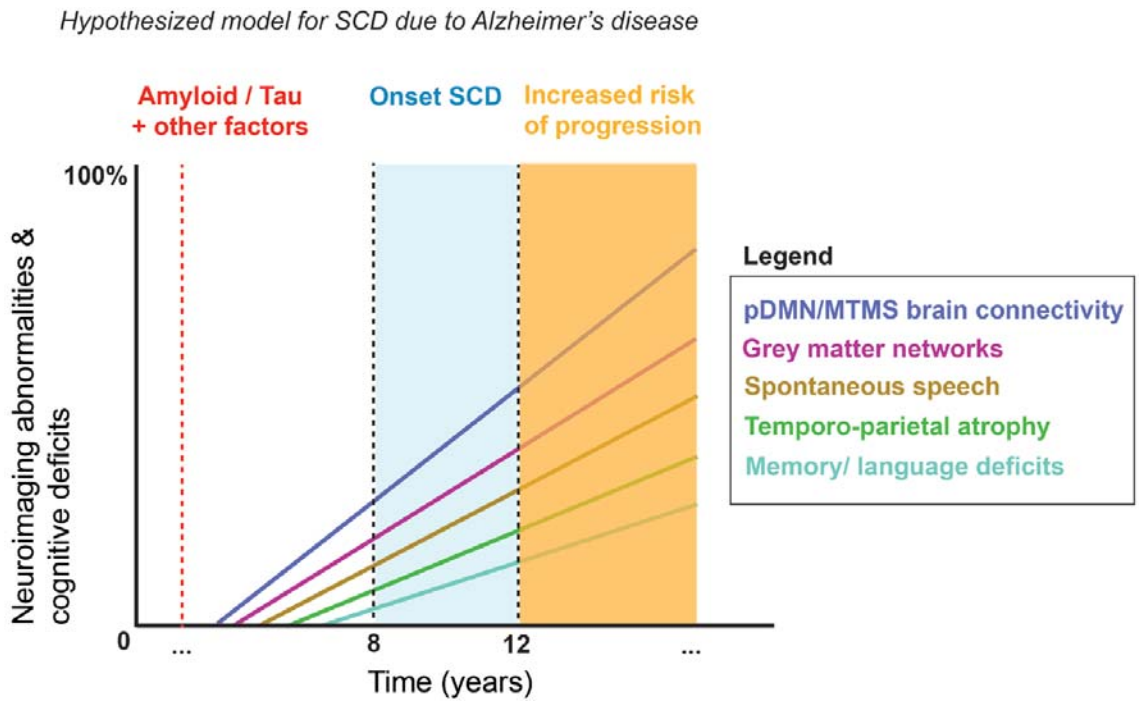

Figure 2. Hypothesized model for SCD due to AD (not based on neuroimaging or cognition data, and individual lines do not reflect individual cases or group data). Neuroimaging and cognitive measures in relation to "SCD onset" are displayed. The area following "SCD onset" is displayed in *orange blur* because of the uncertainty and variable consequences of biomarker results. SCD onset is nonetheless evoked by gradual cognitive changes. It is hypothesized that the majority of individuals have reached a threshold for amyloid deposition and tau pathology (and possibly other pathophysiological mechanisms) when they start to self-perceive decline. At this point, very subtle cognitive changes, related to amyloid, may be measured, especially in the domain of semantic complexity of spontaneous speech. In addition, compared to individuals without SCD, increased brain connectivity in the posterior default-mode network (pDMN) and medial temporal memory system, and more random global grey matter network organization can be observed in "SCD due to AD". Increased functional connectivity and random network organization were associated with cognitive decline in various domains after one and three years (on average) respectively. The previous associations seem to explain variance beyond cortical atrophy (in this thesis). Cortical atrophy, especially in temporo-parietal cortical regions, is associated with increased risk of clinical progression and with subsequent steeper memory decline (after on average after 3 years). Clinical progression to symptomatic stages will rely on interaction of multiple (unknown) pathophysiological events in relation to individuals' brain and cognitive reserve. The hypothetical model was based on findings by CR Jack jr. (2013, *Lancet Neurology*), and based on cross-sectional neuroimaging findings in relation to baseline and longitudinal cognitive data presented in this thesis.

Novel biomarkers

Novel biomarker discovery should remain an important goal for future research, especially biomarkers that can study *in vivo* brain tissue changes. In addition, mechanisms that link amyloid-β to neurodegeneration are poorly understood, and novel biomarkers could help to further elucidate this link. The recent introduction of several Tau PET radioligands offer the potential of more specific biomarkers for degenerative brain processes and could improve the understanding of AD pathophysiology. However, further research is necessary to investigate its potential clinical utility. Also, current PET amyloid and tau biomarkers can be further improved, such as binding properties of these tracers to amyloid-β oligomers or other tau isoforms.[63] Furthermore, biomarkers of neuronal damage, such as the novel [^{11}C]UCB-J PET radiotracer, which binds to synaptic protein (SV2a),[64] could improve the understanding of synaptic density, toxic effects of amyloid and tau, and neuronal damage in AD. Furthermore, there are a number of other pathways (cerebro- and microvascular, diabetes mellitus, inflammation) suggested to be related to AD pathogenesis.[65–68] These pathways, e.g. in conjunction polygenetic risk estimates, can be investigated with PET and MRI studies *in vivo,* preferably in preclinical stages.

CONCLUDING REMARKS

The dementia field is advancing rapidly toward early diagnosis in preclinical stages. Ultimately, clinicians would like to be able to identify individuals who are asymptomatic but unmask those at increased risk for developing dementia. Further unravelling of AD etiopathogenesis and pathophysiological mechanisms in preclinical stages are likely to provide novel insights, which remain crucially important to delay or halt the progression of the AD. Whilst amyloid plaques, neurofibrillary tangles and brain atrophy have been hallmarks of AD for over 100 years, other causative mechanisms should also be investigated by means of novel methodology (e.g. PET radioligands and MRI techniques). These data indicate that SCD proved to be an effective conceptual framework for studying preclinical AD. We provided evidence that cortical atrophy, brain connectivity failure, and brain amyloid deposition foreshadow early cognitive changes related to AD in individuals with SCD. Clinically, we showed that certain aspects of cognitive complaints, spontaneous speech and cognition-related worries, are very relevant to further investigate. Much of the research presented in this thesis, however, is performed on groups, with large inter-individual variation. The next steps will be to further examine concomitant causal mechanisms on a – preclinical - individual level to ultimately improve the understanding of the various pathways of neurodegenerative changes leading to AD.

REFERENCES

1. Jessen F, Wiese B, Bachmann C, et al. Prediction of dementia by subjective memory impairment: effects of severity and temporal association with cognitive impairment. *Arch Gen Psychiatry*. 2010;67:414-422. doi:10.1001/archgenpsychiatry.2010.30.
2. Van Harten AC, Smits LL, Teunissen CE, et al. Preclinical AD predicts decline in memory and executive functions in subjective complaints. *Neurology*. 2013;81(16):1409-1416. doi:10.1212/WNL.0b013e3182a8418b.
3. Van Harten AC, Visser PJ, Pijnenburg YAL, et al. Cerebrospinal fluid Aβ42 is the best predictor of clinical progression in patients with subjective complaints. *Alzheimer's Dement*. 2013;9(5):481-487. doi:10.1016/j.jalz.2012.08.004.
4. Comijs HC, Deeg DJH, Dik MG, Twisk JWR, Jonker C. Memory complaints; The association with psycho-affective and health problems and the role of personality characteristics: A 6-year follow-up study. *J Affect Disord*. 2002;72(2):157-165. doi:10.1016/S0165-0327(01)00453-0.
5. Jessen F, Amariglio RE, van Boxtel M, et al. A conceptual framework for research on subjective cognitive decline in preclinical Alzheimer's disease. *Alzheimer's Dement*. 2014:1-9. doi:10.1016/j.jalz.2014.01.001.
6. Cooper C, Bebbington P, Lindesay J, et al. The meaning of reporting forgetfulness: A cross-sectional study of adults in the English 2007 Adult Psychiatric Morbidity Survey. *Age Ageing*. 2011;40(6):711-717. doi:10.1093/ageing/afr121.
7. Rattanabannakit C, Risacher SL, Gao S, et al. The cognitive change index as a measure of self and informant perception of cognitive decline: Relation to neuropsychological tests. In: *Journal of Alzheimer's Disease*. Vol 51. ; 2016:1145-1155. doi:10.3233/JAD-150729.
8. van der Flier WM, van Buchem MA, Weverling-Rijnsburger AWE, et al. Memory complaints in patients with normal cognition are associated with smaller hippocampal volumes. *J Neurol*. 2004;251(6):671-675. doi:10.1007/s00415-004-0390-7.
9. Hafkemeijer A, Altmann-Schneider I, Oleksik AM, et al. Increased functional connectivity and brain atrophy in elderly with subjective memory complaints. *Brain Connect*. 2013;3(4):353-362. doi:10.1089/brain.2013.0144.
10. Saykin AJ, Wishart HA, Rabin LA, et al. Older adults with cognitive complaints show brain atrophy similar to that of amnestic MCI. *Neurology*. 2006;67(5):834-842. doi:10.1212/01.wnl.0000234032.77541.a2.
11. Meiberth D, Scheef L, Wolfsgruber S, Boecker H, Block W T, F, Erk S, Heneka MT, Jacobi H, Spottke A, Walter H W, M, Hu X JF. Cortical thinning in individuals with subjective memory impairment. *J Alzheimers Dis*. 2015. doi:10.3233/JAD-142322.
12. Dickerson BC, Bakkour A, Salat DH, et al. The cortical signature of Alzheimer's disease: Regionally specific cortical thinning relates to symptom severity in very mild to mild AD dementia and is detectable in asymptomatic amyloid-positive individuals. *Cereb Cortex*. 2009;19(March):497-510. doi:10.1093/cercor/bhn113.
13. Van Der Flier WM, Pijnenburg YAL, Prins N, et al. Optimizing patient care and research: The Amsterdam dementia cohort. *J Alzheimer's Dis*. 2014;41:313-327. doi:10.3233/JAD-132306.
14. Villeneuve S, Reed BR, Wirth M, et al. Cortical thickness mediates the effect of β-amyloid on episodic memory. *Neurology*. 2014;82(9):761-767. doi:10.1212/WNL.0000000000000170.
15. Doré V, Villemagne VL, Bourgeat P, et al. Cross-sectional and longitudinal analysis

of the relationship between Aβ deposition, cortical thickness, and memory in cognitively unimpaired individuals and in Alzheimer disease. *JAMA Neurol*. 2013;70(7):903-911. doi:10.1001/jamaneurol.2013.1062.

16. Sowell ER, Peterson BS, Thompson PM, Welcome SE, Henkenius AL, Toga AW. Mapping cortical change across the human life span. *Nat Neurosci*. 2003;6(3):309-315. doi:10.1038/nn1008.
17. Fjell AM, Walhovd KB, Fennema-Notestine C, et al. One-year brain atrophy evident in healthy aging. *J Neurosci*. 2009;29(48):15223-15231. doi:10.1523/JNEUROSCI.3252-09.2009.
18. Jonker C, Geerlings MI, Schmand B. Are memory complaints predictive for dementia? A review of clinical and population-based studies. *Int J Geriatr Psychiatry*. 2000;15(11):983-991. doi:10.1002/1099-1166(200011)15:11<983::aid-gps238>3.0.co;2-5.
19. Driscoll I, Davatzikos C, An Y, et al. Longitudinal pattern of regional brain volume change differentiates normal aging from MCI. *Neurology*. 2009;72(22):1906-1913. doi:10.1212/WNL.0b013e3181a82634.
20. Benzinger TLS, Blazey T, Jack CR, et al. Regional variability of imaging biomarkers in autosomal dominant Alzheimer's disease. *Proc Natl Acad Sci U S A*. 2013;110(47):E4502-9. doi:10.1073/pnas.1317918110.
21. Pegueroles J, Vilaplana E, Montal V, et al. Longitudinal brain structural changes in preclinical Alzheimer disease. *Alzheimer's Dement*. 2016;(September):1-11. doi:10.1016/j.jalz.2016.08.010.
22. Tijms BM, Möller C, Vrenken H, et al. Single-Subject Grey Matter Graphs in Alzheimer's Disease. *PLoS One*. 2013;8(3). doi:10.1371/journal.pone.0058921.
23. Tijms BM, Kate M Ten, Wink AM, et al. Gray matter network disruptions and amyloid beta in cognitively normal adults. *Neurobiol Aging*. 2016;37:154-160. doi:10.1016/j.neurobiolaging.2015.10.015.
24. Yao Z, Zhang Y, Lin L, Zhou Y, Xu C, Jiang T. Abnormal cortical networks in mild cognitive impairment and alzheimer's disease. *PLoS Comput Biol*. 2010;6(11). doi:10.1371/journal.pcbi.1001006.
25. Draganski B, Gaser C, Busch V, Schuierer G, Bogdahn U, May A. Neuroplasticity: Changes in grey matter induced by training. *Nature*. 2004;427(6972):311-312. doi:10.1038/427311a.
26. Andrews TJ, Halpern SD, Purves D. Correlated size variations in human visual cortex, lateral geniculate nucleus, and optic tract. *J Neurosci*. 1997;17(8):2859-2868. doi:Comparative Study Research Support, U.S. Gov't, P.H.S.
27. Humphries MD, Gurney K. Network "small-world-ness": A quantitative method for determining canonical network equivalence. *PLoS One*. 2008;3(4). doi:10.1371/journal.pone.0002051.
28. Watts DJ, Strogatz SH. Collective dynamics of "small-world" networks. *Nature*. 1998;393(6684):440-442. doi:10.1038/30918.
29. Stam CJ, Jones BF, Nolte G, Breakspear M, Scheltens P. Small-world networks and functional connectivity in Alzheimer's disease. *Cereb Cortex*. 2007;17(1):92-99. doi:10.1093/cercor/bhj127.
30. Tijms BM, Wink AM, de Haan W, et al. Alzheimer's disease: connecting findings from graph theoretical studies of brain networks. *Neurobiol Aging*. 2013;34(8):2023-2036. doi:10.1016/j.neurobiolaging.2013.02.020.
31. Quiroz YT, Schultz AP, Chen K, et al. Brain Imaging and Blood Biomarker Abnormalities in Children With Autosomal Dominant Alzheimer Disease: A Cross-Sectional Study. *JAMA Neurol*. 2015;2114(8):1-8. doi:10.1001/jamaneurol.2015.1099.
32. Badhwar A, Tam A, Dansereau C, Orban P, Hoffstaedter F, Bellec P. Resting-state

network dysfunction in Alzheimer's disease: A systematic review and meta-analysis. *Alzheimer's Dement Diagnosis, Assess Dis Monit*. 2017;8:73-85. doi:10.1016/j.dadm.2017.03.007.

33. Jones DT, Knopman DS, Gunter JL, et al. Cascading network failure across the Alzheimer's disease spectrum. *Brain*. 2016;139(2):547-562. doi:10.1093/brain/awv338.
34. Elman J a, Oh H, Madison CM, et al. Neural compensation in older people with brain amyloid-β deposition. *Nat Neurosci*. 2014;17(10):1316-1318. doi:10.1038/nn.3806.
35. Dillen KNH, Jacobs HIL, Kukolja J, et al. Aberrant functional connectivity differentiates retrosplenial cortex from posterior cingulate cortex in prodromal Alzheimer's disease. *Neurobiol Aging*. 2016;44:114-126. doi:10.1016/j.neurobiolaging.2016.04.010.
36. Contreras JA, Goni J, Risacher SL, et al. Cognitive complaints in older adults at risk for Alzheimer ' s disease are associated with altered resting-state networks ın Go n. 2017;6:40-49. doi:10.1016/j.dadm.2016.12.004.
37. van Berckel BNM, Ossenkoppele R, Tolboom N, et al. Longitudinal Amyloid Imaging Using 11C-PiB: Methodologic Considerations. *J Nucl Med*. 2013;54(9):1570-1576. doi:10.2967/jnumed.112.113654.
38. Price JC, Klunk WE, Lopresti BJ, et al. Kinetic modeling of amyloid binding in humans using PET imaging and Pittsburgh Compound-B. *J Cereb Blood Flow Metab*. 2005;25(11):1528-1547. doi:10.1038/sj.jcbfm.9600146.
39. Tolboom N, Yaqub M, Boellaard R, et al. Test-retest variability of quantitative [11C] PIB studies in Alzheimer's disease. *Eur J Nucl Med Mol Imaging*. 2009;36(10):1629-1638. doi:10.1007/s00259-009-1129-6.
40. Ottoy J, Verhaeghe J, Niemantsverdriet E, et al. Validation of the Semiquantitative Static SUVR Method for ^{18}F-AV45 PET by Pharmacokinetic Modeling with an Arterial Input Function. *J Nucl Med*. 2017;58(9):1483-1489. doi:10.2967/jnumed.116.184481.
41. Manenti R, Repetto C, Bentrovato S, Marcone A, Bates E, Cappa SF. The effects of ageing and Alzheimer's disease on semantic and gender priming. *Brain*. 2004;127(10):2299-2306. doi:10.1093/brain/awh264.
42. Roark B, Mitchell M, Hosom JP, Hollingshead K, Kaye J. Spoken language derived measures for detecting mild cognitive impairment. *IEEE Trans Audio, Speech Lang Process*. 2011;19(7):2081-2090. doi:10.1109/TASL.2011.2112351.
43. Gayraud F, Lee H, Barkat-Defradas M. Syntactic and lexical context of pauses and hesitations in the discourse of Alzheimer patients and healthy elderly subjects. *Clin Linguist Phon*. 2011;25(3):198-209. doi:10.3109/02699206.2010.521612.
44. Kemper S, Marquis J, Thompson M, Marquis J. Longitudinal change in language production: Effects of aging and dementia on grammatical complexity and propositional content. *Psychol Aging*. 2001;16(4):600-614. doi:10.1037/0882-7974.16.4.600.
45. Kemper S, Anagnopoulos C, Lyons K, Heberlein W. Speech accommodations to dementia. *J Gerontol*. 1994;49(5):P223-9. http://www.ncbi.nlm.nih.gov/pubmed/8056947.
46. Fraser KC, Meltzer JA, Rudzicz F. Linguistic features identify Alzheimer's disease in narrative speech. *J Alzheimer's Dis*. 2015;49(2):407-422. doi:10.3233/JAD-150520.
47. Berisha V, Wang S, LaCross A, Liss J. Tracking Discourse Complexity Preceding Alzheimer's Disease Diagnosis: A Case Study Comparing the Press Conferences of Presidents Ronald Reagan and George Herbert Walker Bush. *J Alzheimer's Dis*. 2015;45(3):959-963. doi:10.3233/JAD-142763.

48. Perrotin A, La Joie R, de La Sayette V, et al. Subjective cognitive decline in cognitively normal elders from the community or from a memory clinic: Differential affective and imaging correlates. *Alzheimer's and Dementia*. 2016.
49. Hassenstab J, Ruvolo D, Jasielec M, Xiong C, Grant E, Morris JC. Absence of practice effects in preclinical Alzheimer's disease. *Neuropsychology*. 2015;29(6):940-948. doi:10.1037/neu0000208.
50. Mormino EC, Betensky RA, Hedden T, et al. Synergistic Effect of β-Amyloid and Neurodegeneration on Cognitive Decline in Clinically Normal Individuals. *JAMA Neurol*. 2014;71(11):1379. doi:10.1001/jamaneurol.2014.2031.
51. Rowe CC, Ackerman U, Browne W, et al. Imaging of amyloid β in Alzheimer's disease with 18F-BAY94-9172, a novel PET tracer: proof of mechanism. *Lancet Neurol*. 2008;7(2):129-135. doi:10.1016/S1474-4422(08)70001-2.
52. Wong DF, Rosenberg PB, Zhou Y, et al. In Vivo Imaging of Amyloid Deposition in Alzheimer Disease Using the Radioligand 18F-AV-45 (Flobetapir F 18). *J Nucl Med*. 2010;51(6):913-920. doi:10.2967/jnumed.109.069088.
53. Mattsson N, Insel PS, Landau S, et al. Diagnostic accuracy of CSF Ab42 and florbetapir PET for Alzheimer's disease. *Ann Clin Transl Neurol*. 2014;1(8):534-543. doi:10.1002/acn3.81.
54. Schipke CG, Koglin N, Bullich S, et al. Correlation of florbetaben PET imaging and the amyloid peptide Aß42 in cerebrospinal fluid. *Psychiatry Res Neuroimaging*. 2016:1205-1214. doi:10.1016/j.pscychresns.2016.10.011.
55. Slot RER, Sikkes SAM, Verfaillie SCJ, et al. Subjective Cognitive Decline and Progression To Dementia Due To Ad and Non-Ad in Memory Clinic and Community-Based Cohorts. *Alzheimer's Dement*. 2016;12(7):P1073. doi:10.1016/j.jalz.2016.06.2245.
56. Scheltens P, Leys D, Barkhof F, et al. Atrophy of medial temporal lobes on MRI in "probable" Alzheimer's disease and normal ageing: diagnostic value and neuropsychological correlates. *J Neurol Neurosurg Psychiatry*. 1992;55:967-972. doi:10.1136/jnnp.55.10.967.
57. Van Maurik IS, Zwan MD, Tijms BM, et al. Interpreting biomarker results in individual patients with mild cognitive impairment in the Alzheimer's Biomarkers in Daily Practice (ABIDE) project. *JAMA Neurol*. 2017;74(12):1481-1491. doi:10.1001/jamaneurol.2017.2712.
58. Burns JM, Johnson DK, Liebmann EP, Bothwell RJ, Morris JK, Vidoni ED. Safety of disclosing amyloid status in cognitively normal older adults. *Alzheimer's Dement*. 2017;13(9):1024-1030. doi:10.1016/j.jalz.2017.01.022.
59. Villeneuve S, Rabinovici GD, Cohn-Sheehy BI, et al. Existing Pittsburgh Compound-B positron emission tomography thresholds are too high: Statistical and pathological evaluation. *Brain*. 2015;138(7):2020-2033. doi:10.1093/brain/awv112.
60. Johnson KA, Schultz A, Betensky RA, et al. Tau positron emission tomographic imaging in aging and early Alzheimer disease. *Ann Neurol*. 2016;79(1):110-119. doi:10.1002/ana.24546.
61. Schöll M, Lockhart SN, Schonhaut DR, et al. PET Imaging of Tau Deposition in the Aging Human Brain. *Neuron*. 2016;89(5):971-982. doi:10.1016/j.neuron.2016.01.028.
62. Molinuevo JL, Rabin LA, Amariglio R, et al. Implementation of subjective cognitive decline criteria in research studies. *Alzheimer's Dement*. 2017;13(3):296-311. doi:10.1016/j.jalz.2016.09.012.
63. Viola KL, Klein WL. Amyloid β oligomers in Alzheimer's disease pathogenesis, treatment, and diagnosis. *Acta Neuropathol*.

2015;129(2):183-206. doi:10.1007/s00401-015-1386-3.

64. Mercier J, Provins L, Valade A. Discovery and development of SV2A PET tracers: Potential for imaging synaptic density and clinical applications. *Drug Discov Today Technol*. 2017;25:45-52. doi:10.1016/j.ddtec.2017.11.003.

65. Adams HHH, de Bruijn RFAG, Hofman A, et al. Genetic risk of neurodegenerative diseases is associated with mild cognitive impairment and conversion to dementia. *Alzheimers Dement*. 2015;11(11):1277-1285. doi:10.1016/j.jalz.2014.12.008.

66. Walker KA, Power MC, Hoogeveen RC, et al. Midlife Systemic Inflammation, Late-Life White Matter Integrity, and Cerebral Small Vessel Disease: The Atherosclerosis Risk in Communities Study. *Stroke*. 2017:STROKEAHA.117.018675. doi:10.1161/STROKEAHA.117.018675.

67. Gottesman RF, Albert MS, Alonso A, et al. Associations Between Midlife Vascular Risk Factors and 25-Year Incident Dementia in the Atherosclerosis Risk in Communities (ARIC) Cohort. *JAMA Neurol*. 2017. doi:10.1001/jamaneurol.2017.1658.

68. Walker KA, Hoogeveen RC, Folsom AR, et al. Midlife systemic inflammatory markers are associated with late-life brain volume: The ARIC study. *Neurology*. 2017:10.1212/WNL.0000000000004688. doi:10.1212/WNL.0000000000004688.