Neuroimaging in subjective cognitive decline

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CHAPTER 9

Amyloid-b load is related to worries, but not to severity of cognitive complaints in individuals with subjective cognitive decline: the SCIENCe project

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submitted

"the ultimate paradox of thought:
to want to discover something that thought itself cannot think" (S. Kierkegaard)

ABSTRACT

Background. Subjective cognitive decline (SCD) is associated with an increased risk of Alzheimer's Disease (AD). Early disease processes, such as amyloid-β aggregation measured with quantitative positron emission tomography (PET), may help to explain the phenotype of SCD. The aim of this study was to investigate whether amyloid-β load is associated with both self- and informant-reported cognitive complaints and memory deficit awareness in individuals with SCD.

Methods. We included 106 SCD memory-clinic patients (mean±SD age: 64±8, 45%F) 90 minutes dynamic [^{18}F]florbetapir PET scans. We used the following questionnaires to assess SCD severity: cognitive change index (CCI, self & informant reports; 2x20 items), subjective cognitive functioning (SCF, 4 items), and five questions "Do you have complaints?" (yes/no) for memory, attention, organization and language), and "Does this worry you? (yes/no)". The Rivermead Behavioral Memory Test (RBMT)-Stories (delayed recall) was used to assess objective episodic memory. To investigate the level of self-awareness, we calculated a memory deficit awareness index (Z-transformed (inverted self-reported CCI minus episodic memory); higher index, better self-awareness) and a self-proxy index (Z-transformed self- minus informant-reported CCI). Mean cortical [^{18}F]florbetapir binding potential (BP_{ND}) was derived from the PET data. Logistic and linear regression analyses, adjusted for age, sex, education, and depressive symptoms, were used to investigate associations between BP_{ND} and measures of SCD.

Results. Higher mean cortical BP_{ND} was associated with SCD-related worries (standardized Beta=0.53, p=0.03), but not with other SCD questionnaires (informant and self-report CCI or SCF, total scores or individual items, all p>0.05). In addition, higher mean cortical BP_{ND} was associated with a better memory deficit awareness index (Beta=0.25, p=0.01), but not with the self-proxy index (Beta=0.15, p=0.14).

Conclusions. Amyloid-β deposition was associated with SCD-related worries and memory deficit awareness, but not with severity of cognitive complaints. Our findings indicate that worries about self-perceived decline may reflect an early symptom of amyloid-β related pathology rather than subjective cognitive functioning.

INTRODUCTION

Amyloid-β plaques and neurofibrillary tangles are neuropathological hallmarks of Alzheimer's disease (AD), which start to appear 10-20 years before the onset of dementia.[1] Self-perceived cognitive decline in cognitively normal individuals is associated with a three- to six fold increased risk of AD.[2–4] As such, a proportion of individuals with subjective cognitive decline (SCD) may harbor the earliest pathological changes associated with AD,[5,6] particularly amyloid-β accumulation (i.e. preclinical AD).

It is conceivable that individuals with preclinical AD exhibit a specific phenotype of cognitive complaints compared with individuals without underlying AD. There are many questionnaires to investigate the nature and severity of SCD, but the appropriate items enabling prediction of conversion to mild cognitive impairment (MCI) and dementia have not yet been identified.[7,8] There are various methodological challenges associated with SCD assessment, one of which is that cognitive complaints tend to vary as a function of demographic characteristics, such as level of education and age.[7] In addition, these factors can also act in synergy; for example, it has been shown that cognitive complaints in highly educated individuals are associated with increased risk of progression to AD, while this is not found in individuals with less education.[9,10] SCD *plus* criteria were proposed in an effort to increase the likelihood of identifying preclinical AD in individuals with SCD. One of these criteria suggests that especially individuals who worry about their self-perceived cognitive decline are more likely to have preclinical AD, but associations between worries and amyloid-β load have not been confirmed in prospective studies yet.[2,3,11] Furthermore, former studies investigating associations between amyloid-β load and various SCD questionnaires have generated highly inconsistent results in cognitively normal individuals.[12–19] These discrepancies could be due to the less precise amyloid-β positron emission tomography (PET) semi-quantitative cut-off values in preclinical stages of AD,[20] and variability of implemented SCD questionnaires, including the lack of informant reports or objective memory tests relative to self-reports.[7,8]

Another approach is to explore whether preclinical AD is linked to the insight in cognitive deficits (i.e. self-awareness) rather than to the severity of SCD. The degree of memory deficit awareness takes into account the contribution of objective memory performance or informant reports relative to self-reports.[21,22] A lack of awareness of memory deficits, anosognosia, is a striking symptom in patients with AD dementia.[21,22] On the contrary, it is has been suggested that the earliest changes in cognition during preclinical stages of the disease are best perceived by the individual including a heightened sense of self-awareness for early brain changes (i.e. hypernosognosia).[23,24] It has recently been suggested that cognitively normal individuals harboring amyloid-β pathology had a heightened sense of self-awareness.[25] It has, however, not yet been investigated whether the earliest changes

in cognition are best perceived by the individual rather than the observer or objective memory tests in a memory clinic setting.

We hypothesized that increased amyloid-β load is related to specific cognitive complaints and heightened level of self-awareness. Therefore, the purpose of the present study was to investigate whether amyloid-β load, as measured using quantitative PET, may help to explain the phenotype of SCD in cognitively normal individuals who initially have been referred to a memory clinic. A second aim was to investigate whether amyloid-β load is associated with altered levels of self-awareness.

MATERIALS AND METHODS

Participants. We included 106 SCD memory-clinic patients with [^{18}F]florbetapir PET scans from the ongoing Subjective Cognitive ImpairmENt Cohort (SCIENCe) study. Subjects were referred to our memory clinic by their general practitioner or medical specialist because of cognitive complaints. Prior to inclusion via the memory clinic, all patients underwent a standardized dementia screening according to the procedures of the Amsterdam Dementia Cohort.[26] Individuals were selected if they had memory complaints in response to the following question "What complaints do you report?". Screening included extensive neuropsychological assessment, physical and neurologic examination as well as laboratory tests, and brain magnetic resonance imaging (MRI). Clinical diagnosis was established by consensus in a multidisciplinary team. Individuals were labelled as having SCD when they presented with cognitive complaints, and results of clinical investigations were within normal range. Criteria for MCI, dementia, or any other neurological or psychiatric (e.g. major depression) disorders known to cause cognitive complaints were not met. In addition, we used the Center for Epidemiological Studies Depression Scale (CES-D) scale to evaluate subclinical depressive symptoms (cut-off ≥16).[27] The study had been approved by the Medical Ethics Review Committee of the VU University Medical Center. All patients provided written informed consent.

Image acquisition and analyses. Ninety minutes dynamic [^{18}F]florbetapir PET scans were acquired on a PET/CT scanner (n=59 on an Ingenuity TF and n=47 on a Gemini TF, both from Philips Medical Systems, Best, The Netherlands). PET images were corrected for attenuation, scatter, randoms, decay and dead time using standard software. Three-dimensional T1-weighted MRI scans acquired on 3 tesla were co-registered to the PET scans, and regions of interest (Hammers template, n=68 regions of interest [ROI]) were defined on the MRI scan (in native space) and superimposed onto the dynamic PET scan to obtain regional time activity curves using PVElab.[28,29] Receptor parametric mapping (RPM) with optimized settings (parameters settings 0.01-0.1, 50 basis functions) and cerebellar grey matter as reference region was used to generate images of binding potential (BP_{ND})

relative to the non-displaceable compartment.[30,31] From the BP_{ND} images, grey matter volume-weighted mean cortical BP_{ND} values were obtained. To investigate potential regional specificity, volume-weighted bilateral frontal, temporal (medial and lateral), and parietal cortical BP_{ND} values were also extracted. In addition, standardized uptake value (SUV, 50-70 minutes post-injection) images were visually assessed by a trained and experienced reader (BvB), leading to "normal" or "abnormal" classification of amyloid accumulation.

SCD assessment. We used four questionnaires with the following characteristics: two self-, one informant-based questionnaires, and one which was composed of 5 cognitive questions to assess SCD. The maximal time window between these assessments and the PET scan was 1 year (median= 3 months). We used the Dutch translation of the Cognitive Change Index – self (CCI-S) and informant report (CCI-I) (each 20 questions [range 0-4], total score: 20-100) to assess cognitive function compared to five years ago.[32] We used the Subjective Cognitive Functioning (SCF) questionnaire (4 questions, range: -12 to +12) to assess self-experienced cognitive decline over a one-year time period.[26] SCF scores were inverted in such a way that higher scores reflect more complaints, comparable to the CCI. Finally, we used a structured interview to assess SCD. We used the following question "What complaints do you report?". Based on the individuals' spontaneous response the following cognitive domains were scored "yes/no": memory, attention, organization, language, together with the follow-up question: "Does this worry you?".[2,3] In addition, for descriptive purposes, the following question was used to inquire SCD onset "when was the first time that you talked with a physician about these problems?".

Memory self-awareness indexes. To investigate the level of self-awareness, two index scores were calculated. First, the memory deficit awareness index, was defined for each participant by calculating the difference between subjective and objective episodic memory scores.[21,22,25] In concordance with previous studies we used episodic memory (delayed recall) for the memory deficit awareness index, i.e. the Rivermead Behavioral Memory Test (RBMT)-Stories (delayed recall). To allow comparison between both measures, (1) the CCI-self was inverted in such a way that, similar to the objective memory score, a lower score indicated more severe subjective memory impairment; (2) both objective and the subjective memory scores were Z-transformed.[21,22,25] A positive index score reflects heightened self-awareness (hypernosognosia), whereas negative scores lowered self-awareness (anosognosia).[21,22,25] Second, a self-proxy index (self-reported CCI minus informant-reported CCI) was calculated. A lower score reflects more self-reported cognitive complaints than informant-reported complaints (hypernosognosia), whereas negative scores reflect more informant-based complaints than self-reported complaints (anosognosia).

Statistical analyses. Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS, IBM v22). We used linear regression (for continuous outcome measures) or binary logistic regression (for dichotomous outcome measures) analyses

to investigate associations between amyloid-β load BP_{ND} (independent variable) and measures of SCD (i.e. CCI, SCF [total and items scores], complaints questions). Analyses were adjusted for age, sex, education and depressive symptoms (CES-D). As cognitive complaints in highly educated individuals may be more predictive of dementia,[9,16] we also tested for an in teraction education*BP_{ND}. Linear regression analyses, adjusted for age, sex, education and depressive symptoms, were used to investigate associations between BP_{ND} (independent variable) and memory self-awareness indexes (dependent variables; separate models). In addition, we tested for education*BP_{ND} interactions. We report standardized betas were considered significant if $p<0.05$.

Table 1. Clinical and demographic data

Demographics	**Total group** *(N=106)*
Male/female (n, %)	47/60
Age (years)	63.83 (7.65)
Education (range: 1-7)	5.79 (1.07)
SCD onset (% within last 5 years)	83%
Depressive symptoms	8.5 (7.0)
Amyloid imaging	
Net injected dose (MBq)	312 (38)
Specific activity (MBq/µg)	2.72 (1.76)
Visual assessment of SUV_{50-70} images (n abnormal [%])	24 (23%)
Mean cortical amyloid (BP_{ND})	0.18 (0.15)
Frontal cortex	0.18 (0.17)
Temporal cortex	0.13 (0.13)
Parietal cortex	0.22 (0.17)
Episodic memory	
RBMT stories (version A+B) delayed recall	16.73 (6.20)
SCD questionnaires	
SCF	-1.54 (2.92)
CCI self-reported	41.23 (15.05)
CCI informant-based	37.17 (16.44)
Memory question n “yes” (%)	73 (68%)
Attention question n “yes” (%)	27 (25%)
Organization question n “yes” (%)	14 (13%)
Language question n “yes” (%)	36 (34%)
Worry question n “yes” (%)	50 (47%)

Education level was assessed using the Verhage classification in accordance with the Dutch educational system. SCD onset was based upon individuals’ self-reports. Depressive symptoms were assessed with the CES-D.

RESULTS

Demographic and clinical data are presented in Table 1. Individuals (45% females) were (mean±SD) 64±8 years old and had an MMSE of 29±1. Twenty-four individuals (23%) showed abnormal amyloid accumulation. On average, subjects had a mean cortical BP_{ND} of 0.18±0.15 (frontal cortex 0.18±0.18, temporal cortex 0.13±0.13, parietal cortex 0.22±0.17). On average, individuals reported lower subjective cognitive functioning than one year earlier (SCF= -1.54±2.92), and some cognitive changes (CCI self-report: 41.23±15.05; CCI informant report: 37.17±16.44) compared to five years ago. Self- and informant-based reports regarding the degree of cognitive change over a five year period did not differ significantly. About 68% (n=73), 34% (n=36), 13% (n=14) and 25% (n=27) of the individuals reported complaints in the domains of memory, language, organization and attention, respectively, whilst 47% (n=50) felt worried about their self-perceived decline.

Table 2. Associations between mean amyloid load and SCD

SCD questionnaires	Mean cortical
SCF	0.15
CCI self-reported	-0.10
CCI informant-based	0.01
Memory question	-0.32
Worry question	0.53*
Episodic memory	
RBMT delayed recall	-0.17
Indexes	
Self-awareness index	0.25*
Self-proxy index	0.15

Data are presented as std Beta. * p<0.05. Analyses were adjusted for age, sex, and education. Analyses between amyloid-β load, self-proxy and self-awareness indexes were based on mean cortical amyloid-β load. Self-awareness index; a positive index score reflects heightened self-awareness (hypernosognosia), whereas negative scores lowered self-awareness (anosognosia) Self-proxy index; a positive beta estimate reflects a positive association between amyloid and higher self-reported cognitive complaints.

Associations between BP_{ND} and measures of SCD are presented in Table 2. Adjusted for age, sex, and education, higher mean cortical (figure 1A) BP_{ND} was associated with SCD-related worries (Beta=0.53, p<0.05), but neither with any item nor total score of the SCF nor CCI (neither CCI informant nor self-reported) nor dichotomous memory (figure 1A), attention, organization or language questions (all p>0.05). There were no interaction effects between mean cortical BP_{ND} and education for any of the SCD questionnaire outcomes (all p>0.05). These results remained essentially unchanged when using BP_{ND} in specific lobes rather than mean cortical BP_{ND} (data not shown).

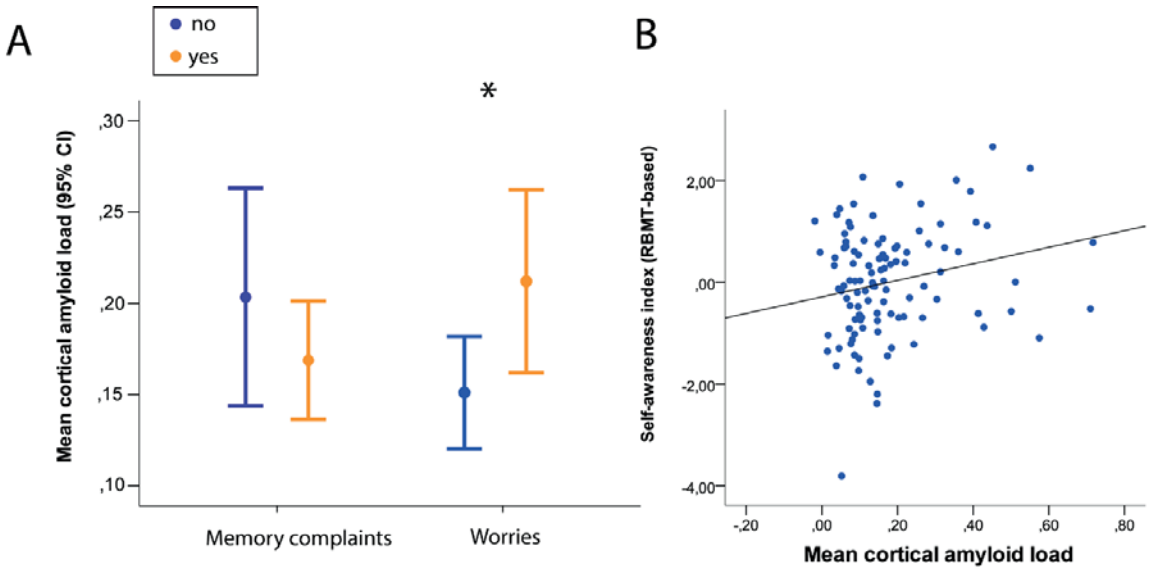

Figure 1. (A) Mean cortical amyloid-beta load stratified for memory complaints (yes/no) and worries (yes/no). (B) Associations between mean cortical amyloid load and self-awareness index. Memory deficit awareness index: a positive index score reflects heightened self-awareness (hypernosognosia), whereas negative scores lowered self-awareness (anosognosia) * indicates p<0.05

We furthermore investigated associations between mean cortical BP_{ND} and two self-awareness indexes. We found that higher mean cortical BP_{ND} (beta=0.25) was associated with a higher memory deficit awareness index (i.e. hypernosognosia) (table 2; figure 1B), but not with the self-proxy index. There were no interactions between mean cortical BP_{ND} and education level (all p>0.05).

DISCUSSION

The main finding of the present study is that amyloid-β load is associated with SCD-related worries and a heightened memory-deficit self-awareness, but not with severity or specific cognitive complaints.

Amyloid-β load may insidiously affect cognition and self-perceived decline prior to symptom onset.[12,18,33] Some population-based and mixed population and memory clinic studies have shown that amyloid-β load is related to SCD,[12–14,16,18] but other studies did not find this association with SCD.[15,17] To the best of our knowledge, associations between amyloid-β load and cognitive complaints have not been investigated in a pure memory clinic sample, and earlier findings could have been affected by the recruitment policy, particularly in the case of mixed recruitment studies.[34] Therefore, it remains unclear to what extent amyloid-β is contributing to the phenotype of SCD in individuals who

seek medical evaluation for their complaints.[9,35] In the present study we investigated relatively young individuals with a recent SCD onset (<5 years), and a substantial fraction of almost one out of four showed abnormal amyloid accumulation.[34,36] We furthermore used quantitative PET (BP_{ND}) because it can more accurately determine amyloid-β load than standardized uptake ratio values (SUVr), which is especially important to capture potentially early – subtle – disease processes, and SCD-related worries are related to a sixteen and six fold increased risk of clinical progression respectively,[2,37] and we now show that they associated with each other in cognitively normal individuals. The SCD *plus* criteria have suggested that the presence of SCD-related worries are associated with an increased risk of future cognitive decline,[11] and our results support this notion.

Apart from the relationship with SCD-related worries, no associations between amyloid-β load and any of the SCD questionnaires or single items that measure various aspects of cognitive change were observed, indicating that these questionnaires are not specific for preclinical AD in a memory clinic. There is much controversy about which questionnaire can be used to unveil cognitive normal individuals at increased risk for AD, but the present results indicate that it does not necessarily matters which questionnaire, but rather whether the SCD assessment includes a "worry" inquiry. Earlier studies have used SUVr to assess abnormal amyloid-β accumulation, which have generated inconsistent results.[12–15,38] Compared with BP_{ND}, SUVr is liable to overestimation of amyloid-β load together with a higher variability,[39] which could hamper a correct interpretation and reduce statistical power especially in early disease stages.[39–41] Other possible explanations for our findings are recruitment criteria used and the operationalisation of SCD.[13,42,43] A recent study has demonstrated elevated levels of amyloid-β load in memory clinic SCD patients compared with community-dwelling individuals without SCD, but not compared with community-recruited subjects with SCD.[13] The present investigations were restricted to individuals with SCD, who had visited a memory clinic for their self-perceived decline. By definition these individuals experience cognitive complaints, but these may be caused by various factors other than preclinical AD. For example, it has been shown that memory clinic SCD patients have higher (subclinical) depressive symptoms compared with community-dwelling individuals with SCD.[13] In the present study, however, individuals with a current psychiatric diagnosis were excluded prior to enrolment. In addition, analyses were adjusted for depressive symptoms, which makes it unlikely that mental illness was responsible for the lack of associations. Nevertheless, irrespective of the nature of cognitive complaints, higher mean cortical amyloid-β load was associated with SCD related worries, and this appeared to be consistent for all cortical regions.

It has been claimed that earliest changes in cognition are best perceived by the individual rather than by an observer.[23] In order to investigate the awareness of memory function, two discrepancy scores were calculated to adjust cognitive complaints for episodic memory performance (i.e. memory deficit awareness index) and informant reports (i.e. self-proxy index). Although SCD conceptually refers to the self-perception

of cognitive decline and does not require confirmation by informants, we did not find different associations between amyloid-β and the self-proxy index. In line with a study on cognitively normal individuals from the community,[25] we found a positive relation between amyloid-β load and memory deficit awareness, which indicated that individuals with increased amyloid-β load showed heightened memory-deficit self-awareness or hypernosognosia. Earlier studies have used this index to investigate anosognosia, and showed that AD patients have an impaired memory deficit awareness, i.e. more severe episodic memory performance compared with self-rated cognitive performance.[21,22]. In the present study we found opposite patterns compared to patients with AD dementia.[22] Although it needs to be interpreted with care, these positive associations could reflect a higher level of memory deficit self-awareness in individuals with preclinical AD. The index scores seemed to be driven by episodic memory performance, and our findings imply that higher amyloid-β load can be observed in cases when individuals' self-rated cognitive complaints are less severe than their episodic memory performance. While it is generally assumed that individuals with SCD perceive cognitive decline better themselves than as indicated by cognitive tests, an alternative explanation for this finding could be that episodic memory performance, rather than subjective cognitive complaints severity, is more strongly related to amyloid pathology, which is in line with studies showing that episodic memory starts to deteriorate early in the disease course.[44,45]

Individuals with SCD who visit a memory clinic are a clinically relevant group since they seek help for their complaints and are at increased risk for clinical progression.[2,3,9] Notwithstanding, some limitations need to be acknowledged. First, while we have incorporated every available SCD item from our cohort, there may be other questionnaires which are better able to isolate SCD due to preclinical AD. On the other hand, the use of other SCD questionnaires may not provide very different results, because questionnaires will likely show high correlations, and predominantly inquire about memory complaints.[7] In addition, questionnaires rely on self-perception of cognitive decline, which in the present study did not show any relation with amyloid-β load or could have been distorted by other non-AD SCD phenotypes.[46] Second, our memory self-awareness index seemed driven by relatively lower, but non-significant, episodic memory performance in individuals with higher amyloid-β burden. Lastly, the present study had a cross-sectional design. Therefore, it is not possible to make inferences as to whether amyloid-β load and SCD related worries are associated with actual clinical progression to symptomatic stages of AD. Future longitudinal studies are necessary to fully elucidate these associations, while taking into account the effects of concomitant pathologies such as tau burden.

In conclusion, amyloid-β load was associated with SCD related worries and higher memory deficit awareness, but not with severity or specific pattern of cognitive complaints. Our findings indicate that worries about self-perceived decline may therefore help to identify amyloid-β related SCD.

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