# Subjective cognitive decline in cognitively normal elders from the community or from a memory clinic: Differential affective and imaging correlates

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**Abstract (150/150 words max)**

**INTRODUCTION.** Subjective cognitive decline (SCD) could indicate preclinical Alzheimer's disease but the existing literature is confounded by heterogeneous approaches to studying SCD. We assessed the differential cognitive, affective, and neuroimaging correlates of two aspects of SCD: reporting high cognitive difficulties on a self-rated questionnaire versus consulting at a memory clinic.

**METHODS.** We compared 28 patients from a memory clinic with isolated SCD, 35 community-recruited elders with similarly high levels of self-reported cognitive difficulties and 35 community-recruited controls with low self-reported cognitive difficulties.

**RESULTS.** Increased anxiety and β-amyloid deposition were observed in both groups with high self-reported difficulties while subclinical depression and (hippocampal) atrophy were specifically associated with medical help seeking. Cognitive tests showed no group differences.

**DISCUSSION:** These results further validate the concept of SCD in both community and clinic-based groups. Yet, recruitment methods influence associated biomarkers and affective symptomatology, highlighting the heterogeneous nature of SCD depending on study characteristics.

**KEYWORDS.** Alzheimer's disease, subjective cognitive decline, cognitive complaint, preclinical, beta-amyloid, Florbetapir-PET, MRI, atrophy, hippocampus, anxiety, depression

# 1. Introduction

Some elder individuals experience subjective cognitive decline (SCD) while showing normal 'objective' cognitive performances (i.e. scores within the normal range on standardized neuropsychological tests). Although these individuals have been described for decades [1], they have received increasing attention over the past few years, with the growing interest in characterizing preclinical stages of Alzheimer's disease (AD) [2,3]. Indeed, several epidemiological studies have shown that, in elders without identifiable cognitive deficits, SCD is associated with a higher risk to develop mild cognitive impairment or AD dementia [4–8]. Recent research has also shown that, at the group level, SCD is associated with neuroimaging biomarkers suggestive of AD (atrophy and/or hypometabolism in temporo-parietal regions [9–21], β-amyloid deposition[18,22–26]), although negative findings have also been reported [27–31] (see Table1 for review).

This converging evidence suggests that SCD could be among the first clinically observable sign of AD. However, individuals with SCD constitute a heterogeneous population [32]: in a considerable proportion of cases, SCD is likely due to non-AD etiologies including poor general health, sleep disorders, medication, or personality traits [33]. The current challenge is thus to identify the specific characteristics of SCD that are associated with an increased likelihood of AD etiology.

The SCD-Initiative working group recently published a conceptual framework for research on SCD in the context of preclinical AD; this initiative is meant to propose SCD criteria and encourage standardized research to refine our understanding of SCD [34]. Indeed, comparison between existing studies is currently hampered by the wide variability in the definition and criteria used to study SCD (aka "subjective cognitive/memory impairment", "cognitive/memory complaint", etc [34]). As recently highlighted [35,36], the recruitment procedure is an important source of variability amongst studies (see Table 1). SCD has been studied in volunteers from the community [18,22,23,25] or, more rarely from population-based samples [14,26]; in these cases, diverse questions or questionnaires are used to quantify SCD [37]. Other studies have used a different approach, specifically assessing patients recruited from a memory clinic [9–11,13,17,24,38–41], i.e. patients who sought help because of SCD. In the latter case, it could be hypothesized that the active process of seeking medical help is motivated by more important subjective cognitive difficulties and/or associated concern, which might have clinical relevance [42,43]. Previous studies generally reported AD-like brain alterations in clinical SCD individuals compared to community-recruited controls (see Table 1). However, groups are generally not matched on the level of self-reported cognitive difficulties: when documented, clinical SCD patients report more subjective difficulties than controls [11,24]. Then, it is not clear whether the presence of

abnormal AD biomarkers is mainly associated with higher subjective difficulties or with the medical seeking help behavior *per se*. Clarifying this point is crucial to determine if selecting medical help seekers has actual added value to study SCD, and potentially to screen participants in the context of enrichment strategies for clinical trials in clinically normal individuals [3,26,44].

In addition, most studies have shown that SCD is more associated with subclinical anxiety and depression than to actual cognitive performances [9–16,33,45–47]. Interestingly, evidence also suggests that the psychoaffective symptomatology usually increases in early or preclinical stages of cognitive decline [48,49] and/or that it could even constitute a risk factor for subsequent cognitive decline [50,51] (for review and discussion, see [52,53]). Overall, the relationship between SCD and affective factors needs to be further refined, notably as anxiety and depression seem to parallel self-reported cognitive difficulties and could be associated with (and maybe trigger) medical help seeking behavior.

Keeping with the aims of the SCD-Initiative and above-mentioned caveats in the literature, the objective of the present study was to assess the relevance of recruitment setting in selecting SCD individuals to identify those with preclinical AD. For this purpose, we compared SCD patients recruited from a memory clinic (SCDclinic group) to individuals recruited from a pool of community-recruited volunteers who scored high on a self-rating cognitive difficulties scale (SCDcommunity group). We assessed the relevance of this feature with regard to neuropsychological performances, affective measures, and neuroimaging biomarkers (grey matter atrophy and β-amyloid deposition). We hypothesized that SCD individuals who seek help in a memory clinic would be more likely to have indicators of preclinical AD than those recruited from the general community.

# 2. Methods

### 2.1. Participants

A total of 100 cognitively normal individuals were included in the present study. They were all right-handed, aged 54 or older, and included in the multimodal neuroimaging study of early Alzheimer's disease (IMAP+) in Caen, France. Participants were recruited from two main sources (see Figure 1).

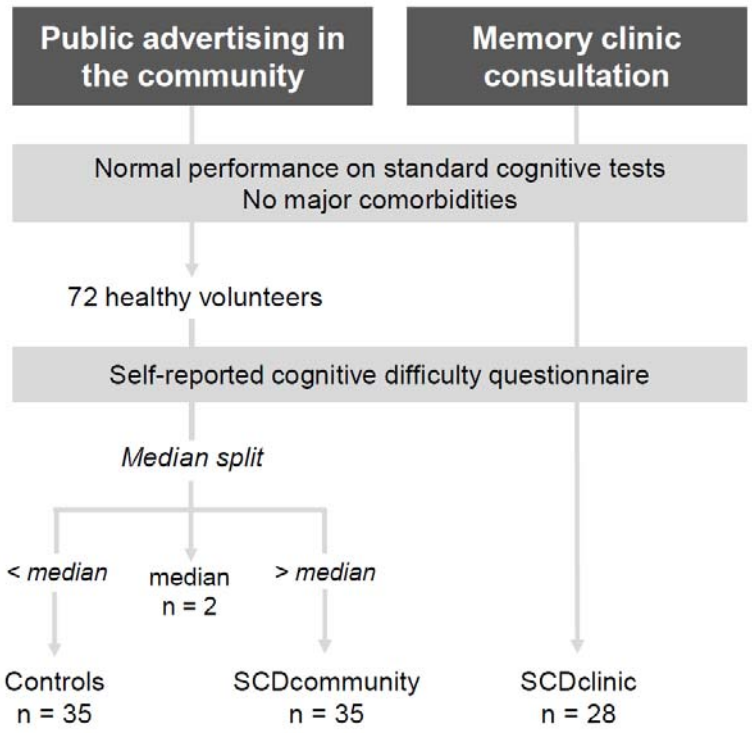


**Figure 1. Flow chart of participant selection and categorization.**

28 patients were recruited from the local memory clinic (SCD-clinic), which they attended because of self-reported cognitive concerns. During the interview, the clinician ensured that the complaint was not related to current medication taking, major psychiatric or neurological conditions (including major depressive disorder or generalized anxiety disorder) or other medical conditions. Patients underwent standardized neuropsychological testing which did not identify any objective cognitive impairment (scores were in the normal range for each neuropsychological test). Patients were then offered to participate to the IMAP+ study to undergo additional cognitive and neuroimaging examinations.

Seventy-two participants were recruited from the community through public advertising, as they volunteered to participate to the IMAP+ study. They had no history of major medical condition, had never consulted a memory clinic, and performed in the normal range on a standardized neuropsychological examination. This group was further divided into two groups depending on their self-reported cognitive difficulties (see 'subjective cognitive scale' below). Using a median-split, 35 individuals with low scores were used as a control group while the 35 individuals with the highest scores were considered as SCD-community; note that two individuals with median values were not included in any group but were still included in the complementary analyses.

All participants were independent in daily life, did not use any psychoactive medication, and gave informed consent to the study. Importantly, none of the participants knew their APOE genotype or Florbetapir status when enrolling in the current study.

### 2.2. Behavioral testing

#### 2.2.1. Self-reported cognitive difficulties

Subjective cognitive decline was assessed with the Cognitive Difficulties Scale [54], a 39-item questionnaire that requires participants to rate on a 5-point scale how often they experience particular cognitive difficulties in everyday life (from “never”=0 to “very often” =4). In the present study, we used the sum of the self-ratings from 26 items as a measure of self-reported cognitive difficulties, higher scores indicating more subjective difficulties. These 26 items were identified in a previous independent study conducted in 1648 cognitively normal elder French individuals [55] using a principal component analysis. The rational for choosing this reduced score, rather than the total 39 item-based score (although they are strongly correlated, r=0.99 [55]) was that it excluded some items that were very rarely endorsed by our participants, not relevant to our main focus, and/or highly gender-biased (e.g. “I need to check or double check whether I locked the door, turned off the stove”; “I misplace my clothing”; “‘I forget steps in recipes I know well and have to look them up”).

#### 2.2.2. Affective measures

Depressive symptomatology and trait-anxiety were assessed using the Montgomery-Asberg depression rating scale (MADRS) and Spielberger state-trait anxiety inventory (STAI), respectively.

#### 2.2.3. Cognitive measures

Participants underwent a comprehensive neuropsychological test battery designed to screen the main cognitive functions including verbal, visual, and autobiographical episodic memory, language abilities, working memory, executive functioning, processing speed, praxis, and visuospatial functioning[56]. To obtain robust proxies of cognitive abilities and minimize the issue of multiple statistical testing when comparing groups, composite scores were created for processing speed, executive functions, language, episodic memory (free recall), and autobiographical memory, considering both people and events (see supplementary material for further detail). For all composite scores, higher values indicate better performances

### 2.3. Brain imaging acquisition and processing

Grey matter volume and β-amyloid deposition were measured in all participants using structural Magnetic Resonnance Imaging (MRI) and Florbetapir-Positron Emission Tomography (PET), obtained on the same 3T-MRI and CT-PET scanners at the Cyceron Centre (Caen, France). For Florbetapir-PET, 6 individuals (4 SCDclinic and 2

SCDcommunity) underwent a 10-min acquisition while the 94 others had a 20-min scan. The data presented in the main manuscript include all 100 participants but results remained highly similar without these 6 individuals (see supplementary material).
The procedures for imaging data handling and transformation are similar to those used in our previous publications[56] and are detailed in the supplementary material. Briefly, MRI data were processed using the Voxel-Based morphometry (VBM5) toolbox while neocortical SUVR values were derived from PET images and used either as a continuous variable or to classify subjects as Florbetapir-positive or negative, using a threshold derived from an independent group of young individuals [56].

### 2.4. Statistical analyses

Group differences on demographic, cognitive, and affective measures were assessed using analysis of variance (ANOVA) for continuous variables with one three-level (group) factor and using Fisher's exact test for categorical variables. When the main effect of group was significant ($p<0.05$), *post hoc* analyses were performed using Fisher's LSD test using the STATISTICA software.
Group differences in grey matter volume were assessed voxelwise using SPM5; between-group differences were considered significant when fulfilling both a $p_{uncorrected} < 0.005$ threshold at the voxel level, and $p<0.05$ threshold at the cluster-level. Mean cortical Florbetapir-PET SUVr and β-amyloid status were compared between groups with one-way ANOVA and Fisher's exact test respectively. All comparisons were repeated covarying for demographic variables, and results remained unchanged (see supplementary material).
Complementary analyses were conducted using the measure of self-reported of cognitive difficulties as a continuous variable, and assessing potential demographical, cognitive, affective, and neuroimaging correlates. These correlations were run separately in participants recruited from the community (n=72, altogether) and from the memory clinic (n=28). This approach was particularly relevant for the community-recruited sample, as dichotomization of continuous variable (as used in the main analyses to split the community-recruited sample into controls and SCDcommunity) can lead to loss of information and inflation of both false positive and false negative findings [57].

# 3. Results

### 3.1. Group characteristics

SCDcommunity were significantly older than the control group (Table 2). The three groups did not differ in terms of sex ratio, education, and APOE4 status. Both SCDclinic and

SCDcommunity reported more cognitive difficulties than the control group, while they did not significantly differ from each other.

### 3.2. Behavioral measures

Out of the 8 measures (Figure 2), only the two affective variables showed significant between-group differences. Both ANOVAs were still significant after applying stringent Bonferroni correction ($\alpha$=0.05/8=0.00625), and when controlling for demographic variables (see supplementary material). Post-hoc comparisons showed distinct patterns of group differences for anxiety and depression. On the one hand, anxiety was associated with higher levels of self-reported cognitive difficulties but not with medical help seeking: both SCD groups had higher STAI scores than the controls but did not differ from one another. On the other hand, increased depressive symptomatology was specifically associated with medical help seeking: only the SCDclinic group differed from the other two. Note that even in the SCDclinic group, values remained subclinical, i.e. in the range of values classically reported in non-depressed healthy individuals [58,59].

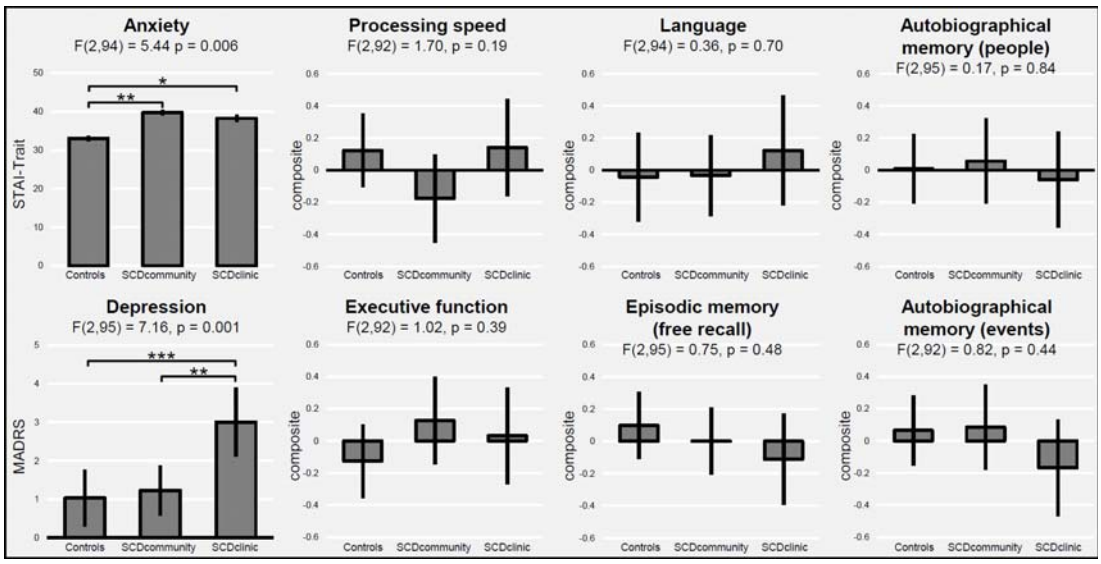


**Figure 2. Group comparison on affective and cognitive scores.**

Graphs indicate mean value and 95% confidence intervals.
F and P values correspond to a one-way ANOVA; post hoc were performed with Fisher's LSD test * p<0.05, **p<0.01, ***p<0.001

Contrastingly, none of the cognitive scores showed significant group difference, whether demographic variables were controlled for or not (supplementary material).

### 3.3. Brain imaging

β-amyloid imaging differed between groups. The proportion of Florbetapir-positive individuals was elevated in both SCD groups compared to Controls (Fig 3A). The similar pattern was observed when Florbetapir-SUVR was treated as a continuous variable (Fig 3B), and results remained unchanged when controlling for demographics (supplementary material).
When comparing the SCDcommunity to the controls, no significant anatomical difference was found. Contrastingly, significantly lower gray matter values were found in the SCD-clinic when compared to the SCD-community, predominantly in the left hippocampus and parahippocampus, bilateral lateral and anterior temporal lobes, bilateral insula and the left parietal cortex (Figure 3.D). There were no differences in the reverse contrasts.

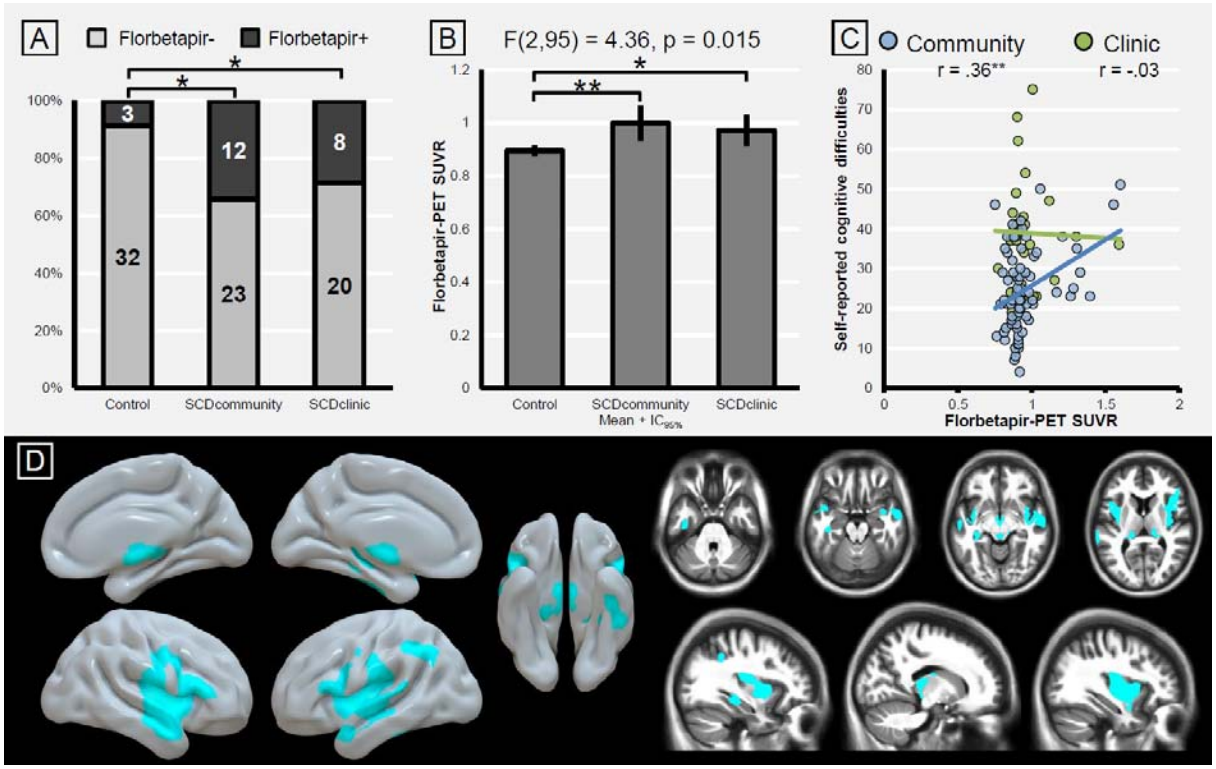


**Figure 3. Neuroimaging results.**

Florbetapir-PET was compared between groups using global neocortical SUVR as a binary (A) or continuous (B) variable (* p<0.05, **p<0.01). Confirmatory analyses (C) showed a significant correlation between Florbetapir SUVR and self-reported cognitive difficulties in the whole community-recruited sample but not in the group of patients recruited in the memory clinic.
Structural MRI was analyzed voxelwise and identified regions of significantly lower volume in SCDclinic as compared to SCDcommunity (D, p<0.005 at the voxel level, p<0.05 at the cluster level).

### 3.4. Complementary analyses.

Within the SCD-clinic group, self-reported cognitive difficulties were not correlated to any demographic, cognitive, affective or neuroimaging measure (all p's>0.05 uncorrected).

In the community-recruited group (n=72), subjective cognitive difficulties were related to age ($r_{(70)}$= 0.34; p=0.003), and anxiety ($r_{(69)}$= 0.49; p<0.001) but no other demographic or cognitive variable (all p's>0.05 uncorrected). Voxel-wise analyses did not identify significant relationships between subjective cognitive difficulties and gray matter volume, while they were related to Florbetapir-SUVR ($r_{(70)}$= 0.36; p=0.002, Figure 3.C). When including all previously-identified predictors in a confirmatory multiple regression model, age, trait-anxiety, and Florbetapir-SUVR independently contributed to subjective cognitive difficulties (see supplementary material for further information).

# 4. Discussion

The present study aimed at further characterizing cognitively normal elders who experience SCD, in line with the idea that SCD could be an early indicator of AD. More specifically, we investigated the differential characteristics associated with two features or potential definitions of SCD to better understand their meaning and relation to preclinical AD: the presence of high self-reported cognitive difficulties and the memory clinic help seeking behavior. Our results suggest that these two aspects have differential affective and neuroimaging correlates: high self-reported cognitive difficulties, independent of recruitment setting, are related to β-amyloid deposition and anxiety while seeking help at a memory clinic is associated with additional subclinical depressive symptomatology and atrophy.

### 4.1. SCD and Amyloid imaging.

Previous studies suggested that SCD was associated with the presence of β-amyloid deposition in elders recruited from the community [18,22,23,25]. However, this effect seems subtle as it was found with some, but not all measures of subjective complaint [23,25]. Moreover, other publications (from the Australian Imaging Biomarkers and Lifestyle cohort) have reported negative results [29,60,61], or found associations only in APOE4 carriers [62,63]. Lastly, data from the population-based Mayo Clinic study of aging indicated that subjective memory concerns predicted β-amyloid PET positivity, especially in young (<80 yo) elders. The present findings reinforce these previous results, showing that, in a community-recruited sample of cognitively normal individuals in their mid-50's to mid-70's, higher self-reported cognitive difficulties were associated with Florbetapir-SUVR.
Contrastingly, only a few papers have assessed β-amyloid imaging in SCDclinic patients; they reported contradicting results showing increased [24] or similar [64,65] PET uptake values compared to community-recruited healthy elders. However, groups were not matched on their level of self-reported cognitive difficulties [24] (or this was not documented [64,65]) so the group differences were potentially driven by this confound factor rather than the help

seeking behavior *per se*. The design of our study enabled us to distinguish the respective influence of these two factors and showed that seeking help at a memory clinic was not associated with higher β-amyloid burden: SCDclinic and SCDcommunity groups had very similar β-amyloid deposition (see figure 3).

These results have important implications for future clinical trials, especially as the field progressively moves toward interventions in preclinical AD [66], and notably in cognitively normal individuals with evidence for β-amyloid deposition [3,67]. Indeed, in order to optimize cost-effectiveness, screening procedures should help identify those individuals with a high likelihood to harbor amyloidosis, therefore minimizing the rate of β-amyloid negative findings and subsequent exclusions. The present study adds to previous data [18,22,23,25,26], indicating that i) selecting individuals with high self-reported cognitive difficulties could help identify β-amyloid-enriched groups and that, ii) selecting patients from a memory clinic does not improve the likelihood of a positive Florbetapir-PET scan compared to their community-recruited counterparts.

### 4.2. SCDclinic versus SCDcommunity: why do patients seek medical help?

Our study also sheds light on why some individuals seek help at a memory clinic as we assessed the idiosyncrasies of these patients compared to community-recruited individuals with similar reports of cognitive difficulties. A few studies [68–72] have assessed factors associated with help seeking behavior, but most were not restricted to elders with formally-assessed normal cognitive performances and, to our knowledge, none of them included neuroimaging biomarkers. Existing literature indicates that medical help seeking can be triggered or facilitated by multiple factors including worry associated with family history of dementia [68,71], low quality of life [68], poor physical health [69], socio-economic barriers (high cost / low access to health care [72]). Help seeking might also be influenced by individuals' knowledge, causal beliefs, and attitudes regarding memory function, aging, and dementia [70–72]. The role of affective factors has been debated as some [69] but not others [68,71] have found higher depression/anxiety symptomatology in SCDclinic compared to SCDcommunity individuals. Similarly, the impact of personality traits like extraversion or neuroticism is unclear [68,69].

Our finding of lower brain volume, and especially in some regions suggestive of AD (medial, anterior, and lateral temporal lobe, parietal cortex [56,73,74]) reveals that the medical help seeking behavior may also have anatomical substrates and could be interpreted as an indicator of participants' awareness of ongoing pathological processes. Interestingly, this preserved awareness might be characteristic of the earliest stages of AD as it strongly contrasts with the anosognosia that can be observed in early dementia [75] and even seems to develop 2-3 years before dementia onset [76]. However, the cross-sectional design of the

present study does not allow to clarify whether these structural brain differences represent life-long features or ongoing neurodegenerative process. Yet, and given the well-known relationships between atrophy in these regions and increased subsequent cognitive decline or AD risk [77–85], our findings support the view that the memory clinic setting is a relevant feature to select SCD individuals with an increased likelihood of developing AD.
Similarly, the slight but significant increased depressive symptomatology observed in the SCDclinic group compared to SCDcommunity, could be consistent with the fact that increased depressive affect is frequently associated with early cognitive deficits [86] or subsequent dementia [49], and could be a prodromal sign of AD [48]. Interestingly, the SCDclinic group showed increases in both anxiety and depression compared to controls. The co-occurrence of these affective symptoms is not uncommon, notably in older individuals [87], and while the relationships between subthreshold anxiety and depression are controversial [88,89], the tripartite model of affective disorders stipulates that they are both manifestations of a more general distress factor characterized by high negative affect [90]. Within this theoretical framework, it is interesting to consider that the between-group increase in neuroimaging biomarker abnormalities (Control<SCDcommunity<SCDclinic) is paralleled by an increment in this general affective burden, reinforcing the idea that psychological distress could be an early sign of AD.

### 4.3. Conclusions, limitations and future directions

As a whole, our results contribute to identify the characteristics of SCD individuals who might be at higher risk of AD, and bring new evidence that, at the group level, elders with SCD but normal neuropsychological examination should not be considered as “worried well”. Investigating the recruitment setting, our study suggests that medical help seeking is an important feature which is specifically associated with increased likelihood of atrophy in AD-sensitive regions as well as higher intensity of depressive symptomatology. This overall increased burden of affective and biomarker abnormalities suggests that SCDclinic, at least at the group level, is probably further along the AD trajectory than SCDcommunity. If so, upcoming longitudinal data should indicate steeper cognitive decline and brain changes in SCDclinic, compared with SCDcommunity.
The strength of this study relies on the comparison of detailed neuropsychology and multimodal neuroimaging data between two groups of individuals with two different aspects of SCD, all assessed on the same MRI and PET scanners. However, it should be noted that patients included in the present study were meticulously selected for having neither major comorbidities nor cognitive deficits, and were recruited from an academic memory clinic, which prevents generalization of our results to all help seeking individuals with SCD. Although group definition was based on a global score derived from a self-rated

questionnaire, complementary approaches could be used to better characterize resulting groups, such as investigating informant reports or performing a qualitative analysis of SCD (e.g. distinguishing self-reports for distinct cognitive domains). In addition, the sample sizes are relatively small: larger studies will be needed to confirm these results. Larger samples would also enable further analysis at the individual level, classifying each individual according to biomarkers of both β-amyloid and neurodegeneration[18,56], as these biomarker-defined stages are associated with differential rates of cognitive decline [91,92]. Lastly, longitudinal studies (including the upcoming follow-up data from the IMAP+ study) will be very important to assess whether the rate of 'objectively measured' cognitive decline and neuroimaging biomarker abnormalities differ between the SCD-clinic, SCD-community, and control groups.

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**Potential conflicts of interest**. Dr Perrotin now works for Piramal Imaging Ltd. However, this study was entirely designed in the Inserm U1077 before her appointment with Piramal Imaging. None of the other authors report any conflict of interest.

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**Table1. Overview of cross-sectional studies assessing associations between SCD and AD neuroimaging biomarkers in cognitively normal elders.**

| Reference | Cohort | Sample of cognitively normals: n (age) | Approach to define/assess SCD | MRI and/or FDG-PET | β-amyloid PET |
|---|---|---|---|---|---|
| **Community-recruited volunteers** | | | | | |
| Rowe 2010 | AIBL# | n=177 (71.6) | 1 binary question | ns | * |
| Chetelat 2010 | AIBL# | n=94 (74.4) | 1 binary question | * | ns |
| Hollands 2012 | AIBL# | n=273 (~69.5) | 1 questionnaire | | ns |
| Zwan 2016 | AIBL# | n=307 (72.7) | 1 binary question | | * |
| Amariglio 2012 | HABS | n=131 (73.5) | 1 composite from 3 questionnaires | | ** |
| Amariglio 2015 | HABS | n=257 (73.7) | 1 composite from 3 questionnaires | ** | ** |
| Schultz 2015 | # | n=261 (54.3) | 1 binary question | ** | |
| Perrotin 2012 | | n=48 (73.5) | 2 questions assessed separately | | * |
| Snitz 2015a | P-ADRC | n=92 (81.2) | 3 questionnaires assessed separately | | * |
| Gardener 2016 | | n=43 (66) | 1 binary question | ns | |
| **SCDclinic versus community-volunteers** | | | | | |
| Van der Flier 2004 | | 28 Cont (75) / 20 SCD (72) | Memory clinic consultation | * | |
| Jessen 2006 | Bonn1 | 14 Cont(66.5) / 12 SCD (66.1) | Memory clinic consultation for <5 year SCD | * | |
| Tepest 2008 | Bonn1 | 13 Cont (67.5) / 13SCD (66.4) | Memory clinic consultation for <5 year SCD | * | |
| Striepens 2010 | Bonn2 | 48 Cont (65.8) / 21 SCD (66.3) | Memory clinic consultation for <10 year SCD, informant confirmed | ** | |
| Scheef 2012 | Bonn2 | 56 Cont (66.4) / 31 SCD (67.6) | Memory clinic consultation for <10 year SCD with worry, informant confirmed | ** | |
| Peter 2014 | Bonn2 | 53 Cont (67.1) / 24 SCD (66.0) | Memory clinic consultation for <10 year SCD with worry, informant confirmed | ** | |
| Erk 2011 | Bonn3 | 20 Cont (66.8) / 19 SCD (68.4) | Memory clinic consultation for <10 year SCD with worry, informant confirmed | ns | |
| Meibert 2015 | Bonn2+3 | 69 Cont (66.1) / 41 SCD (68.9) | Memory clinic consultation for <10 year SCD, (informant confirmed) | * | |
| Rodda 2010 | | 14 Cont (63.9) / 5 SCD (64.2) | Memory clinic consultation | | ns |
| Hafkemeijer 2013 | | 29 Cont (71.3) / 25 SCD (71.4) | Memory clinic consultation | ** | |
| Kiuchi 2014 | | 28 Cont (75.2) / 28 SCD (70.5) | Memory clinic consultation | ns | |
| Ivanoiu 2015 | | 31 Cont (70.0) / 32 SCD (~70) | Memory clinic consultation | * | ns |
| Perrotin 2015 | IMAP+ | 40 Cont (69.4) / 17 SCD (67.1) | Memory clinic consultation + 1 questionnaire[&] | ** | |
| Snitz 2015b | P-ADRC | 84 Cont (73.6) / 14 SCD (68.1) | Memory clinic consultation + 3 questionnaires[&] | | ** |
| Sun 2016 | | 61 Contr (65.5) / 25SCD (64.1) | Memory clinic consultation for < 5 year SCD, informant confirmed | ns | |

**Population-based samples**

| | | | | | |
|---|---|---|---|---|---|
| Stewart 2008 | | n=1779 (72.5) | 2 binary questions (SCD when both positive) | ** | |
| Mielke 2012 | | n=483 (78) | Composite of 5 questions | | ** |
| Cherbuin 2015 | | n=305 (62.6) | 1 binary question | ns | |

**Other**

| | | | | | |
|---|---|---|---|---|---|
| Saykin 2006 | | n=80 (72.2); mixed recruitment (community, clinic…) | Consensus evaluation using a composite index (multiple self and informant based questionnaires) | ** | |
| Mosconi 2008 | | n=28 (59); mixed recruitment (community, clinic…) | Structured informant-corroborated interview | ** | |
| Van Norden 2008 | | n=500 (65.6) ; recruitment of cognitively normals from a neurology clinic (but initial consultation was unrelated to cognition) | Semi-structured interview | ** | |
| Kim 2013 | | 28 Cont (70.7)/ 90 SMD (65.8) ; both groups were recruited in a clinical setting | Reason for seeking help: memory or health promotion? | ** | |
| Cantero 2016 | | n=95 (68.8); mixed recruitment (community, clinic…) | Questionnaire, structured interview | ** | |

**: significant association consistent with SCD as an indicator of preclinical AD (the more SCD, the more amyloid/neurodegeneration)
*: associations are found but seem more subtle/milder:

- Only significant for one but not all tested biomarkers (eg. Avanoiu 2015: effect on FDG-PET but not MRI),
- Only significant in a subgroup (eg. Zwan 2016 and Rowe 2010: relationship between subjective concern and amyloid is only significant in APOE4 carriers)
- Only significant with one but not all SCD measures when several were used (eg Perrotin 2012, Snitz 2015a)
- In regions not classically suggestive of Alzheimer's disease (eg Chételat 2010: atrophy restricted to the bilateral superior frontal sulcus)
- Pattern is suggestive of AD but statistically not significant (eg Tepest 2008: subtle deformations are found the lateral border of the hippocampus)

ns: non-significant association on the imaging modality/region of interest assessed.
The name of the cohort is indicated when several papers are derived from the same cohort and have at least partly overlapping samples.
**AIBL** Australian Imaging Biomarker and Lifestyle Study ; **HABS** Harvard Aging Brain Study ; **IMAP+** Imagerie Multimocale de la maladie d'Alzheimer à un stade Précoce (Multimodal Imaging of early Alzheimer's disease; same as current paper) ; **P-ADRC**: Pittsburg Alzheimer's Disease Research Center ; **Bonn1**, **Bonn2** & **Bonn3**. Three, non-overlapping cohorts recruited in Bonn, Germany. Meiberth 2015 includes data from Bonn2, Bonn3 + additional patients not included in previous papers.

# indicate that cohorts are intentionally enriched in individuals at risk for AD (eg. APOE, Family history)
& for these studies, SCD was solely defined as seeking help at a memory clinic. Additional questionnaires were used to quantify/illustrate the higher self-reported cognitive difficulties in the participants but were not part of the SCD/non SCD classification procedure.

**Table2. Demographics and cognitive scores across groups.**

| | **Controls (n=35)** | **SCDcommunity (n=35)** | **SCDclinic (n=28)** | **tests** | | **pairwise comparison** |
|---|---|---|---|---|---|---|
| Age | 65.6 ± 8.6 | 70.8 ± 7.5 | 67.6 ± 7.7 | F(2, 95)=3.75 | **p = 0.03** | Controls<SCDcommunity** |
| Female: n (%) | 18 (51%) | 21 (60%) | 11 (46%) | Fisher's exact test | p = 0.29 | |
| education | 11.9 ± 3.4 | 12.6 ± 4.2 | 13.3 ± 3.4 | F(2, 95)=1.05 | p = 0.35 | |
| APOE4 carrier: n (% available) | 7 (20%) | 8 (23%) | 4 (17%) | Fisher's exact test | p = 0.95 | |
| CDS (sum of 26 items) | 16.1 ± 4.9 | 33.6 ± 9.5 | 39.0 ± 13.6 | F(2, 95)= 57.51 | **p<0.001** | Controls<SCDcommunity***<br>Controls<SCDclinic*** |
| MMSE | 28.9 ± 1.1 | 28.9 ± 1.0 | 28.8 ± 1.2 | F(2, 95)= 0.11 | p = 0.90 | |
| Mattis | 142.0 ± 2.2 | 141.9 ± 2.8 | 141.7 ± 2.5 | F(2, 95)= 0.2 | p = 0.86 | |

Values indicate mean ± SD or number (percentage).
When the ANOVA reached significance, Fisher's LSD tests were used * p<0.05, **p<0.01, ***p<0.001
CDS: Cognitive Difficulty Scale

# Supplement – Online-only material

## Neuroimaging

### Imaging Data acquisition

MRI data

PET data

### Imaging Data processing

MRI data

PET data

## Neuropsychological scores

## Confirmatory analyses

ANOVA versus ANCOVA

Florbetapir-PET acquisition time

# Neuroimaging

## Acquisition

### MRI data

For each participant, a high-resolution T1-weighted anatomical volume was acquired on a 3-Tesla scanner (Philips Achieva, Eindhoven, The Netherlands) using a 3-dimensional fast field echo sequence (3D-T1-FFE sagittal; TR/TE=20/4.6 ms; flip angle=10; 180 slices; slice thickness=1 mm; field of view=256x256 mm2; matrix=256×256).

### PET data

Florbetapir-PET scans were acquired using a 64-slice Discovery Rx VCT PET-CT scanner (GE Healthcare) with resolution of 3.76x3.76x4.9 mm3 (field of view=157 mm). Forty-seven planes were obtained with a voxel size of 1.95x1.95x3.2 mm3. A transmission scan was performed for attenuation correction before the PET acquisition. Most participants underwent a 20-min PET scan beginning 50 min after the intravenous injection of ≈4 MBq/kg of florbetapir. Note that 4 SCDclinic and 2 SCDcommunity participants only underwent a 10min acquisition starting 50 min after injection.

## Processing

### MRI data

Using the voxel-based morphometry (VBM) 5.1 toolbox implemented in the statistical parametric mapping 5 (SPM5) software (Wellcome Trust Centre for Neuroimaging, London, UK), i) T1-weighted MRI were segmented and spatially normalized to the Montreal Neurological Institute (MNI) space, ii) the normalized grey matter segments were modulated to correct for non-linear warping effects and iii) the resultant images were smoothed using a 12 mm full-width half-maximum (FWHM) Gaussian kernel.

### PET data

Florbetapir-PET data were i) voxel-wise corrected for partial volume effects using T1-weighted MRI and the PMOD software (PMOD Technologies Ltd., Adliswil, Switzerland), ii) coregistered onto the corresponding T1-weighted MRI and spatially normalized using the deformation parameters defined from the VBM procedure performed on the corresponding MRI, iii) quantitatively scaled using the cerebellum grey matter as a reference to obtain standardized uptake value ratio (SUVr) images. A global neocortical Florbetapir SUVr value was obtained in each individual from the Florbetapir-PET SUVr images using a neocortex mask (including all regions but the cerebellum, hippocampus, amygdala and subcortical grey nuclei). These neocortical Florbetapir-PET SUVr values were used both as a continuous variable and to classify subjects as β-amyloid-positive versus negative using a cutoff value based on the SUVr value (mean value plus 2 SD) of young healthy subjects (n=41 between 20 and 39 yo) from the IMAP+ cohort. Using the values derived from our preprocessing pipeline, the resulting threshold value was 0.898 + 2x0.04 = 0.978.

## Neuropsychological scores.

To obtain more robust proxies of cognitive abilities and minimize the issue of multiple statistical testing, composite cognitive scores were used instead of multiple (sub)tests. For that purpose, performances from different tasks that showed neither ceiling nor floor effects were z-transformed and averaged as follows:

- **Processing Speed**
  - time to perform the Trail Making Test (TMT) part A*
  - time to complete the word card from the Stroop test (reading color names presented in black ink)*
  - time to complete the color card from the Stroop test (naming colors presented as rectangles)*
- **Executive function**
  - TMT test (time difference between TMT part B and part A)*
  - Stroop test (time difference between the interference and color cards)*
  - the phonemic verbal fluency (number of words beginning with ‘‘p’’ in 2 min)
- **Language**
  - the semantic verbal fluency (number of animals in 2 min)
  - the number of correct responses in the Mill Hill Vocabulary test
- **Episodic memory (free recalls)**
  - 3 consecutive free recalls + delayed free recall from the Free and Cued Selective Reminding Test
  - Free recall of the BEM (*Batterie d’efficience mentale*) figure
  - 2 free recalls from the *Encoding Storage Retrieval* (ESR) paradigm (two 16-word lists, one being encoded incidentally and superficially, the other after deep and intentional encoding)
  - 2 free recalls from a visual version of the ESR paradigm (based on two lists of nonfigurative graphical signs)
- **Autobiographical memory (people)**
  - 3 scores derived from our autobiographical fluency task. Participants were given three sessions of 2 minutes each to recall the name of people (excluding family members) they met during three time periods: in their twenties [20yo – 30yo], in the last decade (excluding the last year) and last year.
- **Autobiographical memory (events)**
  - 3 scores derived from our autobiographical fluency task. The task was similar to the previous one, except that they were asked to recall memories of specific events from these three time periods. Only episodic memories were considered.

* note that before averaging, z scores derived from reaction times were reversed so that increasing values always indicated better performances

Additional information on the original tests (autobiographical fluency and ESR paradigm) can be found in previous references from our lab:

- Mevel et al, Neurobiology of Aging 2013
- La Joie et al, Neuron 2014
- Tomadesso et al, Neuroimage: Clinical 2015
- Eustache et al, La Revue de Neuropsychologie 2015

# Confirmatory analyses

## ANOVA / ANCOVA

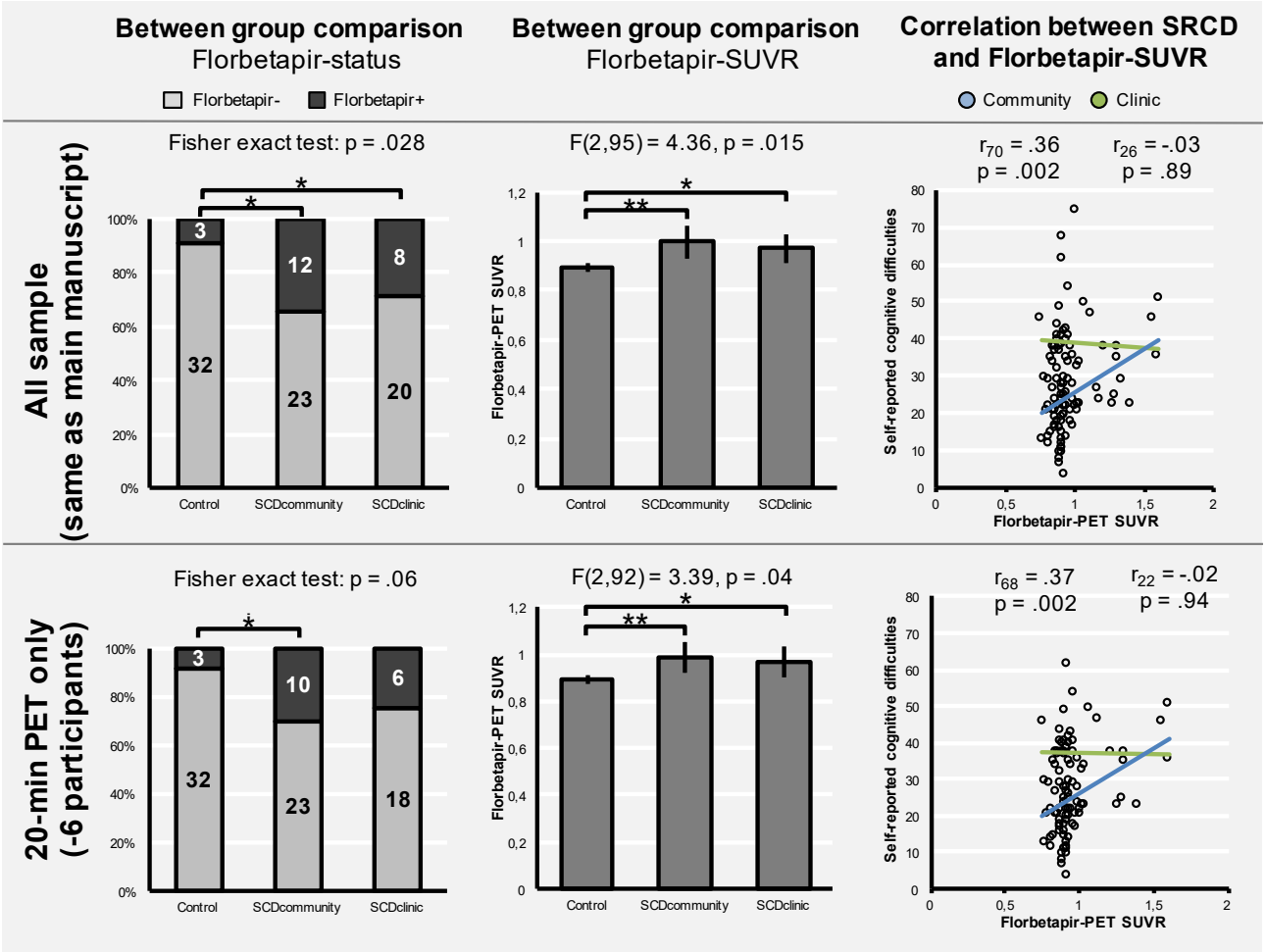
The results presented in the main document show between-group comparisons using Analyses of Variance (ANOVAs).
Because the group slightly differ in age, and because demographic variables are known to influence cognitive scores, the table below shows the group comparison using Analyses of Covariance (ANCOVAs), controlling for age, education and sex. Results remained unchanged.

| | ANOVA (same as main manuscript) | ANCOVA (controlling for age, education and sex) |
|---|---|---|
| Anxiety | **F(2,94) = 5.44 p = 0.006** | **F(2,91) = 5.83 p = 0.004** |
| Depression | **F(2,95) = 7.16, p = 0.001** | **F(2,92) = 7.97, p < 0.001** |
| Processing speed | F(2,92) = 1.70, p = 0.19 | F(2,89) = 1.12, p = 0.33 |
| Executive function | F(2,92) = 1.02, p = 0.39 | F(2,89) = 2.97, p = 0.06 |
| Language | F(2,94) = 0.36, p = 0.70 | F(2,91) = 0.01, p = 0.99 |
| Episodic memory (free recall) | F(2,95) = 0.75, p = 0.48 | F(2,92) = 0.98, p = 0.38 |
| Autobiographical memory (names) | F(2,95) = 0.17, p = 0.84 | F(2,92) = 0.46, p = 0.63 |
| Autobiographical memory (events) | F(2,92) = 0.82, p = 0.44 | F(2,89) = 1.96, p = 0.15 |
| Florbetapir-PET SUVR | **F(2,95) = 4.36, p = 0.015** | **F(2,92) = 3.53, p = 0.03** |

## **Florbetapir-PET acquisition time** (50-70 min post injection and 50-60 min post injection)

As mentioned above, 6 participants only had a 10min Florbetpir-PET acquisition (versus 20 min for the rest of the sample). All the analyses that included Florbetapir-PET are shown below using the full sample (as in the main manuscript) and excluding these 6 individuals.

### **Relationships between Florbetapir-PET and SCD: group comparison**




**Multiple regression model in the community-recruited sample**

- Dependant variable: Self-reported Cognitive Difficulties (sum of the 26 items from the *Cognitive Difficulties Scale*)
- Predictors: Age, Florbetapir-SUVR and STAI-B

Full community-recruited sample: n=72 but 1 missing value for STAI-B

| | **All 71 subjects (same as main manuscript)** F(3,67)=17.9, p<.001, adjusted $R^2$=.420 | | | **Only 69 subjects with 20-min Florbetapir-PET** F(3,65)=18.9, p<.001, adjusted $R^2$=.427 | | |
|---|---|---|---|---|---|---|
| | Unstandardized B | Standardized β | p | Unstandardized B | Standardized β | p |
| Age | .32 | .249 | .01 | .352 | .259 | .008 |
| Florbetapir-SUVR | 19.09 | .300 | .003 | 20.51 | .307 | .002 |
| STAI-B | .53 | .502 | <.001 | .52 | .488 | <.001 |
| (intercept) | -34.9 | - | <.001 | -38.0 | - | <.001 |

→ Overall, all results remained unchanged when excluding these 6 individuals, except when considering Florbetapir status (dichotomising the continuous Florbetapir-SUVR values into a binary category); in that case, the group difference went from a statistically significant difference (p=.03) to a statistical trend (p=.06).