Low Cognitive Awareness, but Not Complaint, is a Good Marker of Preclinical Alzheimer's Disease

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Abstract.
Background: Subjective cognitive decline (SCD) may result from many conditions, including Alzheimer's disease (AD).
Objective: In this study, we searched for a specific pattern of SCD in asymptomatic individuals at risk for AD.
Methods: Cognitively normal older adults ($N = 318$) reporting SCD and their informants were enrolled in the INSIGHT-PreAD cohort. We examined the relationship between six SCD measures and both cognitive scores and AD neuroimaging markers (amyloid burden, hippocampal atrophy and brain hypometabolism). An awareness of cognitive decline index (ACDI) has been introduced based on the subject-informant discrepancy in a questionnaire of SCD and participants with low versus high awareness were compared.
Results: Scores in the INSIGHT-PreAD SCD questionnaires did not correlate with AD neuroimaging markers. As well, no correlation has been found between SCD measures and cognitive scores. Comparing subjects with a low ($n = 19$) and high ($n = 86$) level of awareness, no significant difference in terms of demography, neuropsychiatric symptoms, autonomy, quality of life, cognition, and hippocampal volume was found. However, the "low awareness" group showed greater amyloid burden and lower cortical metabolism, compared to the "high awareness" group.
Conclusion: This study provided additional evidence that reporting SCD by itself is not a specific symptom of preclinical AD. Conversely, a low cognitive awareness (namely, when subjects report fewer difficulties than their relatives do) may represent a very early form of anosognosia and serve as a specific indicator of preclinical AD. This finding is of key importance as an enrichment factor to consider in both clinical practice and research trials.

Keywords: Alzheimer's disease, awareness, biomarkers, cognitive complaints, subjective cognitive decline

INTRODUCTION

Subjective cognitive decline (SCD) [1] is one of the most common reasons bringing elderly individuals to seek medical advice. SCD was proposed to be an early indicator of Alzheimer's disease (AD) [2],

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even if etiologically diverse [3–5]. Indeed, the simple comparison between the frequency of cognitive complaints (51.6% of individuals aged between 70 and 85 years) [6] and the prevalence of AD (2–8% of individuals aged 60 and above) [7] indicates that AD affects only a fraction of individuals complaining about their memory.

The role of relatives of individuals with SCD in confirming or infirming cognitive complaints has also been studied. Informants' ratings seem to better predict the progression to dementia than self-reported complaints [8, 9]. In addition, the discrepancy of judgment between the subject and the informant, both evaluating subject's cognitive abilities, can provide information on his/her awareness of cognitive decline. AD patients generally fail in recognizing their own cognitive changes, exhibiting decreased awareness to actual anosognosia in the more advanced stages [10, 11].

We investigated the interplay between SCD, awareness of cognitive decline, psychological disorders and neuroimaging markers of AD pathology in a large sample of cognitively normal complainers. The aim of the present study was to understand whether the level of cognitive complaints or of cognitive awareness was associated with the presence of *in vivo* evidence of AD pathology [12]. An awareness of cognitive decline index (ACDI) has been introduced resorting to the subject-informant discrepancy method. We hypothesized that the subject's awareness of his/her difficulties might be a good marker of preclinical AD, rather than self-reported complaints.

MATERIALS AND METHODS

Participants

The present research was part of the INSIGHT-PreAD study, conducted by the Institute of memory and Alzheimer's disease, Pitié-Salpêtrière Hospital, Paris (France). Subjects were French individuals between 70 and 85 years, with normal scores on Mini Mental State Examination (MMSE, ≥ 27), Clinical Dementia Rating scale (CDR, $= 0$), and Free and Cued Selective Rating Test (FCSRT, total score ≥ 41) [13], who reported cognitive complaints, defined as follows: subjects answered "YES" to both questions «Are you complaining about your memory?» and «Is it a regular complaint that has lasted now more than 6 months?». In addition, subjects must have no visual/auditory acuity deficit and no evidence of monogenic AD mutation and neurological disorder. One study-partner for each subject also took part in the study. Each participant signed an informed consent and Paris VI ethical committee approved the study protocol.

Measures

Investigations have been conducted on three different days. On the first day, subjects underwent clinical and neuropsychological assessments, as well as questionnaires of SCD. When relevant, subjects' relatives also received questionnaires (see below). The second day included fluorodeoxyglucose (FDG)-PET and MRI, and the third day included the amyloid PET imaging.

Questionnaires of SCD

A large set of questionnaires was administered to comprehensively describe SCD. The Healthy Aging Brain Care Monitor (HABC-M) [14, 15] and a 15-item version of the McNair Frequency of Forgetting Questionnaire (15-item McNair) [16] were performed by both the subject and the informant. Four scales developed by INSIGHT-PreAD investigators were also administered: the INSIGHT Questionnaire of Cognitive Decline (IQCD), the Assessment of Complaints (AC), the Analogic Scale for Complaints (ASC) and the Alzheimer's disease related anxiety questionnaire (AD-NOS). A full description of all SCD questionnaires is given in the Supplementary Material.

Neuropsychiatric symptoms, autonomy, and quality of life measures

Subjects were asked to fill the Anxiety, Dysphoria/Depression, Irritability and Sleep disorders scales from the Neuropsychiatric Inventory (NPI) [17]; the State-Trait Anxiety Inventory (STAI) Y-B form [18]; the Geriatric Depression Scale (GDS) [19]; the Bristol Activities of Daily Living (Bristol ADL) [20], assessing autonomy in everyday life, as judged by the informant; and the EuroQoL 5D Test (EQ-5D-3L) [21], evaluating quality of life.

Cognitive measures

The following cognitive tests were performed: MMSE and CDR, for global assessment of cognitive functioning; FCSRT, Delayed Matching-to-Sample 48 (DMS-48), and Rey-Osterrieth Figure (3-min and 30-min recall) for episodic memory; Digit and Visu-

ospatial span, Frontal Assessment Battery (FAB), Trail Making Test (TMT), and Lexical Fluency (P-words in 2 min) for working memory and executive functions; Semantic Fluency (animals in 2 min) and Rey-Osterrieth Figure (copy) for instrumental functions.

To reduce the risk of Type 1 error, we also computed four composite scores based on published literature and adapted to the INSIGHT-PreAD neuropsychological battery, by averaging and adding standardized scores ("mean to standard deviation" method). The ZAVEN-like [22] composite included scores from the FCSRT (total and delayed free recall), FAB and TMT A and B (number of errors). The ADCS-PACC-like [23] included scores from the FCSRT (total recall), DMS-48 (delayed) and TMT-A (number of errors and time to complete the test). Finally, we adapted the AIBL-EM composite [24] obtaining two different scores: the AIBL-immediate included scores from the FCSRT (free recall), DMS-48 (immediate), and Rey-Osterrieth Figure (3-min delay); the AIBL-delayed included scores on FCSRT (delayed free recall), DMS-48 (1-h delay), and Rey-Osterrieth Figure (30-min delay).

Brain imaging

Amyloid PET imaging was conducted using ^{18}F-AV-45 (^{18}F-florbetapir), considered as a good amyloid-β tracer for AD detection [25]. We computed ^{18}F-florbetapir standardized uptake value (SUV) in target regions (bilateral precuneus, anterior cingulum, posterior cingulum, parietal, temporal and orbitofrontal cortices) [26], following the method developed by the CATI group (Centre d'acquisition et traitement des images, available at cati-neuroimaging.com). ^{18}F-florbetapir SUV was normalized to cerebellum and pons, resulting in a SUV ratio (SUVr). The SUVr positivity threshold was set at 0.79, which was analogous to the threshold found using a method validated by Gael Chételat in the IMAP study [27]. We also examined the presence of hippocampal atrophy and brain hypometabolism, which are topographical AD markers [28, 29]. Hippocampal volume was measured at MRI and normalized to the mean intracranial volume computed across all participants [30]. Metabolic indices were calculated via FDG-PET in 86 neocortical and limbic regions from the revised Automated Anatomical Labelling atlas (AAL2) [31], and in four additional bilateral regions specifically involved in AD (namely, posterior cingulate cortex, inferior parietal lobule, precuneus and inferior temporal gyrus) [32].

Determination of the awareness of cognitive decline index

Beside cognitive complaints, we were also interested in studying differences in awareness within our population of cognitively normal complainers. Thus, we adopted the subject-informant discrepancy method to identify the ACDI. We subtracted the score obtained by the informant from that obtained by the subject in the HABC-M Cognitive scale, proposed as a valid, reliable, and practical tool for assessing cognitive failures of older adults attending primary healthcare services [14, 15]. The ACDI consequently ranged from –18 to 18. To define individuals with low cognitive awareness, we used the percentile distribution of ACDI (Fig. 1): subjects with an ACDI lower than –2 (namely, the 10th percentile) were classified as the "low awareness" group. To define individuals with high levels of awareness, we used the symmetrical cut-off (i.e., 2): subjects with an ACDI >2 were classified as the "high awareness" group. The "concordance" group (namely, subjects with an ACDI between and including –2 and 2) was therefore excluded from the following analyses.

Statistical analysis

SPSS software was used for statistical analyses. Variables are presented as means and standard errors of the means when continuous, and as counts and percentages when categorical. Pearson's correlations were computed to examine the relationship between SCD measures and both AD neuroimaging markers and cognitive scores, as well as between ACDI and cognitive scores, and between AD neuroimaging markers and cognitive scores ($|r| \leq 0.30$ was indicative of a weak correlation, $0.30 < |r| < 0.70$ of a moderate correlation and $|r| \geq 0.70$ of a strong correlation). Between-group ANOVA was used to compare "high" and "low awareness" groups. In addition, univariated ANOVA was performed to compare ACDI of subjects with positive and negative amyloid PET scans. The normality assumption for continuous variables was tested graphically. In case of categorical variables, we used χ^2 test to compare the two groups. We adjusted the results by multiple comparisons using Bonferroni correction, controlling for the effect of age, gender, education, and *APOE* ε4 genotype. Effect size was computed using Cohen's d (small

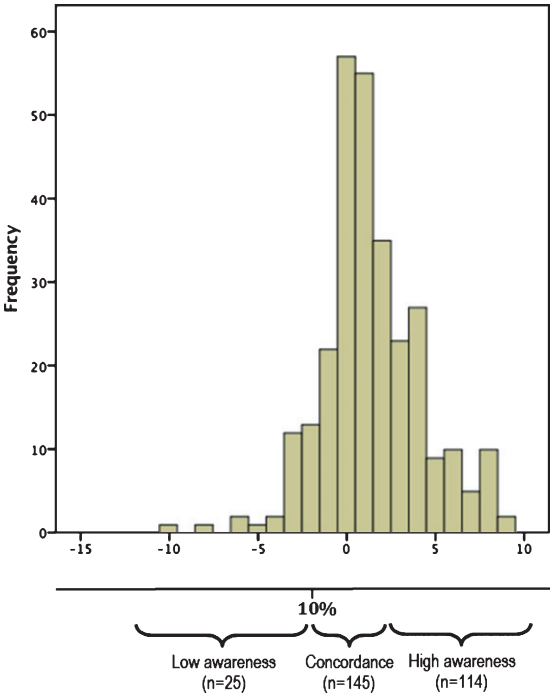

Fig. 1. Percentile distribution of ACDI and method for assigning subjects to groups.

but not trivial ≥ 0.20; medium ≥ 0.50; large ≥ 0.80) and φ (small but not trivial ≥ 0.10; medium ≥ 0.30; large ≥ 0.50). A p-value < 0.05 was considered significant.

RESULTS

A flowchart describing screening and enrolment of study participants, as well as group allocation, is given as Supplementary Figure 1. Three hundred and eighteen subjects took part in the study, and just as many informants. Subjects were aged on average 76.1 years, with a female predominance (63.2%), and the majority (67.6%) had a high level of education (i.e., equal to or higher than high-school diploma). Eighty-eight subjects (27.7%) had a positive amyloid status and 16 (18.6%) were *APOE* ε4 carriers. Informants were aged on average 60.2 years, they were mostly women (68.8%) and highly educated (70.4%). Most of them (81.8%) were close family members and 43.4% lived with the subject.

Pearson's correlations were computed in the whole INSIGHT-PreAD population ($N = 318$). The six SCD measures correlated neither with the presence of neuroimaging markers of AD pathology (all $r < 0.206$), nor with cognitive scores (all $r < 0.180$). As well, cognitive scores correlated neither with the ACDI (all $r > 0.142$), nor with AD neuroimaging markers (all $r < 0.188$). Correlation matrices are given in the Supplementary Material.

No significant difference was found comparing ACDIs in subjects with positive ($M = -1.21$; SEM = 0.34) and negative ($M = -1.53$; SEM = 0.18) amyloid PET ($F_{1,285} = 0.713$; $p = 0.399$). Table 1 describes the characteristics of subjects from the two groups and their relatives. Subjects assigned to the "high awareness" group ($n = 86$) outnumbered those from the "low awareness" group ($n = 19$) by 4.5 to 1. One hundred eighty-two subjects were assigned to the "concordance" group. Subjects with high and low level of awareness were similar with respect to age, gender, education and *APOE* ε4 status (all $p > 0.153$). 47% of subjects with low awareness had positive amyloid PET (versus 24% of subjects with high awareness), the difference being significant, even if the effect size was small ($p = 0.045$; $\varphi = 0.196$). Informants from the two groups were similar in all characteristics considered (all $p > 0.269$).

Subjects from the "high awareness" group obtained higher scores in the majority of SCD questionnaires, compared to the "low awareness" group. In addition, the two groups were similar with respect to all measures of cognitive functioning (all $p > 0.169$). All the other measures of neuropsychiatric symptoms, autonomy, and quality of life were not found to be significantly different (all $p > 0.102$).

The ^{18}F-AV45-SUVr was higher for the "low awareness" group ($p = 0.011$), being on average above the positivity threshold ($M = 0.90$; SEM = 0.06), than for the "high awareness" group, being below the threshold ($M = 0.77$; SEM = 0.02). This difference was still significant after controlling by multiple comparisons using Bonferroni correction and adjusting for age, gender, education and *APOE* ε4 genotype (corrected and adjusted $p = 0.025$). The "low awareness" group showed on average a lower glucose metabolism compared to the "high awareness" group in several AAL2 regions, mainly including frontal but also temporal and parietal areas, with a slight right lateralization (Fig. 2). Furthermore, glucose metabolism was significantly decreased for the "low awareness" group within all AD specific regions considered (all $p < 0.045$). The effect size was found to exceed Cohen's conventions for medium effects in all these analyses. Such differences were still significant after controlling for multiple comparisons and adjusting for age, gender, education and *APOE* ε4 genotype. Normalized hippocampal vol-

Table 1
Characteristics of subjects with high and low cognitive awareness and their informants

	High awareness ($n = 86$)	Low awareness ($n = 19$)	Group comparison				
			df	Error	χ^2 *or F*	*p*	φ or *d*
Subject characteristics							
Age [y; M (SEM)]	76.08 (0.36)	76.11 (0.82)	1	103	0.001	0.978	0.009
Gender [male; n (%)]	30 (34.88)	10 (52.63)	1		2.079	0.149	0.141
Education [high[§]; n (%)]	52 (60.47)	14 (73.68)	1		1.165	0.280	0.105
Amyloid status [positive; n (%)]	21 (24.42)	9 (47.37)	1		4.016	0.045*	0.196
APOE [ε4; n (%)]	18 (20.93)	2 (10.53)	1		1.092	0.296	0.102
Informant characteristics							
Age [y; M (SEM)]	59.91 (1.64)	60.79 (6.42)	1	102	0.053	0.818	0.058
Gender [male; n (%)]	63 (73.26)	12 (63.16)	1		0.928	0.335	0.094
Education [high[§]; n (%)]	57 (66.28)	10 (52.63)	1		0.866	0.352	0.094
Residence [living with the subject; n (%)]	33 (38.37)	10 (52.63)	1		1.221	0.269	0.108
Relationship of informant to subject [n (%)]			1		4.157	0.385	0.200
Spouse or partner	33 (38.37)	11 (57.89)					
Child	26 (30.23)	5 (26.32)					
Sibling	9 (10.47)	0 (0.00)					
Friend	10 (11.63)	1 (5.26)					
Other	7 (8.14)	2 (10.53)					

M, mean; SEM, standard error of the mean. [§]Equal to or higher than high-school diploma. *Statistically significant at $p < 0.05$.

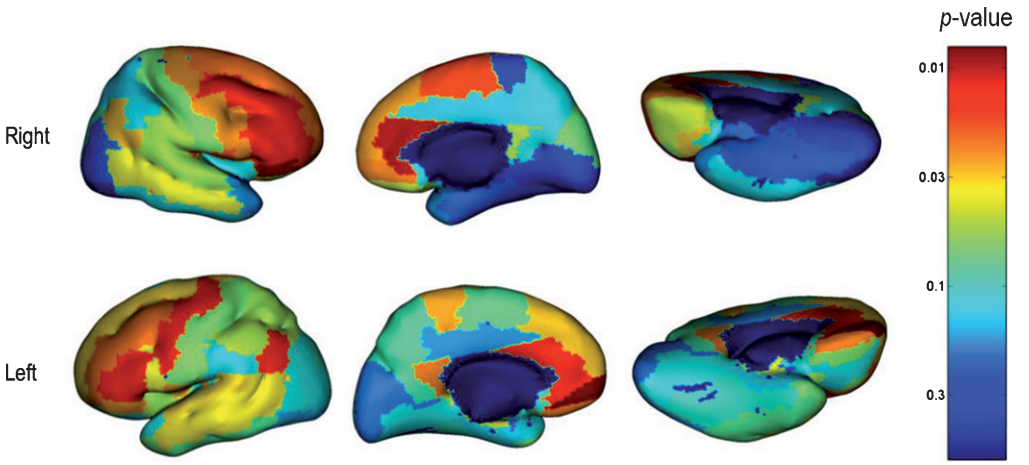

Fig. 2. Difference in brain glucose metabolism assessed by FDG-PET between subjects with high and low awareness. Warmer colors (from yellow to red) indicate significantly lower metabolism in the "low awareness" group, compared to the "high awareness" group. Cooler colors (from blue to green) indicate non-significant differences between the two groups in brain glucose metabolism. *p*-values are corrected by multiple comparisons and adjusted for age, gender, education and *APOE* ε4 status.

ume was not statistically different between the two groups ($p = 0.490$). Table 2 reports test performance and imaging results for the two groups.

DISCUSSION

There is conflicting evidence suggesting that complaints may [1, 2] or may not [3–5] have clinical utility when screening for AD. Such a lack of concordance may be due to diverse biases, including small sample size and variability in how SCD is operationalized. Indeed, multiple approaches are currently used to assess SCD, with no agreed-upon standard [33]. In order to avoid potential methodological biases, we studied a large monocentric cohort, including 318 complainers with normal cognitive performance at testing. All subjects were investigated by the same neuropsychologists and physicians, and using the same imaging machines and parameters. We also performed a very comprehensive evaluation to assess many aspects of SCD (6 questionnaires, with a total of 88 items). This study provided evidence that reporting some degree of complaints by itself is not a specific symptom of preclinical AD and the likelihood of progression to clinical AD does not increase as a function of the intensity of complaints [34]. In our cohort of elderly complainers free of cognitive

Table 2
Test, amyloid PET, and MRI results of subjects with high and low cognitive awareness

	High awareness ($n = 86$)		Low awareness ($n = 19$)		Group comparison				
	Range	*M* (*SEM*)	Range	*M* (*SEM*)	*df*	Error	*F*	*p*	*d*
Subjective Cognitive Decline									
IQCD	1–14	6.34 (0.36)	0–14	4.47 (0.85)	1	103	4.709	0.032*	0.552
AC									
Physical condition	0–8	2.43 (0.24)	0–4	1.11 (0.33)	1	99	5.838	0.018*	0.630
Attention	0–9	3.61 (0.22)	0–9	2.39 (0.59)	1	99	5.000	0.028*	0.578
Memory	0–9	3.95 (0.22)	0–8	2.17 (0.57)	1	99	10.868	0.001*	0.857
Language	0–8	2.96 (0.20)	0–6	2.00 (0.42)	1	99	4.197	0.043*	0.534
Mood	0–8	2.65 (0.25)	0–7	1.67 (0.52)	1	99	2.722	0.102	0.428
Health state	0–10	3.08 (0.25)	0–6	2.33 (0.40)	1	99	1.741	0.190	0.346
Life stress	0–9	3.85 (0.28)	0–8	2.89 (0.66)	1	99	2.022	0.158	0.370
Senses	0–10	3.75 (0.26)	0–7	2.22 (0.52)	1	99	6.387	0.013*	0.658
Total	4–61	26.28 (1.29)	0–48	16.78 (2.89)	1	99	9.110	0.003*	0.791
ASC	0–65	25.44 (2.05)	0–52	13.21 (4.70)	1	103	6.268	0.014*	0.635
McNair	4–37	15.30 (0.68)	2–32	10.61 (1.60)	1	102	8.078	0.005*	0.737
AD-NOS	6–60	27.20 (1.17)	9–37	26.06 (2.32)	1	93	0.165	0.686	0.111
Neuropsychiatric symptoms									
NPI									
Anxiety	0–4	0.17 (0.08)	0–12	0.67 (0.67)	1	100	2.063	0.154	0.372
Dysphoria/depression	0–3	0.07 (0.04)	0–1	0.06 (0.06)	1	100	0.026	0.873	0.026
Irritability	0–1	0.04 (0.02)	0-0	0.00 (0.00)	1	100	0.581	0.448	0.229
Sleep disorders	0–6	0.36 (0.13)	0–4	0.33 (0.24)	1	100	0.006	0.936	0.026
STAI-B	11–61	41.71 (2.10)	30–60	44.67 (8.67)	1	29	0.181	0.673	0.259
GDS	0–11	2.72 (0.53)	0–4	2.67 (1.33)	1	30	0.001	0.973	0.018
Autonomy and quality of life									
Bristol ADL	0–5	0.21 (0.07)	0–2	0.47 (0.19)	1	99	1.901	0.171	0.371
EQ-5D-3L	5–10	6.56 (0.12)	5–7	6.16 (0.18)	1	103	2.383	0.126	0.391
Cognitive functioning									
MMSE	27–30	28.64 (0.10)	28–30	28.53 (0.18)	1	103	0.237	0.627	0.121
FCSRT	41–48	46.00 (0.22)	42–48	46.16 (0.42)	1	103	0.095	0.758	0.079
AIBL Episodic Memory									
Immediate	–4.71–1.24	0.00 (0.08)	–0.81–0.85	–0.04 (0.10)	1	103	0.047	0.829	0.055
Delayed	–1.30–1.21	–0.01 (0.07)	–0.72–0.86	0.05 (0.10)	1	103	0.171	0.680	0.100
ZAVEN-like	–1.40–1.31	0.03 (0.06)	–1.12–1.48	–0.12 (0.14)	1	103	0.976	0.325	0.255
ADCS-PACC-like	–2.89–0.98	–0.06 (0.07)	–0.61–0.59	–0.03 (0.07)	1	103	0.028	0.868	0.047
Amyloid PET imaging									
^{18}F-AV45-SUVr	0.54–1.52	0.77 (0.02)	0.61–1.58	0.90 (0.06)	1	103	6.782	0.011*,¥	0.680
FDG-PET									
Right inferior parietal lobule	1.85–3.53	2.61 (0.03)	2.07–2.87	2.45 (0.05)	1	103	4.131	0.045*,¥	0.521
Left inferior parietal lobule	1.84–3.39	2.49 (0.03)	2.02–2.70	2.32 (0.04)	1	103	5.378	0.045*,¥	0.620
Left posterior cingulate cortex	1.87–3.36	2.48 (0.03)	1.82–2.76	2.31 (0.05)	1	103	4.900	0.029*,¥	0.574
Right posterior cingulate cortex	2.03–3.63	2.57 (0.03)	1.43–2.79	2.37 (0.07)	1	103	6.022	0.016*,¥	0.635
Left precuneus	1.84–3.51	2.55 (0.03)	2.01–2.77	2.40 (0.04)	1	103	4.122	0.022*,¥	0.501
Right precuneus	1.94–3.49	2.60 (0.03)	2.01–2.84	2.45 (0.05)	1	103	4.145	0.044*,¥	0.492
Left inferior temporal gyrus	1.64–2.76	2.17 (0.02)	1.73–2.28	2.05 (0.03)	1	103	5.158	0.025*,¥	0.573
Right inferior temporal gyrus	1.92–3.27	2.37 (0.03)	1.87–2.60	2.24 (0.04)	1	103	4.663	0.033*,¥	0.549
Structural MRI									
Hippocampal volume	2.08–3.30	2.70 (0.03)	2.14–3.42	2.65 (0.07)	1	103	0.479	0.490	0.183

M, mean; SEM, standard error of the mean. *Statistically significant at $p < 0.05$; ¥Still significant after controlling for multiple comparisons (Bonferroni correction) and adjusted for age, gender, education, and *APOE* ε4 genotype.

symptoms, only 88 (about 30%) had evidence of amyloid deposition and may be classified as "asymptomatic at risk" [35]. This proportion was similar to that found in general population (10–30%) [32, 36–39]. In addition, cognitive complaints correlated neither with the presence of neuroimaging markers of AD pathology, nor with cognitive scores, indicating that referring cognitive complaints did not increase the risk of AD. Indeed, cognitive complaints may result from many other conditions: age-related reduction of attentional capacities that makes encoding and recall sub-optimal; anxiety and fear of potentially

developing dementia (nosophobia); psycho-affective disorders [3] including depression, neuroticism [4] and sleep disturbances [5], among other conditions. Reporting cognitive complaints suggests the presence of AD pathology only in a minority of cases, namely when storage failures are present. Indeed, tests controlling encoding and recall in order to specifically assess the stage of storage (e.g., the FCSRT [13]) are widely used as screening tools for AD.

On the other hand, since anosognosia is a major symptom of AD dementia [10], we assumed that being poorly aware of the cognitive failures encountered in everyday life—even if they are not evident at testing - might be a better indicator of preclinical AD than SCD. We tested this hypothesis resorting to the subject-informant discrepancy method to identify the index of cognitive awareness and define and compare two groups (with high and low awareness). Interestingly, subjects poorly aware of their cognitive failures showed on average a greater amyloid burden. 47% of them had evidence of amyloid deposition (versus 24% of subjects highly aware), being more than in general cognitively healthy elderly population (10–30%) [32, 36–39]. This suggests that a low awareness of cognitive decline might better predict an increased risk of AD than SCD by itself. In line with this hypothesis, the "low awareness" group showed a decreased glucose metabolism in several frontal and temporoparietal regions, which are generally involved in both AD and anosognosia [28]. Indeed, temporal dysfunctions may lead to memory deficits, preventing a correct comparison between current and past performance; frontal dysfunctions may determine an inadequate update of self-knowledge; finally, a temporoparietal damage may impair the capacity of judging the own performance assuming a third-person perspective, which is a component of awareness [40]. Given the consensus in considering amyloid burden and brain hypometabolism as markers of AD pathology, we propose that subjects poorly aware of their cognitive failures (judging them as less severe than their relatives do) were at risk of progressing to clinical AD (Fig. 3). There was also a slight difference in terms of hippocampal volume, showing reduced values in the "low awareness" group, which was not statistically significant. Volume loss is another major marker of AD, which is however considered to be detectable later than amyloid burden and functional dysfunction (FDG-PET hypometabolism) [29]. In other words, identifying a low cognitive awareness may represent a very early form of anosognosia and serve as a specific indicator

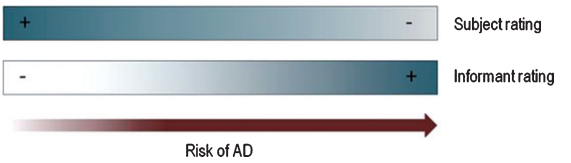

Fig. 3. Risk of AD as function of the subject-informant discrepancy in judging subject's cognitive performance.

of AD pathology, prior to structural brain changes and impaired cognitive scores. Conversely, the condition where the subject judges his/her cognitive functioning as more impaired than his/her relative does may result from diverse etiologies, corresponding to those listed above, such as nosophobia, attentional failures or psycho-affective disorders.

It should be noticed that we also analyzed the demographic characteristics of informants. Little is known about which concomitant factors may affect the informant's perception and judgment. For instance, informants who were women, older, less educated, and with less individual exposure were the most inaccurate [8]. In our study, the two groups of informants were similar regarding the characteristics considered, suggesting that all differences found between participants with high and low awareness were not due to differences in informant ratings accuracy. However, a possible bias in informants' ratings might be present since their anxiety, depression and personality traits were not assessed.

Other potential sources of bias need to be taken into account. First, the prevalence of females and the high mean level of education in both groups of subjects and informants may negatively affect the generalization of our results. Secondly, the size of the two studied groups ("high" and "low awareness") was small, determining a potential low statistical power. Thus, further studies with larger samples and using a longitudinal approach are needed to confirm our findings. In conclusion, taken together our findings suggest that cognitive complaints by themselves might have a limited utility for detecting AD at preclinical stages, due to their high frequency in general population and their aspecificity. Conversely, we found a clear risk of developing AD in subjects who failed in appreciating the severity of their cognitive difficulties. Our findings should be taken into account in both clinical practice and research trials. First, assessing cognitive awareness might represent a practical and valuable screening tool, which should always integrate cognitive tests in clinical assessments. Secondly, subjects with high levels of complaints should not be the pop-

ulation to include in trials targeting preclinical AD. To this end, the ACDI, introduced in this study could prove a valuable tool in the scope of preclinical AD diagnosis.

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