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PERSPECTIVE

Subjective cognitive decline: Memory complaints, cognitive awareness, and metacognition

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Abstract

Cognitive complaints are common in elderly subjects and are a frequent reason for referral to memory clinics. If the complaints are not associated with objective cognitive impairment, the condition is labelled subjective cognitive decline (SCD). SCD is often considered as a stage antedating objective impairment, and an at-risk condition for subsequent dementia. Recent large-scale studies indicate that a significantly increased risk of clinical progression in subjects with SCD is associated with positivity for Alzheimer's disease (AD) biomarkers, a finding supporting the notion that SCD can be due to different mechanisms not associated with neurodegeneration, including functional cognitive disorders. In this paper we present a selective review of research on the relations among SCD, cognitive awareness, and metacognitive abilities. We propose that longitudinal studies of metacognitive efficiency in SCD may provide useful cues about the risk of progression to dementia and the possible presence of a functional cognitive disorder, with different implications for the management of this prevalent aging-related condition.

KEYWORDS
cognitive awareness, memory complaints, metacognition, subjective cognitive decline

Highlights

- Subjective cognitive decline (SCD), a common cause of referral to memory clinics, can be due to multiple conditions.
- The predictive value of SCD for progression to Alzheimer's disease (AD) dementia is high in association with AD biomarker positivity.
- The awareness of cognitive decline is the mechanism responsible for the emergence of SCD and metacognition is the underlying neuropsychological function.
- The awareness of cognitive decline in clinical patients is usually assessed comparing an informant rating to the patient self-assessment, a method that can be affected by informant bias.

- While there is strong evidence that awareness starts to decline with the onset of objective cognitive impairment, progressively leading to the anosognosia of AD, the status of metacognitive efficiency in SCD needs to be further investigated.
- Quantitative, performance-based indexes of metacognitive efficiency may contribute both to the assessment of progression risk and to the management of subjects with functional cognitive disorders.

1 | INTRODUCTION

Increasing clinical interest in the early diagnosis of Alzheimer's disease (AD) has contributed to place under the spotlight the condition of subjective cognitive decline (SCD), an extremely frequent complaint of healthy aging adults. In this paper we discuss, on the basis of a selective literature review, some of the theoretical issues linked to the concept of SCD and its relationship to metacognitive abilities, with possible implications for diagnosis and clinical management.

2 | SUBJECTIVE COGNITIVE DECLINE

In clinical practice, the presence of complaints of cognitive decline is a major driver for individuals to seek medical attention in memory clinics. Cognitive complaints, present in 50% to 80% of the elderly population (> 75 years[1]), are the most common cause of referral and access to memory clinics. The presence and the severity of complaints, however, do not necessarily represent a direct indicator of the objective level of performance,[2] nor of the individual level of awareness. Severe complainers can achieve normal cognitive performance as they underestimate their capabilities,[3] while others with minimal or no complaints may actually overestimate their abilities.[4]

In memory clinics, complainers usually undergo neuropsychological assessment to rule in or out cognitive impairment. Approximately 20% to 30% of subjects seeking evaluation at a memory clinic show preserved objective performance.[5] The condition is labelled SCD.[1] SCD is defined based on complaints of cognitive decline, often of memory, in the face of normal function based on objective testing. If objective performance is impaired, but the subject does not show defective functional abilities of other dementia features, the subject fulfils the National Institute on Aging–Alzheimer's Association (NIA-AA) core clinical criteria for mild cognitive impairment (MCI).[6] The definition of "normal performance" deserves careful consideration. It is often based on cut-off scores, set between 1 and 2 standard deviations (SDs) of the normative group. The NIA-AA criteria[6] indicate that "scores on cognitive tests for individuals with MCI are typically 1 to 1.5 standard deviations below the mean for their age and education matched peers on culturally appropriate normative data" (i.e., for the impaired domain[s], when available) but emphasize that "these ranges are guidelines and not cut-off scores." One of the reasons for this caution in referring to a psychometrically defined "normality" is that it does not consider the subject's baseline performance, which, if known, may serve as a reference to denote the occurrence of a potential decline. The definition of Stage 2 in the NIA-AA numerical clinical staging of the AD continuum,[7] which includes, besides normal performance on objective cognitive tests: the possible presence of "transitional cognitive decline"—that is, a decline in previous level of cognitive function that is of concern to the participant; a change from individual baseline within the past 1 to 3 years; persistence for at least 6 months; and corroboration by informant (not required). Other possibilities are the evidence of subtle decline on longitudinal cognitive testing and subjective report of decline and objective evidence on longitudinal testing. It is also underlined that changes in mood, anxiety, or motivation, of recent onset and not explained by life events, may coexist or even be the primary complaint. The "fuzzy borders" between SCD and MCI are further indicated by the clinical concept of "pre-MCI." Two definitions have been proposed for this "intermediate stage between normal cognition and MCI." According to Storandt et al.[8] pre-MCI diagnosis should rely on decline from a previous level of function, even though current objective performance has not yet fallen below a cut-point for MCI based on group norms. Duara et al.'s[9] " algorithmic" definition is based on a discrepancy between a clinical judgment of MCI and a normal neuropsychological performance. A major consequence of these conflicting definitions is that the same subject can be considered in the SCD or MCI stage depending on the criteria and test used to define a "normal" objective performance, and on the weight assigned to subjective complaints.

While it is recognized that SCD can be due to multiple causes beyond AD, within the dynamic biological model of AD SCD is often considered an intermediate stage between normal cognition and MCI. A series of studies by Edmonds et al.[10,11] are particularly relevant in this regard, indicating that relying on the presence of subjective complaints in subjects with borderline performance on objective tests with different psychometric properties (sensitivity and specificity), may lead to assigning an MCI label to subjects with a low probability of AD biomarker positivity (false positives),[10] as well as to false negative assignments to the SCD group of subjects with evidence of AD biomarker positivity.[11]

While there is epidemiological evidence of an increased risk of progression to MCI and dementia in SCD,[12] many subjects with SCD do not progress to objective decline. The strongest predictor of progression to objective cognitive decline is AD biomarker positivity.[13] The

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed the literature using traditional (e.g., PubMed) sources. Our search focused on key terms including "awareness of cognitive decline," "metacognition," and "memory complaints." While existing literature extensively covers these mechanisms in patients with cognitive impairments, there is a notable gap in data concerning individuals with subjective cognitive decline (SCD).
2. **Interpretation**: Our findings suggest that longitudinal studies investigating metacognitive efficiency in SCD may offer valuable insights into the risk of progression to dementia and the potential presence of functional cognitive disorders. Understanding these mechanisms could have significant implications for the management of SCD patients.
3. **Future directions**: The current paper proposes a framework wherein cognitively unimpaired patients evaluated at memory clinics undergo a metamemory assessment before undergoing a dementia risk assessment. By initiating an initial metamemory screening, individuals at lower risk of developing dementia (i.e., functional cognitive disorders) could be identified. These individuals may benefit more from metacognition training rather than structured prevention interventions. This approach could lead to more tailored and effective interventions for SCD patients.

prevalence of positivity in SCD is extremely variable even among specialized research centers,[14] reflecting the heterogeneous case mix, with inclusion of patients with functional cognitive disorders.

The clinician confronted with an individual fulfilling the criteria for SCD is thus now confronted with a conundrum. The traditional "wait and see" approach leads to the loss of precious time for AD diagnosis, preventing the access to new treatments of patients in the very early phase of disease. Moreover, a biomarker evaluation of all SCD subjects, which has a high predictive value for progression to dementia, represents an organizational, financial, and ethical challenge. Even if the diagnosis of neurodegenerative diseases is expected to change with the future clinical availability of plasma biomarkers, the SCD condition remains in need of a precision medicine approach at the individual level. Jessen et al.[12] proposed that some clinical features of SCD increase the likelihood of progression to dementia. These features define "SCD plus" and include: subjective decline in memory, irrespective of other cognitive domains; a relatively recent SCD onset (in the past 5 years); age of ≥ 60 years; persistence of SCD over time; a high level of concern.[15] The presence of minor neurological signs can also be a risk factor.[16] The way SCD is measured has also been shown to be relevant: asking subjects to compare their performance to their peers (similar age) was associated with worse scores of sensitive memory test than retrospective judgement (comparison to 5 years ago).[17] Recent evidence suggests that the study of metacognition and of its neural mechanisms may provide useful additional insights for the clinical assessment of SCD.

3 | THE NEURAL FOUNDATIONS OF AWARENESS, METACOGNITION, AND METAMEMORY

The first criterion for the current definition of SCD[12] is "a self-experienced persistent decline in cognitive capacity, compared with a previously normal cognitive status, which is unrelated to an acute event." The criteria underline that the focus is on the "state of cognitive decline from the perspective of the individual" ("observation of such a decline by others is not required"), clearly entailing the notion of self-awareness. The dictionary definition of awareness (Merriam Webster) is "knowledge and understanding that something is happening or exists." Self-awareness is then defined as "the capacity of becoming the object of one's own awareness." A rich taxonomy of "dimensions" of self-awareness has been proposed, from interoception to autobiographical memory, associated with different neurobiological mechanisms and thus liable to dysfunction in multiple brain disorders (see Mograbi et al.[18]). Metacognition, that is, the awareness and control of one's own cognition, is the aspect of self-awareness at play in the case of self-experienced cognitive decline. Individual self-awareness is of course not directly accessible, but can be inferred from behavioral observation or, in the case of humans, verbal reports. In the case of SCD, this takes the form of complaints, concerns, and worries, which may be considered emotional reactions to the perception of decline of a cognitive function.

While the status of metacognition, in particular for memory, has been a topic of extensive investigation, its status over the time course of healthy aging and AD is far from being understood. It is worth underlining that other aspects of self-awareness beyond memory may be impaired in AD and may actually be at the forefront of clinical presentation in other causes of dementia (i.e., emotional self-awareness in frontotemporal dementia [FTD]).

The mechanisms responsible for the monitoring of one's own mental processes may be shared among multiple domains (perception, decision making, memory, etc.) or they might be task specific. At the neural level, the shared model predicts global metacognition impairment after brain damage, while the task-specific model is compatible with selective metacognition disorders associated with damage to different domain-specific subsystems. These contrasting views are reconciled by the cognitive awareness model,[19] proposing a distinction between "modular" performance monitoring systems, and a "central" mechanism of cognitive awareness, associated with different neural substrates. This model is supported by neurological evidence. A meta-analysis of imaging studies[20] identified a "common" system for metacognitive performance, involving medial and lateral prefrontal cortex, precuneus, and insula, but also evidence of distinct

neural substrates for visual and memory metacognition. Metacognitive efficiency[21] in visual performance is correlated with volume of frontal polar regions, while variation in memory metacognitive efficiency correlates with the precuneus volume.[22] A lesion study in patients with focal prefrontal and temporal lesions found a selective reduction of metacognitive accuracy after anterior frontal damage, while metamemory accuracy was unimpaired. Both perceptual and memory metacognition were preserved after temporal damage.[23]

There are two additional neurologically relevant distinctions, with important implications for metacognition assessment. The first is between retrospective and prospective judgement of performance, which have been associated, respectively, with dorsolateral and ventromedial prefrontal cortical function.[24] Second, the distinction between local and global metacognitive performance also deserves careful consideration. In our daily life we can estimate our confidence in an isolated decision, but this trial-by-trial assessment is taking place within a background of overall sense of confidence in our abilities. It is this "global" evaluation, rather than each individual instance of performance awareness, that is a core component of our self-knowledge and is responsible for future planning and goal setting in health and disease.[25] Recent imaging evidence of overlapping, but partially different neural substrates, for these two aspects of metacognition in healthy subjects is available.[26] Separate components of the "metacognition network," involving midline frontoparietal regions (dorsal anterior cingulate, ventromedial prefrontal cortex, and precuneus) and anterior prefrontal areas, respond differently to levels of global self-evaluation. Only activity in the cortical areas associated with local confidence-related activity was modulated by the level of global self-evaluation. In contrast, the bilateral ventral striatum tracked only global confidence level, irrespective of the local level.

4 | THE CLINICAL ASSESSMENT OF AWARENESS

Self-awareness is a central aspect of subjective mental experience, and several approaches have been proposed for its assessment in health and disease. The most commonly used are:

1. Clinician rating of anosognosia
2. Questionnaire-based assessment of discrepancies between an informant rating and the patient self-assessment
3. "Performance-based" methods based on the comparison between an objective measurement of performance and a self-estimation of performance

Table S1 in supporting information summarizes the pros and cons of the different approaches. A detailed description can be found in the supporting information. Here we focus only on performance-based methods, which are necessary for an assessment of metamemory abilities. The assessment of metamemory requires a comparison between the subject's actual performance and their judgement, which can be accurate, or may indicate an under- or overestimation of objective performance. Many different methods have been developed to provide quantitative measurements of metacognitive performance.[27,28] One common approach is the assessment of simple correlations between performance and confidence, which, however, can be affected by the actual level of performance and other sources of bias. Recent alternative approaches are based on the measurement of metacognitive sensitivity (meta-d') in the theoretical framework of signal detection theory.[21] A widely used measure is based on the meta-d'/d' ratio, a measure of metacognitive efficiency taking into account the performance level.[27]

5 | AWARENESS OF COGNITIVE DECLINE IN THE AD CONTINUUM

A unique feature of brain diseases is that they affect the same organ that is responsible for subjective awareness, including awareness of cognitive performance. This may lead to a "decoupling" between symptoms and subjective awareness. The fact that brain diseases can result in defective awareness of functional impairment is well known in clinical neurology and is called "anosognosia." The possible occurrence of anosognosia in AD has been reported for many years, on the basis of different definitions and assessment methods.[29] The early studies were devoted to advanced stages of disease, that is, to dementia. The presence of anosognosia was documented mostly on the basis of clinical ratings or comparison between an informant rating and the patient self-assessment, and consistently indicate reduced awareness of cognitive decline (anosognosia) (reviewed in Cacciamani et al.[30]). Several studies used performance-based approaches, allowing an estimation of metamemory functioning. Overall, AD patients are impaired on the monitoring of performance level, showing an overestimation of global performance in memory tests (see reviews in Souchay[31] and Consentino et al.[32]]. An important study,[32] however, reported a wide variation of performance, with the clinically evaluated level of anosognosia showing a relation with the degree of local (item by item) prediction accuracy during an episodic memory test. Another noteworthy finding of this study is that the overconfidence of unaware patients increased during the course of the test, suggesting a deficit in error monitoring as a possible mechanism responsible for the metamemory impairment. The possible presence of sparing of local metamemory judgments, associated with global anosognosia as assessed with the Anosognosia Questionnaire in AD has been confirmed in Gallo et al.[33] It is noteworthy that several studies comparing local metamemory performance in AD and FTD report worse metamemory abilities in the latter condition.[33] Some studies assessed AD dementia patients longitudinally, and generally indicate increasing unawareness of disease progression.[29] Clare and Wilson, using both subjective and performance based measures, showed a wide variability in the amount of decline over a year in a small sample of AD patients.[34]

The status of awareness of cognitive decline (ACD) has also been extensively investigated in MCI subjects by many cross-sectional studies. A meta-analysis[30] concluded for the presence of anosognosia also at prodromal stage, again mostly on the basis of comparison between an informant rating and the patient self-assessment.

Defective performance in the item-specific prediction of performance in a verbal recognition memory test was shown by MCI subjects compared to healthy controls.[35] A subsequent study confirmed this finding, but reported preserved retrospective judgment, indicating the non-unitary nature of performance monitoring mechanisms.[36] Several studies have reported that reduced ACD in MCI is a predictor of progression to dementia (e.g., Spalletta et al.[37]). An interesting observation[38] is that the measured discrepancy is generally due to an increase in caregiver awareness, rather than to a decrease in awareness in the MCI subject. Impaired metamemory (overestimation in item-specific performance prediction) was also found to be a predictor of progression.[39]

ACD level in the relatively recent construct of SCD is controversial. Cross-sectional studies have reported conflicting results on the association between awareness and AD biomarkers in SCD. For example, Verfaillie et al.[15] showed a direct association between amyloid load and worries, rather than severity of cognitive complaints, a finding confirmed in another study.[40] Metamemory has been investigated using pre- and post-prediction of performance accuracy with conflicting results. Both normal accuracy[41] and overestimation of performance[42] have been reported. The accuracy of metamemory performance was associated with a stronger correlation between complaints and objective performance in a memory test (semantic proactive interference) in a sample of SCD subjects.[43]

Several longitudinal studies have suggested that the occurrence of SCD is associated with first signs of cognitive decline as indexed by decreased test performance.[44–46] In contrast, Cacciamani et al.[30] reported a lack of correlation between amyloid load, objective performance, and severity of complaints in SCD individuals. A higher amyloid load was associated with a low level of awareness. Gagliardi et al., using the metamemory score the meta-memory ratio (MMR) scores increased, indicating a complaint without objective decline, with increasing amyloid load, up to a certain threshold, above which the increase in amyloid load was associated with a lower MMR score, indicating a decline in the ACD.[47]

Longitudinal studies of cognitive awareness in the AD continuum are generally based on clinical ratings or self–caregiver judgment comparison. An early study, based on the three large US cohort studies of cognitively intact elderly subjects ($N = 2092$), included a self-assessment of memory function and memory testing on a yearly basis.[48] A total of 239 individuals with no memory or cognitive impairment at baseline had at least four annual assessments, with memory self-ratings and performance, and a diagnosis of dementia before their last evaluation. In this group, a sharp decline of memory awareness was found on average 2.6 years before dementia onset. Neuropathological data were available for 385 individuals with no cognitive impairment at baseline, at least two assessments of residual episodic memory awareness, and *post mortem* data on the seven neuropathologic markers of interest (amyloid, tangles, TAR DNA-binding protein 43 [TDP-43] deposits, hippocampal sclerosis, Lewy bodies, gross-, and microinfarcts). In this group, decline of memory awareness was significantly correlated to TDP-43 and tau pathology, as well as to gross cerebral infarction, suggesting a relevant contribution of non-AD pathology.

A recent study, based on the Alzheimer's Disease Neuroimaging Initiative cohort, included cognitively normal (CN) subjects, MCI, and AD dementia patients, evaluated longitudinally.[49] ACD was assessed on the basis of the discrepancy between self- and partner report. A decline in memory awareness was related to amyloid beta (Aβ) load in all groups, with the strongest effect in dementia patients. In a subgroup of CN subjects progressing to MCI, however, heightened awareness was observed up to 1.6 years before MCI diagnosis, followed by a progressive decline until the time of diagnosis. This decline was due to a faster increase in caregiver awareness, rather than to a decline in the subjects' awareness. Similarly, in a study of AD mutation carriers, increased memory complaints compared to the control group were observed in both carriers and non-carriers, suggesting a non-specific effect. In contrast, only in AD mutation carriers' awareness was increased until the mean age of 35.0 years, with a subsequent decline in the ratio between subject and caregiver assessment at 43 years of age, ≈ 6 years before their estimated median age of dementia onset (49 years).[50] Also in the case, however, the effect is due to a faster increase of caregiver estimation of memory dysfunction, rather than to subjects' underestimation. Overall, these findings suggest that discrepancy estimation, widely used to infer anosognosia, is prone to multiple assessment bias. The longitudinal evolution of awareness in SCD was investigated by Cacciamani et al.[51] estimating the discrepancy between the score on the Healthy Aging Brain Care Monitor of participants and their study partners. This is a questionnaire asking about difficulties in everyday life. The authors observed three trajectories of awareness in SCD individuals: 77% had normal awareness and no changes over time; 19% presented high awareness consistently over time; and 4% showed low awareness, which increased within 6 months after the baseline assessment and afterward declined over time. They also observed that individuals in the low awareness group (4%) had higher amyloid burden, and they were more frequently declining during follow-ups compared to the other two groups, consistently with the known higher risk of AD dementia. It has been proposed that a high level of complaints (sometimes referred to as hypernosognosia), followed by progressive reduction, may be two subsequent stages in the continuum leading to AD dementia.[52] This result is in line with a cross-sectional study of amyloid-positive CN subjects, in which memory awareness, evaluated on the basis of discrepancy between self-assessment and objective performance, was found to be heightened compared to amyloid-negative CN subjects.[53] These findings suggest that the concept of a linear relationship among multiple dimensions involved (cognitive dysfunction, level of awareness, severity of complaints, concerns, worries) may be oversimplified. SCD can be present in aging when cognitive performance is within normal limits, but the comparison to a control group is not always a faithful reflection of the individual level of performance. The assessment of metacognitive sensitivity provides additional information about the status of metacognition. The presence of a metacognitive bias, resulting in performance underestimation or overestimation, may be a useful marker of risk of progression. The presence of preserved metacognitive sensitivity in complainers has been suggested to be an indicator of functional cognitive disorder.[3] On the contrary, a metacognitive bias may thus suggest the presence of an

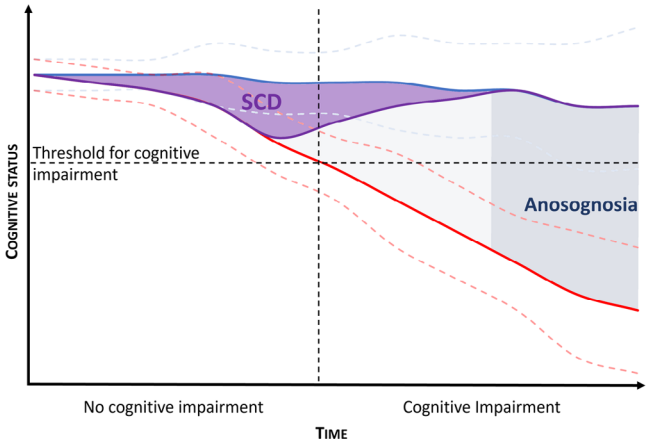

FIGURE 1 Trajectory of objective and subjective cognitive performance. This figure shows the potential dynamic course of normal aging, pathological cognitive changes in the AD continuum, and subjective judgment of cognitive performance. The blue line shows the mean trajectory of normal cognition in aging, while the red line shows the mean trajectory of cognitive decline of a pathological subject; dashed lines indicate the confidence intervals. The distance between the purple line and the red one represents the level of awareness of cognitive decline. AD, Alzheimer's disease; SCD, subjective cognitive decline.

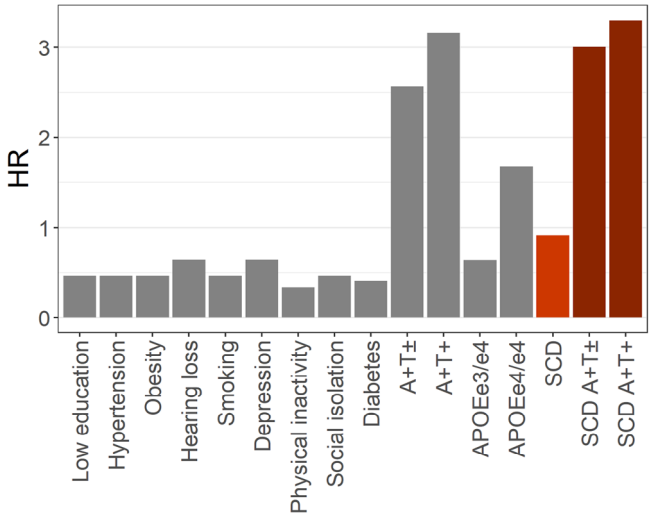

FIGURE 2 Risk factors for dementia and Alzheimer's disease and their corresponding hazard ratio. Modified from Frisoni et al.[70] This figure shows the HR of lifestyle,[71] biological,[72] and genetic[73] risk factors as detailed in the review of Frisoni et al.[70] with the addition of SCD as a risk factor with or without positivity of Alzheimer's disease biomarkers. A, amyloid; *APOE*, apolipoprotein E; HR, hazard ratio; SCD, subjective cognitive decline; T, tau.

at-risk condition. Further studies are needed to support this hypothesis. Whether the presence of increased or decreased confidence in performance represents a useful cue to the risk of progression needs to be established by longitudinal studies.

While there is extensive evidence that subjective perception of cognitive impairment declines together with cognitive performance resulting in increasing anosognosia in the MCI and dementia stages, some studies suggest that in individual cases an incoherent judgment of cognitive performance may start before the onset of objective impairment (Figure 1). This variability may be the consequence of different patterns of cortical involvement,[54] which may be present from the preclinical stages as suggested by imaging studies.[55] At the neural level, the severity of anosognosia in AD dementia is associated with the extent of frontal involvement,[56] and the related severity of executive dysfunction.[57] Prefrontal involvement was correlated both with reduced awareness and performance overestimation in MCI.[37,39] Several studies support a crucial role in self-awareness of midline cerebral structures,[58,59] and for the insula,[54] with a right hemispheric prevalence. An extensive literature relates metacognition and its modifications to connectivity changes in the default mode network.[60]

6 | ACD: IMPLICATIONS FOR DIAGNOSIS AND CLINICAL MANAGEMENT OF SCD PATIENTS

SCD, especially in association with biomarker positivity, is an at-risk condition for cognitive decline (see Figure 2). To offer biomarker assessment to all SCD subjects coming to memory clinics, however, is presently unsustainable in memory clinics.

The identification of early clinical markers of risk of cognitive decline progression in this population thus remains a relevant challenge that researchers in this field face. Therefore, based on the current, although limited, knowledge, some implications for the clinical management of SCD individuals may be considered. Figure 3 provides a possible memory clinic workflow for the SCD population.

The possible contribution of ACD assessment to the identification of individuals at lower risk of developing dementia needs to be further investigated. All individuals with SCD should undergo an in-depth risk profiling for dementia.[61] Cognitively unimpaired patients could benefit from a detailed ACD evaluation. The assessment of ACD is often limited to a questionnaire-based comparison between an informant rating of cognitive (typically memory) performance and the subjects' self-assessment. This measure is useful but is prone to multiple biases. We recommend the introduction in the neuropsychological assessment of an objective measure of performance evaluation. There is no "gold standard" for this form of assessment, an "unmet need" which needs to be addressed in the future. Among the multiple possible formats, the measurement of the "meta-memory ratio"[62] and the meta-d'/d' ratio, a measure of metacognitive efficiency taking into account the performance level,[27] appear to be promising measures. An adequate estimation of cognitive performance (with a focus on metamemory abilities), as well as an underestimation of decline, are indications for a comprehensive evaluation of the risk profile, which may lead to biomarker assessment. Underestimation, in particular, has been considered a possible risk marker for progression,[51,63] likely related to early metacognitive impairment.

The overestimation of cognitive decline may suggest the presence of a functional cognitive disorder. This finding, however, cannot be

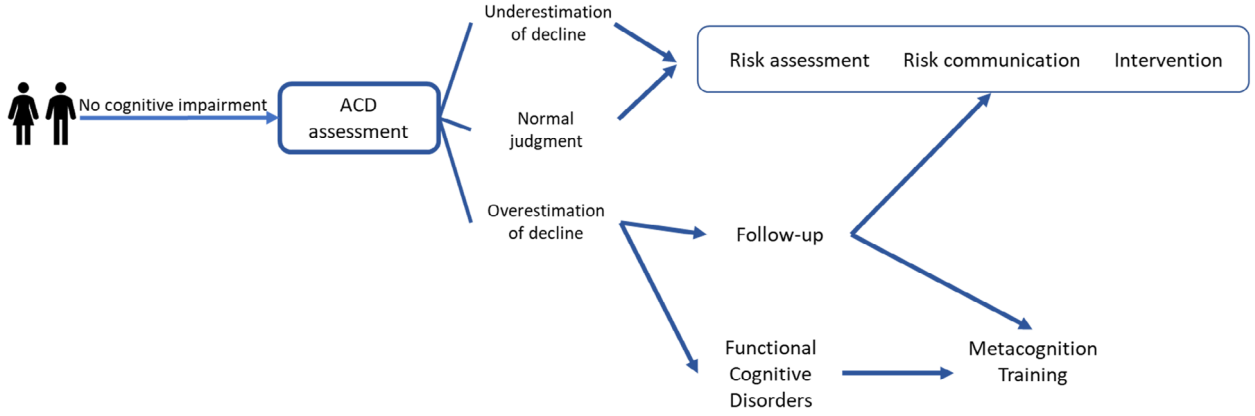

FIGURE 3 Proposed workflow for SCD patients. Modified from Altomare et al.,[74] this figure illustrates a possible memory clinic work-up for SCD individuals. Cognitively unimpaired patients evaluated at memory clinics could benefit from a metamemory assessment before going through a dementia risk assessment, at least before the possible changing clinical scenario associated with the availability of validated blood-based biomarkers. Based on the limited knowledge available, an initial metamemory screening could identify those at lower risk of developing dementia (functional cognitive disorders) that could benefit from a metacognition training instead of risk reduction protocols. However, there may be individuals who overestimate their decline and are at risk of cognitive decline. Therefore, we recommend monitoring these patients to ensure that their judgment and objective cognition remain stable. ACD, awareness of cognitive decline; SCD, subjective cognitive decline.

considered in isolation. Subjective concerns, rather than objective performance, were associated with Aβ load and neurodegeneration in the study by Amariglio et al.[64] A high level of concern has been associated with severity of Aβ load[15] and overestimation of cognitive decline has been reported in amyloid-positive SCD subjects.[53] A comprehensive psychological assessment, to indicate the possible presence of additional cues for a functional disorder, a program of regular follow-up, and the inclusion in cognitive training programs are also indicated in these subjects. There is preliminary evidence that cognitive (or mental) training, using a variety of methodological approaches, has a positive impact on SCD individuals, in particular in the domain of metamemory abilities.[65] In particular, evidence for a beneficial effect is available for repeated practice (such as mindfulness meditation) and for strategic learning (combined with psychoeducation) approaches (see Brioschi Guevara et al.[65] for a meta-analysis). Furthermore, metamemory training shows positive effects on everyday memory performance and related executive functions.[66] Of particular interest, the multi-strategic metamemory training program has recently shown positive effects on cognitive performance of cognitively unimpaired older adults with subjective memory complaints.[67] This approach consists of a psychoeducational program and a multi-strategic training based on the concept of metamemory, including knowledge, monitoring, and judgment processes. An alternative approach, the Everyday Memory and Metacognitive Intervention (EMMI), has also shown promising results.[68] The training program is based on the observation of limited transfer of trained strategies to untrained tasks and contexts and to everyday memory challenges. The intervention is thus focusing on helping people to improve habits of mind in daily life, using simple everyday strategies to manage cognitively demanding tasks. More specifically, the program consists of an individualized assessment of the individual's current approaches to metamemory self-regulation, based on the group training of memory strategies, self-management skills, and new habits of mind, followed by a behavioral shaping period in which individuals receive coaching and feedback on their efforts to use trained procedures to improve everyday cognition. Preliminary results indicate that participants who received a 10 day EMMI training reported more memory successes and fewer memory failures, higher life satisfaction, and better subjective memory than the control group.

These examples of training programs with a focus on metamemory may enhance cognitive control abilities in SCD subjects with a functional cognitive disorder,[69] with a resulting reduction of personal distress.

The proposed workflow should be confirmed by large-scale longitudinal studies but acknowledges the need of an inclusive management of all SCD subjects seeking medical advice for a worrisome, stress-inducing condition with possible negative effects on brain health. While the availability of inexpensive biomarker assessment (e.g., blood based) can be expected to have a major impact, they will not eliminate the need for a careful clinical assessment of SCD. These individuals come to memory clinics with specific complaints, expectations, and hopes, and generic recommendations and reassurance should not be the only alternative to biomarker assessment.

6.1 | Cases report

In the following paragraphs, we present two illustrative cases that align with our perspective and findings from the literature, supporting our proposed approach for future memory clinic workup (see Figure 3).

6.1.1 | Example of a potentially at-risk subject

The patient was referred to the Geneva Memory Center by her general practitioner at the age of 81, reporting with 5 years of insidious and progressively worsening memory issues. These issues had not

significantly impacted her daily functioning. She mentioned increased difficulty in locating objects, forgetting recently learned information, and occasional word-finding difficulties. She referred no signs of anxiety or depression (Hospital Anxiety and Depression Scale, 3/21 and 1/21, respectively) and maintained an active lifestyle involving leisure and physical activities. She had 12 years of education. During the assessment of global cognitive function, she performed well on the Mini-Mental State Examination (MMSE; 27/30), Clock Drawing Test (CDT; 10/10), and Three-Objects-Three-Places Psychological Test (3O3P; 8/9). Specific cognitive function tests for memory, attention, executive function, visuoconstructional abilities, and language all yielded results within normal ranges. To assess the concordance of complaints between the patient and the informant, we used the Cognitive Change Index (CCI). Both the patient and the informant reported the same level of complaints (38 CCI self – 38 CCI informant = 0).

Further investigation using AD biomarkers, including amyloid positron emission tomography (PET), tau PET, and magnetic resonance imaging (MRI), revealed positive results. Subsequently, the patient was enrolled in an observational research study of progression. Upon a follow-up visit 2 years later, the patient demonstrated a decline of 3 points on the MMSE, along with borderline scores in episodic memory tests and impaired executive functions. Notably, both the patient and the informant reported increased severity in complaints; however, the informant's complaints exceeded those of the patient (58 CCI self – 66 CCI informant = −8). This discrepancy suggests a divergence between their perceptions, indicating an underestimation of the patient's self-reported symptoms.

6.1.2 | Example of a functional cognitive disorder subject

The patient was referred to the Geneva Memory Center by his general practitioner at the age of 78 due to self-reported forgetfulness and difficulty concentrating over the past year. Notably, these issues had not significantly affected his daily functioning. He mentioned increased difficulty in remembering appointments, names, words, or following rapid conversations, along with mild orientation problems. Despite maintaining an active lifestyle involving leisure and physical activities, he exhibited clinically significant signs of anxiety and depression, as indicated by scores of 10/21 and 8/21 on the Hospital Anxiety and Depression Scale. In the assessment of global cognitive function, the patient performed well on the MMSE (28/30), CDT (10/10), and the 3O3P (9/9). Specific cognitive function tests for memory, attention, executive function, visuoconstructional abilities, and language all were within normal ranges. Both the patient and the informant reported significant degree of complaints, but the informant's ratings were notably lower (55 CCI self – 38 CCI informant = 17). The patient also underwent a metacognitive task (for further details, see Ribaldi et al.[75]), revealing an underestimation of his memory performance compared to his actual performance.

Further investigation using AD biomarkers, including amyloid PET, tau PET, and MRI, revealed negative results. Subsequently, the patient was enrolled in an observational research study of progression. During a follow-up visit 5 years later, the patient exhibited no decline on the MMSE (29/30) and showed no impairment in specific cognitive functions.

7 | CONCLUSIONS

In conclusion, SCD is a common reason for people to seek help from memory clinics, and the ability to predict the onset of AD is maximally useful in combination with positivity of AD biomarkers. The emergence of SCD is related to the awareness of cognitive decline, which is a metacognitive function. Assessment of ACD is typically done by comparing informant ratings to patient self-assessment, a measure which may be affected by informant bias. Over time, ACD deteriorates progressively in AD, leading to anosognosia in the cognitive impairment and dementia stage. Quantitative, performance-based measures of metacognitive abilities can identify over- or underestimation of true performance, and may provide useful insights into the risk of progression of SCD patients. Overestimation of cognitive decline is common in healthy aging and functional cognitive disorder, while overestimation of objective performance may indicate a higher risk of AD. Overall, understanding the mechanisms underlying SCD and awareness of cognitive decline is critical for accurate diagnosis and patient management in the early and prodromal phases of the disease.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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