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REVIEW

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Biochemical and Neuroimaging Studies in Subjective Cognitive Decline: Progress and Perspectives

Yu Sun,[1] Fu-Chi Yang,[2] Ching-Po Lin[3] & Ying Han[1,4]

1 Department of Neurology, Xuan Wu Hospital of Capital Medical University, Beijing, China
2 Departments of Neurology, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan
3 Brain Connectivity Lab, Institute of Neuroscience, National Yang-Ming University, Taipei, Taiwan
4 Center of Alzheimer's Disease, Beijing Institute for Brain Disorders, Beijing, China

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Correspondence
Dr. Ching-Po Lin, Institute of Neuroscience, National Yang-Ming University, 155, Li-Nong Street 112, Taipei, Taiwan.
Tel.:+886-2-2826-7338;
Fax: +886-2-2826-2285;
E-mail: chingpolin@gmail.com
and
Dr. Ying Han, Department of Neurology, Xuan Wu Hospital of Capital Medical University, 45, Chang-Chun Street, Beijing, China.
Tel.: +13621011941;
Fax: +86-10-83171070;
E-mail: 13621011941@163.com
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SUMMARY

Neurodegeneration due to Alzheimer's disease (AD) can progress over decades before dementia becomes apparent. Indeed, patients with mild cognitive impairment (MCI) already demonstrate significant lesion loads. In most cases, MCI is preceded by subjective cognitive decline (SCD), which is applied to individuals who have self-reported memory-related complaints and has been associated with a higher risk of future cognitive decline and conversion to dementia. Based on the schema of a well-received model of biomarker dynamics in AD pathogenesis, it has been postulated that SCD symptoms may result from compensatory changes in response to β-amyloid accumulation and neurodegeneration. Although SCD is considered a prodromal stage of MCI, it is also a common manifestation in old age, independent of AD, and the predictive value of SCD for AD pathology remains controversial. Here, we provide a review focused on the contributions of cross-sectional and longitudinal analogical studies of biomarkers and neuroimaging evidence in disentangling under what conditions SCD may be attributable to AD pathology. In conclusion, there is promising evidence indicating that clinicians should be able to differentiate pre-AD SCD based on the presence of pathophysiological biomarkers in cerebrospinal fluid (CSF) and neuroimaging. However, this neuroimaging approach is still at an immature stage without an established rubric of standards. A substantial amount of work remains in terms of replicating recent findings and validating the clinical utility of identifying SCD.

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Introduction

Neurodegeneration due to Alzheimer's disease (AD) can progress over decades before dementia becomes apparent. Indeed, patients with mild cognitive impairment (MCI) already demonstrate significant lesion loads [1,2]. MCI refers to an intermediate state between normal aging and dementia that has been used for the early detection of emerging dementia. The National Institute on Aging-Alzheimer's Association has emphasized the relevance of a subtype of MCI known as amnestic mild cognitive impairment (aMCI) in this regard [3]. In terms of clinical presentation, aMCI is characterized by slight memory impairment with relative preservation of other cognitive domains. aMCI is often found to be a prodromal state of AD, presaging subsequent conversion to AD [4,5]. Notably, in a prospective, longitudinal inception study [6], a 10–15% annual conversion rate to AD among subjects with aMCI was observed.

In most cases, MCI is preceded by subjective cognitive decline (SCD). The term SCD, coined in 1982 [7], is applied to individuals who have self-reported memory-related complaints, such as having difficulty with remembering names and recalling where one has placed things, but exhibit a normal range neuropsychological test performance. SCD has been associated with a higher risk of future cognitive decline and conversion to dementia [8]. Based on the schema of a well-received model of biomarker dynamics in AD pathogenesis [9], it has been postulated that SCD symptoms may result from compensatory changes in response to β-amyloid accumulation and neurodegeneration. Accordingly, in 2014, the SCD initiative [10] proposed that SCD be considered stage 3 of preclinical AD, which is described as the stage in which the first

changes in cognition emerge, before MCI can be detected [11]. Furthermore, the SCD Initiative proposed a broad research criteria for pre-MCI SCD, which includes two presentations. First of all, the subjects had to report self-experienced persistent decline in cognitive compared to previous statue and unrelated to an acute event. Secondarily, they have normal age-, gender-, and education-adjusted performance on standardized cognitive tests, which are used to classify MCI [10].

It should be noted, however, that although SCD is considered as a prodromal stage of MCI, it is also a common manifestation in old age, independent of AD [12]. Furthermore, SCD has been associated with depression or personality traits [13,14] as well as numerous other conditions, including psychiatric conditions, neurological and medical disorders, substance abuse, and medication use. Hence, the predictive value of SCD for AD pathology remains controversial. Nevertheless, researchers have begun to examine the specific features of SCD that may distinguish its occurrence in association with preclinical AD. Anatomic, pathologic, and biochemical studies have generated a convergence of evidence supporting the notion that SCD can be the result of the neurodegenerative processes of AD [15–18]; and community-based studies have shown some predictive value of SCD for cognitive decline and dementia [12,19]. However, this controversial association is further complicated by the fact that different research groups have used different strategies and terminologies (e.g., subjective memory complaints, subjective memory impairment, and subjective cognitive impairment), making it difficult to compare results across studies directly. Here, we provide a review focused on the contributions of cross-sectional and longitudinal analogical studies of biomarkers and neuroimaging evidence in disentangling under what conditions SCD may be attributable to AD pathology.

Biochemical Biomarkers

Because SCD is not a simple symptom, it alone may never be sufficient to diagnose preclinical AD. Thus, to improve recognition of AD conversion, there is a need for reliable biomarkers of AD beyond the presence of SCD. A number of studies, reviewed below, have reported the presence of biomarkers in patients with SCD that resemble those found in patients with aMCI and AD, supporting the view that it may be possible to recognize AD earlier, even before aMCI can be detected.

Several protein biomarkers in cerebrospinal fluid (CSF) have been shown to provide good diagnostic accuracy and prediction of conversion from MCI to AD pathology, including amyloid-β42 (Aβ42), total tau (t-tau), and phosphorylated tau (p-tau) [20,21]. Patients with AD differ from those healthy controls in that they tend to show an early decrease in CSF levels of Aβ42, followed by later increases in CSF levels of t-tau and p-tau [15]. However, these CSF biomarkers did not differ between subjects with SCD and healthy controls, but it is possible that this negative finding was due to insignificant statistical power. In a larger study, Visser et al. [22] investigated the prevalence of AD-predicting CSF profile and cognitive evolution in three groups of patients: SCD, aMCI, and nonamnestic MCI. They found that the CSF profiles of patients in all three groups who showed subsequent cognitive decline were consistent with the AD-predicting profiles, with these profiles are more common in these groups than in healthy controls (i.e., low $A\beta_{42}$ and high tau levels). These findings suggest that patients with SCD might be in the early stages of AD, although clinically detectable cognitive decline might not become apparent for many years. Interestingly, Rolstad et al. [23] reported that CSF levels of Aβ42 could be used to predict semantic memory test performance in both an MCI group and a control group, whereas tau levels reflected the performance of individuals in the MCI group. Meanwhile, in a group of patients with MCI, Rami et al. [24] found a positive correlation between Aβ42 levels and memory performance, but an inverse correlation between tau levels and memory performance. These findings again suggest that Aβ42 decline may be linked to early cognitive changes, whereas tau-related changes may reflect an intermediate stage of AD pathology. Together, the above-reviewed studies suggest that, in the continuum from healthy aging to AD dementia, memory performance is first related to Aβ42 levels and then related to t-tau and/or p-tau levels, before becoming independent of CSF biomarker levels after dementia has set in.

Structural Neuroimaging

Structural MRI

Medial temporal atrophy had been thought to be the most prominent prodromal MRI marker of progression toward AD, and hippocampal atrophy is the most consistent [25]. According to the study by Villemagne et al. [2], there may be a prolonged preclinical phase of AD in which β-amyloid deposition, hippocampal atrophy, and behavioral memory impairment can be detected 17.0 years, 4.2 years, and 3.3 years before the onset of dementia (clinical dementia rating score 1), respectively.

Evidence is accumulating in relation to the associations between SCD and structural brain changes (Table 1). Using magnetic resonance imaging (MRI), van der Flier et al. [26] found that SCD patients had a lesser left hippocampal volume than healthy controls. In a subsequent MRI study, volumetric reductions were found in SCD patients that were analogous to changes observed in patients with aMCI, including reductions in medial temporal and frontotemporal regions [27]. Moreover, they found that the degree of atrophy observed was related to the magnitude of the patients' self-reported cognitive complaints. In a longitudinal study of SCD patients, Scheef et al. [28] found a trend toward an association between a smaller right hippocampal gray matter volume and subsequent cognitive decline. Recently, Cherbuin et al. [29] found that SCD at follow-up, but not at baseline, was associated with longitudinal hippocampal atrophy over 4 years, suggesting that SCD tends to follow rather than precede cerebral changes. Moreover, Peter et al. [30] found that the gray matter volumetric pattern observed in subjects with SCD often resembled that in patients with AD more than that in healthy control subjects, and that resemblance of the AD-like pattern in subjects with SCD was predictive of episodic memory decline. Stewart et al. [31] also noticed that the presence of hippocampal and gray matter atrophy and white matter lesions was predictive of SCD (including SCD with MCI) 4 years later.

Table 1 Overview of structural neuroimaging studies in SCD

Study	Methods	Subjects	Subjects numbers (Male)	Main results
van der Flier et al. 2004 [26]	sMRI	SCD NC	20 28	1. SCD has smaller left hippocampal volumes than controls 2. The reduced volume of left hippocampus in SCD had a moderate association with memory score
Saykin et al. 2006 [27]	sMRI	SCD aMCI NC	40 40 40	1. SCD and aMCI showed similar patterns of decreased GM relative to the NC on whole-brain analysis 2. The degree of GM loss was associated with extent of both subjective and objective memory deficits
Stewart et al. 2011 [31]	sMRI 4-year follow-up	SCD NC	Total 1336	1. There was a significant association between baseline SCD and subsequent hippocampal volume change 2. Associations between SCD and prior CSF or hippocampal volume changes were stronger for new-onset SCD over the follow-up period
Striepens et al. 2011 [32]	sMRI	SCD NC	21 47	1. APOE ε4 carriers with SCD performed worse on the episodic memory and showed smaller left hippocampal volumes 2. The interaction of SCD and APOE genotype was significant for episodic memory and right and left hippocampal
Scheef et al. 2012 [28]	sMRI FDG-PET	SCD NC	31 56	1. SCD showed hypometabolism in the right precuneus and hypermetabolism in the right medial temporal lobe 2. SCD showed reduced GM volume in the right hippocampus
Cherbuin et al. 2014 [29]	sMRI 4-year follow-up	SCD NC	Total 305	1. SCD at follow-up was associated with longitudinal hippocampal atrophy 2. SCD tends to follow rather than precede cerebral changes
Peter et al. 2014 [30]	SVM 4-year follow-up	SCD NC	24 53	1. Individuals with SCD showed greater similarity to an AD GM pattern compared with control
Lamar et al. 2011 [37]	MRI-LA	SCD aMCI NC	12 20 11	1. SCD showed a steeper learning slope compared to NC and aMCI 2. White matter burden contributed to SCD performance variance in learning slope only
Bartley et al. 2011 [38]	PVH/DWMH	SCD NC	30 30	1. SCD was not significantly associated with the severity of WMH in either the periventricular or deep white matter areas
Selnes et al. 2012 [33]	sMRI/DTI	SCD MCI NC	16 (11) 50 (24) 21 (16)	1. WM tracts underlying the posterior cingulate, retrosplenial, and middle temporal cortices had higher DR and MD in SCD compared to NC
Wang et al. 2012 [34]	DTI	SCD MCI NC	29 28 35	1. SCD demonstrated intermediate changes of all diffusivity measures, with values falling between those of the MCI and NC except FA of left parahippocampal
Wang et al. 2013 [35]	DTI	SCD MCI NC	22 28 19	1. SCD demonstrated significantly higher nodal efficiency than the NC and MCI in the parahippocampal region 2. The significant differences were found for the values of degree, strength, and nodal efficiency (NC>SCC>MCI)
Selnes et al. 2013 [36]	CSF/DTI/ sMRI	SCD MCI NC	11 (9) 43 (20) 21 (9)	1. DTI indices FA, DR, and MD predict cognitive decline and medial temporal lobe atrophy

sMRI, structural magnetic resonance imaging; SCD, subjective cognitive decline; NC, normal control; aMCI, amnestic mild cognitive impairment; GM, gray matter; CSF, cerebrospinal fluid; FDG-PET, [18F]fluorodeoxyglucose positron emission tomography; AD, Alzheimer's disease; WM, white matter; SVM, support vector machine; MRI-LA, diffuse leukoaraiosis on MRI; PVH/DWMH, periventricular hyperintensities/deep white matter hyperintensities; DTI, diffusion tensor imaging; DR, radial diffusivity; FA, fractional anisotropy; MD, mean diffusivity.

These longitudinal study results are consistent with the view that SCD may represent a pre-MCI stage of compromise, at least in some individuals. Furthermore, these studies underscore the utility of employing multivariate pattern recognition approaches to identify subtle brain changes over time.

Recent evidence taking *APOE* genotype into account has supported the notion that SCD may be a harbinger of AD pathology. Striepens et al. [32] compared episodic memory performance and volumes of medial temporal lobe structures between subjects with and without SCD, subdivided by *APOE*

genotype. They found that among subjects with SCD, the *APOE ε4* allele carriers performed worse on an episodic memory test and had smaller left hippocampal volumes than noncarriers. Meanwhile, among subjects without SCD, *APOE ε4* allele carriers had better episodic memory and larger right hippocampal volumes than noncarriers. There was a significant interaction between self-reported SCD and *APOE* genotype for episodic memory and right and left hippocampal volumes. These findings support the notion that *APOE ε4* is a risk factor for AD that otherwise, in the absence of AD pathogenesis. Moreover, the interaction between SCD and *APOE* genotype is consistent with the hypothesis that SCD may be a precondition of AD and suggests that the co-occurrence of SCD with the *APOE ε4* allele may be an indicator of AD risk.

Diffusion MRI

Recently, several research groups have begun to investigate SCD-associated white matter changes using diffusion MRI analyses. Selnes et al. [33] observed prominent white matter tract degeneration in patients with SCD and MCI that was at least partly independent of adjacent gray matter atrophy. Similar findings were presented by Wang et al. [34], which showed the degree of white matter tract degeneration in bilateral parahippocampal in SCD was intermediate to the MCI and healthy controls groups. Furthermore, to evaluate the connectome patterns in SCD and MCI, Wang et al. found significant group differences in degree, strength, and nodal efficiency as well as differences in precuneus, orbitofrontal, and middle frontal cortex path lengths. The SCD group demonstrated higher nodal efficiency as compared to healthy control and MCI groups in the parahippocampal region [35]. The authors postulated that the changes observed in the SCD group relative to controls, particularly the enhanced nodal efficiency, could reflect a compensatory mechanism [35]. Selnes et al. [36] found that diffusion MRI findings could be combined with CSF biomarker results to predict future cognitive change and medial temporal lobe atrophy. Lamar et al. [37] found that a greater leukoaraiosis load (i.e., more white matter hyperintensities in MRI assumed to be due to small vessel disease) was associated with poorer learning in individuals with SCD. However, when Bartley et al. [38] conducted a cross-sectional study investigating whether SCD was associated with white matter changes, they found no evidence of an association. Thus, it remains to be clarified whether, and if so to what extent, white matter changes contribute to SCD.

In summary, there is a convergence of structural neuroimaging findings that support the view of a progression from SCD to MCI in the evolution of neurodegeneration leading to clinical AD.

Functional Neuroimaging

Findings from functional neuroimaging studies of SCD have complemented the findings of structural neuroimaging findings. Noteworthy contributions of evidence with regard to fluoro-2-deoxyglucose (FDG)-position emission tomography (PET), functional MRI (fMRI), and Pittsburgh Compound B (PiB)-PET are summarized below (Table 2).

FDG-PET

Using [18F]fluorodeoxyglucose positron emission tomography (FDG-PET), Mosconi et al. [39] found that subjects with SCD had lower metabolic rates for glucose bilaterally in the parahippocampal gyrus and middle temporal gyrus, as well as lower rates in the left inferior parietal lobe, inferior frontal gyrus, fusiform gyrus, and thalamus, and in the right putamen. The greatest SCD-associated reduction (18%) was observed in the parahippocampal gyrus. In an FDG-PET follow-up study comparing an SCD group to a healthy control group, Scheef et al. [28] found that the SCD group, at baseline, already showed hypometabolism in the right precuneus and hypermetabolism in the right medial temporal lobe relative to the control group. Moreover, reduced glucose metabolism in the right precuneus of SCD subjects at baseline was associated with subsequent declines in episodic memory performance, supporting the concept that SCD may be the earliest manifestation of AD.

Reduced neural metabolism, as evidenced by FDG-PET, has also been observed in subjects with SCD relative to controls in parahippocampal parieto-temporal regions, the frontal inferior twist spindle, and thalamus of SCD subjects [40]. Interestingly, these findings replicate the pattern found in healthy subjects with a genetic risk of AD (family history or *APOE ε4* homozygote) and in patients with MCI [40].

PiB-PET

The development of PiB-PET represents a potential breakthrough technology for AD research. Postmortem amyloid plaque histology has been the gold standard of AD diagnoses. However, the discovery of PiB as an *in vivo* amyloid tracer shows great promise of providing a more definitive AD diagnostic tool in living patients. Chetelat et al. [41] found that β-amyloid deposition evidenced via PiB-PET correlated with local brain atrophy in subjects with SCD but not in healthy controls. Interestingly, Perrotin et al. [42] observed increased amyloid deposition, demonstrated by PiB-PET, in right prefrontal regions, the anterior cingulate cortex, right precuneus, and cingulate cortex of healthy cognitively normal elderly subjects with SCD (i.e., reduced memory confidence) relative to that observed in controls. The authors concluded that the subjects' reduced confidence might be related to the observed amyloid deposition, the neuropathological hallmark of AD.

fMRI

Researchers have used fMRI to examine the relationships between SCD, cognitive task performance, and concurrent brain activity. In a small study (N = 10 per group), Rodda et al. [43] found that although subjects with SCD performed as well as healthy controls on an encoding task, they exhibited more activation in the dorsolateral prefrontal cortex than the controls (see Figure 1). In a subsequent study, they observed increased activation in the bilateral thalamus, caudate, and posterior cingulate and the left hippocampus and parahippocampal gyrus, relative to controls, in subjects with SCD performing a divided attention conditions task (see Figure 2) [44]. As in their previous study, task performance did not differ between the SCD and control groups.

Table 2 Overview of functional neuroimaging studies in SCD

Study	Methods	Subjects	Subjects numbers (male)	Main results
Mosconi et al. 2008 [39]	FDG-PET/CSF	SCD NC	13 15	1. SCD showed reduced CMRglc in PHG and parieto-temporal 2. SCD with the APOE ε4 (+) showing the lowest CMRglc in PHG as compared with all other groups
Chetalat et al. 2010 [41]	PiB-PET/sMRI	SCD MCI AD NC	49 (25) 34 (17) 35 (20) 45 (25)	1. Global and regional gray matter atrophy were strongly related to Aβ load in SCD but not MCI or AD 2. Global neocortical Aβ deposition correlated with atrophy in hippocampus, medial frontal and parietal areas, and lateral temporo-parietal cortex
Perrotin et al. 2012 [42]	PiB-PET	SCD	48	1. SCD with high PiB uptake showed significantly lower performance than those with low PiB uptake on an episodic memory measure 2. SCD was significantly correlated with regional PiB uptake in the right MPFC and ACC and in the right precuneus and PCC
Rodda et al. 2009 [43]	Task-related fMRI	SCD NC	10 10	1. SCD showed increased activation in left PFC during encoding task, where activation strength correlated with memory task performance 2. SCD demonstrated extended activation in the MPFC and left medial temporal and occipitoparietal
Rodda et al. 2011 [44]	Task-related fMRI	SCD NC	11 10	1. SCD demonstrated increased activation in left medial temporal lobe, bilateral thalamus, and posterior cingulate and caudate in divided attention task
Erk et al. 2011 [45]	Task-related fMRI	SCD NC	19 20	1. SCD was associated with a reduction in right hippocampal activation during episodic memory recall in the absence of performance deficits 2. There may be a compensation by increased activation of the right dorsolateral PFC
Wang et al. 2013 [46]	Resting-state fMRI	SCD MCI NC	23 18 16	1. Both SCD and MCI showed decreased DMN connectivity in the right hippocampus compared to controls, as well as SCD showing greater connectivity than MCI
Wang et al. 2013 [47]	ASL	SCD MCI NC	15 15 16	1. SCD showed increased rCBF in PCC compared with NC

CSF, cerebrospinal fluid; FDG-PET, [18F]fluorodeoxyglucose positron emission tomography; PiB-PET, Pittsburgh Compound B-PET; CMRglc, cerebral metabolic rate for glucose consumption; sMRI, structural magnetic resonance imaging; fMRI, functional magnetic resonance imaging; ASL, arterial spin labeling; SCD, subjective cognitive decline; NC, normal control; MCI, mild cognitive impairment; AD, Alzheimer's disease; PHG, parahippocampal gyrus; Aβ, β-amyloid; MPFC, medial prefrontal cortex; PFC, prefrontal cortex; ACC, anterior cingulate cortex; PCC, posterior cingulate cortex; DMN, default mode network; rCBF, regional cerebral blood flow.

However, other researchers have reported more nuanced changes with regard to activation in subjects with SCD. For example, employing an associative face-profession episodic memory task (encoding, recall, and recognition components) and a working memory task, Erk et al. [45] found reduction in right hippocampal activation accompanied but increased activation of the right dorsolateral prefrontal cortex in patients with SCD relative to controls, although, as in the aforementioned studies, no task performance differences were detected between the groups. Locally increased activation in individuals with SCD, but with no clinically detectable performance deficits, might reflect a form of compensation, similar to what occurs in patients with MCI. In particular, SCD may involve functional alterations in hippocampal integrity that reflect early neuronal dysfunction together with compensatory mechanisms that preserve memory performance.

In a recent series of neuroimaging studies, Wang et al. [46] observed reduced regional cerebral blood flow (rCBF) in bilateral temporal regions of patients with MCI, but increased rCBF along midline default mode network (DMN) regions, including the posterior cingulate cortex, in patients with SCD, compared to normal controls. The results suggest a nonlinear relationship between rCBF changes and disease progression in preclinical AD. While hypoperfusion in MCI is consistent with the hypometabolism observed in FDG-PET, the increased rCBF in the SCD group may also reflect compensatory responses to neurodegeneration in preclinical stages that could have pathophysiological implications.

Wang et al. [47] examined SCD-related changes in the resting-state brain activity of subjects with SCD relative to healthy controls and patients with MCI. The SCD group showed more DMN connectivity in the right hippocampus and precuneus than the

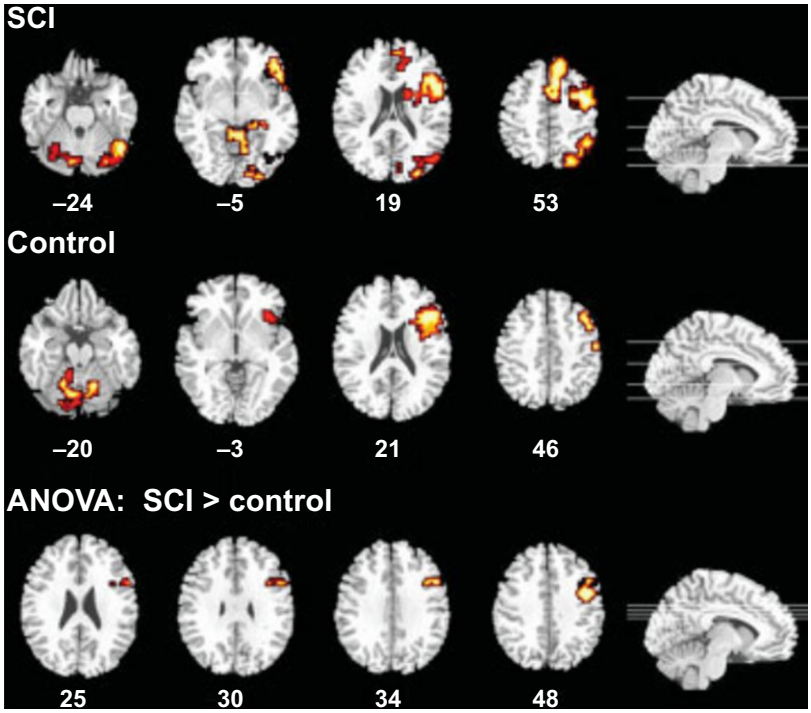

Figure 1 Group activation maps during encoding in subjective cognitive decline (SCD) (top) and controls (middle). Difference map (bottom) showing increased activation in the left prefrontal cortex in SCD during verbal episodic encoding on ANOVA [43].

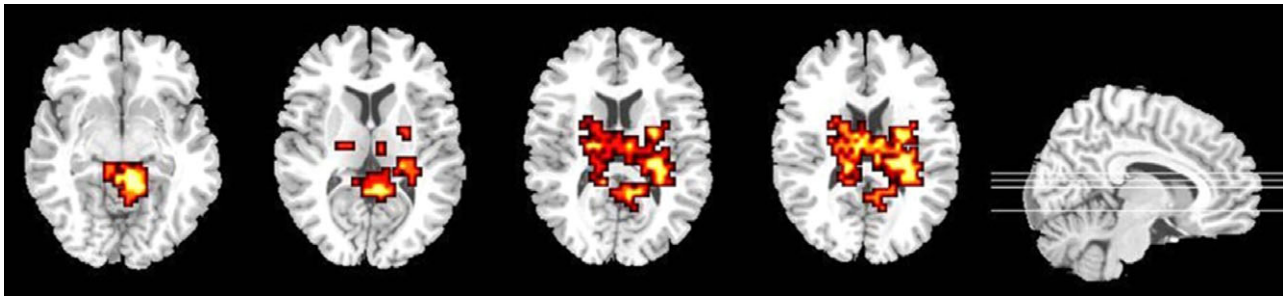

Figure 2 SCI subjects demonstrated increases in the bilateral thalamus, caudate and posterior cingulate (BA 30), left hippocampus, left parahippocampal gyrus (BA 30), and bilateral medial cerebellum as compared to controls during a divided attention on ANOVA [44].

MCI group, but demonstrated less DMN connectivity in the right hippocampus than the control group. Meanwhile, the MCI group had reduced DMN connectivity in the right hippocampus, parahippocampal gyrus, precuneus, and thalamus relative to the control group [47].

In conclusion, fMRI provides a noninvasive and readily available method to detect functional alteration in SCD patients, which may complement the absence of standardized cognitive testing in discriminating SCD from normal individuals.

Future Directions

Although SCD has attracted a great deal of attention, it remains a controversial research area due to the fact that there is no objective clinical assessment sensitive and specific enough to detect it. Consequently, researchers must rely on participants' self-reports. Furthermore, there are concerns regarding SCD group heterogeneity across different research groups. Some researchers, for example, may not exclude people with psychiatric and mood disorders, such as depression, which could raise subjects' risk of developing cognitive impairments [48]. Based on their findings in an extensive review of SCD studies, Abdulrab and Heun proposed a standardized set of criteria for identification of SCD, as follows: (1) onset age of >50 years old with the presence of gradual memory decline that has persisted for ≥6 months; (2) memory has deteriorated to a state that is worse than any earlier period of life; (3) memory problems occur frequently; and (4) objective memory performance within normal range [48]. Based on additional research findings, this conceptual framework was updated in 2014 to reduce false positives. In particular, it suggested that the onset age criterion should be raised to >60 years old with onset within 5 years and SCD symptoms being described as worrisome by the patient. In addition, they suggest that researchers seek independent corroborating evidence (i.e., confirmation by an informant) or risk factors (i.e., *APOE ε4* allele positivity and/or the presence of an associated biomarker). Cleary, an early diagnosis is necessary

to ensure that patients will benefit from early intervention and obtain the appropriate treatments in a timely manner.

If individuals with SCD who are at an elevated risk of AD can be identified, they can potentially be targeted for early intervention [49]. In particular, the finding that brain atrophy was strongly related to β-amyloid load in patients with SCD but not in those with MCI or AD [41] points to there being a strong relationship between β-amyloid deposition and atrophy very early in the disease process. If this relationship holds, then administration of anti-amyloid therapy very early in AD evolution could minimize synaptic and neuronal loss, and thereby reduce or delay the clinical progression of AD. In a study investigating the effects of 2 months of episodic memory training on brain atrophy in patients with SCD and healthy volunteers, versus no training, Engvig et al. [50,51] found that, following the training intervention, the SCD subjects exhibited structural GM volume increases in brain regions encompassing the episodic memory network, with a cortical volume expansion that was comparable to that seen in the trained healthy control group. Therefore, the SCD phase may be an opportune time to begin behavioral interventions.

Conclusions

Accumulating neuroimaging and biochemical evidence points to SCD as an early, pre-MCI precursor of dementia and AD [31,52,53]. Specifically, a pre-AD phase should be suspected in patients who have SCD together with AD risk factors (e.g., *APOE ε4* homozygosity and/or PiB-PET positivity for β-amyloid). Evidence from functional neuroimaging studies suggests that there may be compensatory mechanisms at work in the brains of individuals with SCD that allow them to maintain clinically normal cognitive function despite the presence of mild neuronal damage.

In conclusion, there is promising evidence indicating that clinicians should be able to differentiate pre-AD SCD based on the presence of pathophysiological biomarkers in CSF and neuroimaging. Owing to the fact that it is less invasive, those with suspected SCD may be more willing to accept neuroimaging examinations over CSF extractions. However, the neuroimaging approach is still at an immature stage without an established rubric of standards. A substantial amount of work remains in terms of replicating recent findings and validating the clinical utility of identifying SCD.

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Conflict of Interest

The authors declare no conflict of interest.

References

1. Jack CR Jr, Knopman DS, Jagust WJ, et al. Tracking pathophysiological processes in Alzheimer's disease: An updated hypothetical model of dynamic biomarkers. *Lancet Neurol* 2013;**12**:207–216.
2. Villemagne VL, Burnham S, Bourgeat P, et al. Amyloid β deposition, neurodegeneration, and cognitive decline in sporadic Alzheimer's disease: A prospective cohort study. *Lancet Neurol* 2013;**12**:357–367.
3. Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* 2011;**7**:270–279.
4. Dubois B, Feldman HH, Jacova C, et al. Revising the definition of Alzheimer's disease: A new lexicon. *Lancet Neurol* 2010;**9**:1118–1127.
5. Petersen RC, Roberts RO, Knopman DS, et al. Mild cognitive impairment: Ten years later. *Arch Neurol* 2009;**66**:1447–1455.
6. Petersen RC, Smith GE, Waring SC, et al. Mild cognitive impairment: Clinical characterization and outcome. *Arch Neurol* 1999;**56**:303–308.
7. Reisberg B, Ferris SH, de Leon MJ, Crook T. The Global Deterioration Scale for assessment of primary degenerative dementia. *Am J Psychiatry* 1982;**139**:1136–1139.
8. Jessen F, Wolfsgruber S, Wiese B, et al. AD dementia risk in late MCI, in early MCI, and in subjective memory impairment. *Alzheimers Dement* 2014;**10**:76–83.
9. Jack CR Jr, Knopman DS, Jagust WJ, et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. *Lancet Neurol* 2010;**9**:119–128.
10. Jessen F, Amariglio RE, van Boxtel M, et al. A conceptual framework for research on subjective cognitive decline in preclinical Alzheimer's disease. *Alzheimers Dement* 2014;**10**:844–852.
11. Sperling RA, Aisen PS, Beckett LA, et al. Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* 2011;**7**:280–292.
12. Jonker C, Geerlings MI, Schmand B. Are memory complaints predictive for dementia? A review of clinical and population-based studies. *Int J Geriatr Psychiatry* 2000;**15**:983–991.
13. Derouesne C, Lacomblez L, Thibault S, LePoncin M. Memory complaints in young and elderly subjects. *Int J Geriatr Psychiatry* 1999;**14**:291–301.
14. Smith GE, Petersen RC, Ivnik RJ, et al. Subjective memory complaints, psychological distress, and longitudinal change in objective memory performance. *Psychol Aging* 1996;**11**:272–279.
15. Antonell A, Fortea J, Rami L, et al. Different profiles of Alzheimer's disease cerebrospinal fluid biomarkers in controls and subjects with subjective memory complaints. *J Neural Transm* 2011;**118**:259–262.
16. Barnes LL, Schneider JA, Boyle PA, et al. Memory complaints are related to Alzheimer disease pathology in older persons. *Neurology* 2006;**67**:1581–1585.
17. Striepens N, Scheef L, Wind A, et al. Volume loss of the medial temporal lobe structures in subjective memory impairment. *Dement Geriatr Cogn Disord* 2010;**29**:75–81.
18. Wang L, van Belle G, Crane PK, et al. Subjective memory deterioration and future dementia in people aged 65 and older. *J Am Geriatr Soc* 2004;**52**:2045–2051.
19. Reisberg B, Prichep L, Mosconi L, et al. The pre–mild cognitive impairment, subjective cognitive impairment stage of Alzheimer's disease. *Alzheimers Dement* 2008;**4**:S98–S108.
20. Dubois B, Feldman HH, Jacova C, et al. Advancing research diagnostic criteria for Alzheimer's disease: The IWG-2 criteria. *Lancet Neurol* 2014;**13**:614–629.
21. van Harten AC, Visser PJ, Pijnenburg YA, et al. Cerebrospinal fluid Abeta42 is the best predictor of clinical progression in patients with subjective complaints. *Alzheimers Dement* 2013;**9**:481–487.
22. Visser PJ, Verhey F, Knol DL, et al. Prevalence and prognostic value of CSF markers of Alzheimer's disease pathology in patients with subjective cognitive impairment or mild cognitive impairment in the DESCRIPA study: A prospective cohort study. *Lancet Neurol* 2009;**8**:619–627.
23. Rolstad S, Berg AI, Bjerke M, et al. Amyloid-β_{42} is associated with cognitive impairment in healthy elderly and subjective cognitive impairment. *J Alzheimers Dis* 2011;**26**:135–142.
24. Rami L, Fortea J, Bosch B, et al. Cerebrospinal fluid biomarkers and memory present distinct associations along the continuum from healthy subjects to AD patients. *J Alzheimers Dis* 2011;**23**:319–326.
25. Risacher SL, Saykin AJ, West JD, et al. Baseline MRI predictors of conversion from MCI to probable AD in the ADNI cohort. *Curr Alzheimer Res* 2009;**6**:347–361.
26. van der Flier WM, van Buchem MA, Weverling-Rijnsburger AW, et al. Memory complaints in patients with normal cognition are associated with smaller hippocampal volumes. *J Neurol* 2004;**251**:671–675.
27. Saykin AJ, Wishart HA, Rabin LA, et al. Older adults with cognitive complaints show brain atrophy similar to that of amnestic MCI. *Neurology* 2006;**67**:834–842.

28. Scheef L, Spottke A, Daerr M, et al. Glucose metabolism, gray matter structure, and memory decline in subjective memory impairment. *Neurology* 2012;**79**:1332–1339.
29. Cherbuin N, Sargent-Cox K, Easteal S, et al. Hippocampal atrophy is associated with subjective memory decline: The PATH through life study. *Am J Geriatr Psychiatry* 2014. doi:10.1016/j.jagp.2014.07.009. [Epub ahead of print].
30. Peter J, Scheef L, Abdulkadir A, et al. Gray matter atrophy pattern in elderly with subjective memory impairment. *Alzheimers Dement* 2014;**10**:99–108.
31. Stewart R, Godin O, Crivello F, et al. Longitudinal neuroimaging correlates of subjective memory impairment: 4-year prospective community study. *Br J Psychiatry* 2011;**198**:199–205.
32. Striepens N, Scheef L, Wind A, et al. Interaction effects of subjective memory impairment and ApoE4 genotype on episodic memory and hippocampal volume. *Psychol Med* 2011;**41**:1997–2006.
33. Selnes P, Fjell AM, Gjerstad L, et al. White matter imaging changes in subjective and mild cognitive impairment. *Alzheimers Dement* 2012;**8**:S112–S121.
34. Wang Y, West JD, Flashman LA, et al. Selective changes in white matter integrity in MCI and older adults with cognitive complaints. *Biochim Biophys Acta* 2012;**1822**: 423–430.
35. Wang Y, West J, Shen L, et al. Altered connectome mapping in people with MCI and older adults with cognitive complaints. *Alzheimer's Imaging Consortium Poster Presentations* 2013: IC-P118.
36. Selnes P, Aarsland D, Bjornerud A, et al. Diffusion tensor imaging surpasses cerebrospinal fluid as predictor of cognitive decline and medial temporal lobe atrophy in subjective cognitive impairment and mild cognitive impairment. *J Alzheimers Dis* 2013;**33**:723–736.
37. Lamar M, Dannhauser TM, Walker Z, et al. Memory complaints with and without memory impairment: The impact of leukoaraiosis on cognition. *J Int Neuropsychol Soc* 2011;**17**:1104–1112.
38. Bartley M, Bokde AL, Ewers M, et al. Subjective memory complaints in community dwelling healthy older people: The influence of brain and psychopathology. *Int J Geriatr Psychiatry* 2012;**27**:836–843.
39. Mosconi L, De Santi S, Brys M, et al. Hypometabolism and altered cerebrospinal fluid markers in normal apolipoprotein E E4 carriers with subjective memory complaints. *Biol Psychiatry* 2008;**63**:609–618.
40. Mistur R, Mosconi L, Santi SD, et al. Current challenges for the early detection of alzheimer's disease: Brain imaging and CSF studies. *J Clin Neurol* 2009;**5**:153–166.
41. Chetelat G, Villemagne VL, Bourgeat P, et al. Relationship between atrophy and beta-amyloid deposition in Alzheimer disease. *Ann Neurol* 2010;**67**:317–324.
42. Perrotin A, Mormino EC, Madison CM, et al. Subjective cognition and amyloid deposition imaging: A Pittsburgh Compound B positron emission tomography study in normal elderly individuals. *Arch Neurol* 2012;**69**:223–229.
43. Rodda JE, Dannhauser TM, Cutinha DJ, et al. Subjective cognitive impairment: Increased prefrontal cortex activation compared to controls during an encoding task. *Int J Geriatr Psychiatry* 2009;**24**:865–874.
44. Rodda J, Dannhauser T, Cutinha DJ, et al. Subjective cognitive impairment: Functional MRI during a divided attention task. *Eur Psychiatry* 2011;**26**:457–462.
45. Erk S, Spottke A, Meisen A, et al. Evidence of neuronal compensation during episodic memory in subjective memory impairment. *Arch Gen Psychiatry* 2011;**68**:845–852.
46. Wang Y, West J, Risacher S, et al. Characterization of regional cerebral blood flow in mild cognitive impairment and older adults with cognitive complaints. *Alzheimer's Imaging Consortium Poster Presentations* 2013: IC-P117.
47. Wang Y, Risacher S, West J, et al. Altered default mode network connectivity in older adults with cognitive complaints and amnestic mild cognitive impairment. *J Alzheimers Dis* 2013;**35**:751–760.
48. Abdulrab K, Heun R. Subjective memory impairment. A review of its definitions indicates the need for a comprehensive set of standardised and validated criteria. *Eur Psychiatry* 2008;**23**:321–330.
49. Sperling RA, Jack CR Jr, Aisen PS. Testing the right target and right drug at the right stage. *Sci Transl Med* 2011;**3**:111cm33.
50. Engvig A, Fjell AM, Westlye LT, et al. Hippocampal subfield volumes correlate with memory training benefit in subjective memory impairment. *NeuroImage* 2012;**61**:188–194.
51. Engvig A, Fjell AM, Westlye LT, et al. Effects of cognitive training on gray matter volumes in memory clinic patients with subjective memory impairment. *J Alzheimers Dis* 2014;**41**:779–791.
52. Dickerson BC, Sperling RA, Hyman BT, et al. Clinical prediction of Alzheimer disease dementia across the spectrum of mild cognitive impairment. *Arch Gen Psychiatry* 2007;**64**:1443–1450.
53. Jessen F, Wiese B, Bachmann C, et al. Prediction of dementia by subjective memory impairment: Effects of severity and temporal association with cognitive impairment. *Arch Gen Psychiatry* 2010;**67**:414–422.