



Degeneration of the cholinergic system in individuals with subjective cognitive decline: A systematic review

Marta A. Rodriguez-Hernandez^a, Iris Alemany^a, Jonas K. Olofsson^b, Patricia Diaz-Galvan^c, Milan Nemy^{d,e,g,f,h}, Eric Westman^{g,f,h,i}, Jose Barroso^a, Daniel Ferreira^{g,f,h}, Nira Cedres^{a,b,g,f,h,*}

^a Department of Psychology, Faculty of Health Sciences, University Fernando Pessoa-Canarias, Santa María de Guía, Spain

^b Department of Psychology, Sensory Cognitive Interaction Laboratory (SCI-lab), Stockholm University, Stockholm, Sweden

^c Department of Radiology, Mayo Clinic, Rochester, MN, USA

^d Department of Cybernetics, Faculty of Electrical Engineering, Czech Technical University in Prague, Prague, Czech Republic

^e Department of Biomedical Engineering and Assistive Technology, Czech Institute of Informatics, Robotics and Cybernetics, Czech Technical University in Prague, Prague, Czech Republic

^f Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Stockholm, Sweden

^g Center for Alzheimer Research, Stockholm, Sweden

^h Division of Clinical Geriatrics, Care Sciences and Society, Karolinska Institutet, Stockholm, Sweden

ⁱ Department of Neuroimaging, Centre for Neuroimaging Sciences, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK

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ABSTRACT

Background: Subjective cognitive decline (SCD) is a risk factor for future cognitive impairment and dementia. It is uncertain whether the neurodegeneration of the cholinergic system is already present in SCD individuals. We aimed to review the current evidence about the association between SCD and biomarkers of degeneration in the cholinergic system.

Method: Original articles were extracted from three databases: Pubmed, Web of Sciences, and Scopus, in January 2023. Two researchers screened the studies independently.

Results: A total of 11 research articles were selected. SCD was mostly based on amnesic cognitive complaints. Cholinergic system biomarkers included neuroimaging markers of basal forebrain volume, functional connectivity, transcranial magnetic stimulation, or biofluid. The evidence showed associations between basal forebrain atrophy, poorer connectivity of the cholinergic system, and SCD.

Conclusions: Degenerative changes in the cholinergic system can be present in SCD. Subjective complaints may help when identifying individuals with brain changes that are associated with cognitive impairment. These findings may have important implications in targeting individuals that may benefit from cholinergic-target treatments at very early stages of neurodegenerative diseases.

1. Introduction

Subjective Cognitive Decline (SCD) refers to the presence of self-reported complaints about cognitive performance that cannot be confirmed in a formal neuropsychological evaluation (Jessen et al., 2014). In 2014, the SCD initiative (SCD-I) published a research framework for SCD as a risk factor for mild cognitive impairment (MCI) and Alzheimer's disease (AD) (Jessen et al., 2020). A recent systematic review and meta-analysis showed that between 10% and 76% of 70-year-old individuals with SCD showed positive amyloid levels (Janssen et al.,

2022); Tau-positive levels have also been reported in up to 20% of SCD individuals (Altomare et al., 2019; Ebenau et al., 2020). This evidence supports SCD as a preclinical stage of AD by demonstrating abnormal levels of AD biomarkers as well as an AD signature pattern of brain degeneration (Diaz-Galvan et al., 2021). Longitudinal studies have shown that SCD entails an increased risk for future cognitive impairment and dementia, especially dementia due to AD (Jessen et al., 2020; Mitchell et al., 2014; Slot et al., 2019). Self-reported cognitive complaints may reveal the presence of insidious AD pathology, postulating SCD as a promising indicator at the preclinical stage where the benefits

* Correspondence to: Department of Psychology, Faculty of Health Sciences, University Fernando Pessoa-Canarias, Santa María de Guía, Canary Islands, Spain.
E-mail address: ncedres@ufpcanarias.es (N. Cedres).

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of interventions may be maximized.

The cholinergic system is recognized for its involvement in cognitive functioning, and its impairment has been associated with the severity of AD dementia symptoms (Mufson et al., 2008). Briefly, the cholinergic neurons of the basal forebrain are located at several nuclei, including the complex Ch1–4, neurons close to the pedunculopontine nucleus (Ch5), and neurons close to the laterodorsal tegmental nucleus (Ch6) (Mesulam, 2004; Mesulam et al., 1986). The Ch1–4 complex consists of (1) Ch1, cells associated with the medial septal nucleus; (2) Ch2, cells associated with the vertical branch of the diagonal band; (3) Ch3, cells associated with the horizontal branch of the diagonal band; and (4) Ch4, cells associated with the nucleus basalis of Meynert (NBM) (Mesulam, 2013). This last group is the largest, both by volume and by number of neurons.

In AD, neurons in the Ch4 nucleus are one of the earliest to be affected by pathological changes, which have been associated with memory problems (Mesulam, 2013; Mufson et al., 2008; Sassini et al., 2000). The enzyme choline acetyltransferase (ChAT), synthesizes acetylcholine (ACh) in the cytosol of cholinergic nerve terminals and the disruption of its postsynaptic activity is due to two enzymes: acetylcholinesterase hydrolytic enzyme (AChE) and butyrylcholinesterase hydrolytic enzyme (BuChE), which are found in the synaptic cleft (Karami et al., 2021). Therefore, ACh levels are regulated through the net result of synthesis by ChAT and degradation by AChE and BuChE. In AD, the regulation is altered either to decreased ChAT activity and/or increased AChE and BuChE activity (Giacobini et al., 1989), or decreased AChE has also been described in AD (Perry et al., 1978). The degeneration of the cholinergic system has been detected as early as in MCI patients (Haense et al., 2012; Herholz et al., 2001; Karami et al., 2019; Richter et al., 2017a).

Until recently, all the available treatments for AD patients targeted the cholinergic system using AChE inhibitors, blocking the action of acetylcholinesterase and resulting in increased levels of acetylcholine in the brain (Cummings et al., 2018). Nevertheless, the neurodegeneration and the loss of cholinergic neurons already present during MCI and AD stages have a negative impact on the effectiveness of AChE inhibitors (Machado et al., 2020). Despite these well-established pathological changes in the cholinergic system in later stages of cognitive decline, its status during SCD has not been as thoroughly studied. To understand the status of the cholinergic system in SCD represents a crucial gap in the characterization of disease progression.

In order to increase the potential of preventive programs and therapeutic effects of treatments targeting the cholinergic system, it is essential to establish whether changes in the cholinergic system are already present in the early stages, such as SCD, before the onset of dementia. This systematic review aimed at a state-of-the-art review on the possible degeneration of the cholinergic system in SCD.

2. Methods

2.1. Search strategy

This review was carried out following the PRISMA guidelines, which serve as a framework for writing systematic reviews and meta-analyses (Liberati et al., 2009; López de Argumedo González de Durana et al., 2017). The search was launched in January 2023 (Supplementary Table S1). No filters were applied for the year of publication, language, or type of publication. We searched for published studies in the following databases: PubMed, Web of Science (WOS), and Scopus and we obtained 123 articles. The search strategy was built for each database combining the different terms referred to as “subjective cognitive decline” and “cholinergic system”.

2.2. Eligibility criteria of the selected studies

Eligibility criteria for this systematic review included: (1) studies to

be published in English, (2) reporting original research studies, (3) studies reporting data on the status of the cholinergic system, and (4) studies including adult individuals with a normal level of cognitive performance as assessed by valid cognitive tests such as the Mini-Mental State Examination (MMSE) (Folstein et al., 1975), but endorsing subjective cognitive complaints, who met the diagnostic criteria proposed by the SCD-I (Jessen et al., 2014). These criteria involved, a) absence of mild cognitive impairment (MCI) or dementia; b) preservation of normal cognition and functionality; c) absence of abnormalities such as tumors or cerebrovascular pathology; absence of psychiatric, neurological illness, and traumatic brain injury (TBI); and d) absence of history of substance abuse. We excluded: (1) animal studies or studies conducted in children; (2) postmortem studies (3) studies not reporting data on the cholinergic system; and (4) systematic reviews, meta-analyses, case-report studies, reviews, editorials, letters, posters and, conference abstracts. Two researchers worked independently to select studies based on title, abstract and, full text (M. R-H. & I.A.). If consensus between the two parties was not achieved, a third person made the decision (N.C.).

2.3. Data extraction and risk of bias

Data analysis and synthesis were carried out by a single researcher (M. R-H.). Subsequently, a second researcher (N.C.) was responsible for confirming that the selected studies were suitable for the review and for approving the application of the exclusion criteria. After excluding 39 duplicate studies, 73 articles were excluded based on title and abstract screening. Studies were excluded when they were considered off-topic (i.e., animal studies, absence of SCD group, or absence of cholinergic system data). Screening of the title and abstract led to the identification of 15 potentially eligible studies. Finally, 13 articles were selected for review after a full-text content assessment (Fig. 1).

To assess the methodological quality and risk of bias of the included studies, we used the FLC 3.0 web platform (<http://www.lecturacritica.com/en/>) (López de Argumedo González de Durana et al., 2017). This platform allows for critical appraisal and standardized analysis of both the quality and reliability of different types of studies, following a series of criteria divided into several areas that facilitate the systematic extraction of data of interest. The requirements established to evaluate the quality of the studies were as follows: 1) to correctly describe the design, aims, and year of publication; 2) to adequately describe the population, pathology, and diagnostic criteria for the definition of the study group; 3) to make use of reliable measurement instruments and

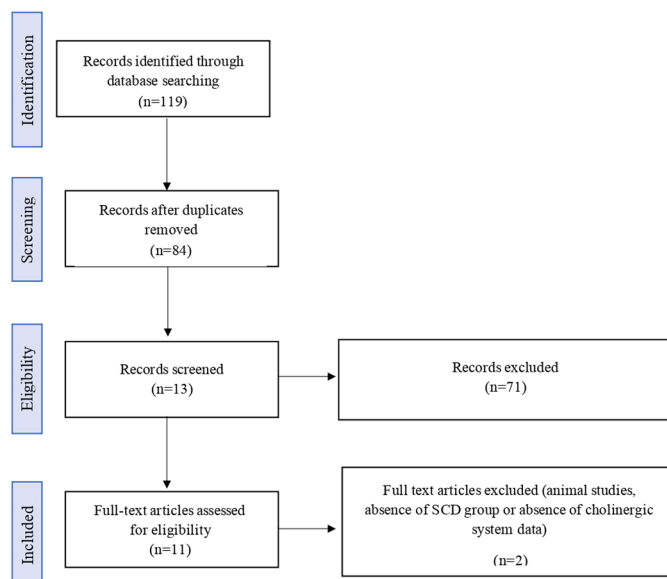


Fig. 1. Search strategy for primary studies.

control for possible confounding factors; 4) to correctly describe the results and justify the conclusions; and 5) to have external validity.

2.4. Data synthesis and qualitative analysis

A data extraction sheet was elaborated where the following aspects were collected: 1) authors and year of publication, 2) design, 3) cohort and sample size of the SCD group and other potential groups, 4) aims of the study, 5) clinical and demographic characteristics of the SCD individuals, 6) instruments used to assess the cholinergic system; 7) statistical analyses used, 8) risk factors included, 9) results obtained, and 10) conclusions of the analyzed studies.

3. Results

3.1. Study selection and characteristics

After analyzing full-text articles, 13 were eligible for our qualitative synthesis (Fig. 1). The main reason for the exclusion of the remaining two articles was the inclusion of individuals who did not fulfill the established criteria for SCD. We selected those studies that included a group of participants with SCD, as well as measures of the cholinergic system, and where the presence of objective cognitive impairment was ruled out in the complaint group using comprehensive neuropsychological assessment. The main characteristics of the selected studies are

detailed in Table 1.

First, regarding the design, four studies used longitudinal designs (Cavedo et al., 2020; Scheef et al., 2019; Teipel et al., 2018; Vergallo et al., 2021) and the remaining nine studies applied cross-sectional designs (Cavedo et al., 2018; Chen et al., 2021; Chiesa et al., 2019; Fu et al., 2021; Herdick et al., 2020; Karami et al., 2021; Nardone et al., 2015; Nemy et al., 2023; Teipel et al., 2022) (Table 1). Regarding the origin of the sample, eight studies included participants from memory clinics (Cavedo et al., 2018, 2020; Chiesa et al., 2019; Fu et al., 2021; Karami et al., 2021; Scheef et al., 2019; Teipel et al., 2018; Vergallo et al., 2021), three studies included participant from a neurodegenerative disease's center (Herdick et al., 2020; Nemy et al., 2023; Teipel et al., 2022) while the remaining two studies included community-based cohorts (Chen et al., 2021; Herdick et al., 2020; Nardone et al., 2015; Nemy et al., 2023) (Table 1, column "sample's origin" and Fig. 2B). Note that five of the 13 studies selected for the systematic review used the same cohort (Cavedo et al., 2018, 2020; Chiesa et al., 2019; Teipel et al., 2018; Vergallo et al., 2021) (INSIGHT-PreAD; Table 1).

The sample size of the SCD groups ranged between 20 and 318 participants (Table 1, column "sample size SCD"). Regarding socio-demographic characteristics, the age of the SCD participants ranged from 50 to 85 years old (Table 1). SCD participants were most frequently women in 10 out of the 13 studies included (Cavedo et al., 2018, 2020; Chiesa et al., 2019; Fu et al., 2021; Herdick et al., 2020; Karami et al., 2021; Nemy et al., 2023; Teipel et al., 2018; Vergallo et al., 2021)

Table 1
Description of the selected studies.

Authors (Year)	Design	Sample's origin	Cohort	Sample size	Age (mean $\pm$ SD)	Sex (M/F)	Type of complaints	Measurement of the cholinergic system	Measurement of other markers	Comparison group (s)
Nardone et al. (2015)	Cross-sectional	Community-based	-	20	67.8	12/8	Memory	TMS	-	CG (20)
Cavedo et al. (2018)	Cross-sectional	Memory institute	INSIGHT-PreAD ^a	318	76.5 $\pm$ 3.5	114/204	Memory	MRI, fMRI	Amyloid PET FDG-PET APOE	-
Teipel et al. (2018)	Longitudinal	Memory institute	INSIGHT-PreAD ^a	265	76.3 $\pm$ 3.4	101/164	Memory	MRI	Amyloid PET APOE	-
Chiesa et al. (2019)	Cross-sectional	Memory institute	INSIGHT-PreAD ^a	267	75.8 $\pm$ 3.5	100/167	Memory	fMRI	Amyloid PET APOE	-
Scheef et al. (2019)	Longitudinal	Memory clinic	KBFZ ^b	24	67 $\pm$ 6.1	18/6	Memory	MRI	FDG-PET	CG (49)
Cavedo et al. (2020)	Longitudinal	Memory institute	INSIGHT-PreAD ^a	276	75.7 $\pm$ 3.4	106/170	Memory	MRI	Amyloid PET APOE Tau (plasma)	-
Herdick et al. (2020)	Cross-sectional	Research-oriented	DELCODE ^c	88	71.5 $\pm$ 5.6	43/45	Multiple	MRI, fMRI, DTI	Amyloid PET	CG, MCI, AD (88, 40, 27)
Vergallo et al. (2020)	Longitudinal	Memory institute	INSIGHT-PreAD ^a	302	76.04 $\pm$ 3.45	110/192	Memory	MRI	β -amyloid and tau (plasma) ELISA (BACE1) FDG-PET	-
Chen et al. (2021)	Cross-sectional	Community-based	-	31	64.68 $\pm$ 5.21	5/26	Memory	MRI	APOE	CG (24)
Fu et al. (2021)	Cross-sectional	Memory clinic	-	35	64.54 $\pm$ 7.29	15/20	Memory	MRI	-	CG, aMCI, AD (42, 43, 41)
Karami et al. (2021)	Cross-sectional	Memory clinic	-	30	66 $\pm$ 8	9/21	Not specific	CSF and plasma	-	MCI, AD (32, 21)
Nemy et al. (2023)	Cross-sectional	Research-oriented	DELCODE	172	71.6	96/76	Multiple	DTI, MD, FA, sMRI	Tau and Amyloid (CSF)	HC, MCI, AD (112, 66, 52)
Teipel et al. (2022)	Cross-sectional	Research-oriented	DELCODE	82	70.7	36/46	Multiple	sMRI, fMRI	Tau and Amyloid (plasma and CSF)	HC, first degree relatives, MCI, AD (70, 20, 58, 31)

Abbreviations. SCD, subjective cognitive decline; SD, standard deviation; MRI, structural magnetic resonance imaging; fMRI, functional magnetic resonance imaging; DTI, diffusion tensor imaging; TMS, transcranial magnetic stimulation; FA, fractional anisotropy; MD, mean diffusivity; CSF, cerebrospinal fluid; amyloid PET, amyloid positron emission tomography; FDG-PET, 18-fluorodeoxyglucose PET; CG, control group; MCI, Mild Cognitive Impairment; aMCI, amnesic-type MCI; AD, Alzheimer's disease. aINSIGHT-PreAD: Investigation of Alzheimer's Predictors in Subjective Memory Complainers; bKBFZ: Clinical Treatment and Research Center for Neurodegenerative Disorders; cDELCODE: DZNE- Longitudinal Cognitive Impairment and Dementia Study.

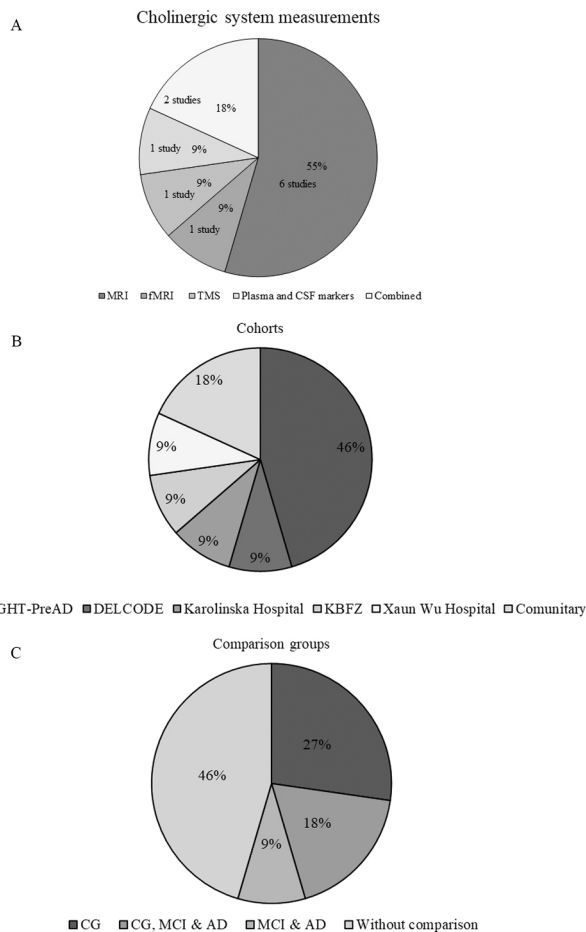


Fig. 2. Cholinergic system measurements, cohorts included in the studies and comparison groups used. Panel A, measures of the cholinergic system used by the included studies. Two of the studies used combined measures, one of them structural MRI (sMRI) and fMRI (functional MRI) and one of them structural MRI, fMRI and DTI (diffusion tensor imaging). Panel B, the cohorts that included each study. Five of the studies used the same cohort, whereas two used community samples. Panel C, comparison groups used. Three studies used a control group, two used a control group, MCI (Mild Cognitive Impairment) and/or AD (Alzheimer's disease). The last one used MCI and AD. Abbreviations. TMS, transcranial magnetic stimulation; CSF, cerebrospinal fluid; INSIGHT-PreAD, Investigation of Alzheimer's Predictors in Subjective Memory Complainers; KBFZ, Memory Clinic of the Clinical Research and Treatment Center for Neurodegenerative Disorders; DELCODE, DZNE- Longitudinal Cognitive Impairment and Dementia Study.

(Table 1, column "sex SCD") and had medium-high level of education ($\bar{X}=13.85$) (Table 1).

Considering the cognitive domain of the complaint, nine studies focused solely on memory complaints (Cavedo et al., 2018, 2020; Chen et al., 2021; Chiesa et al., 2019; Fu et al., 2021; Karami et al., 2021; Scheef et al., 2019; Teipel et al., 2018; Vergallo et al., 2021), three used an interview assessing multiple cognitive domains covering language, planning, attention, and memory (Herdick et al., 2020; Nemy et al., 2023; Teipel et al., 2022); and one study did not specify the cognitive domain (Nardone et al., 2015) (Table 1).

Eleven of the 13 studies used neuroimaging markers to measure the cholinergic system. Six studies used structural magnetic resonance imaging (sMRI) to analyze the volume of the cholinergic basal forebrain (Cavedo et al., 2020; Chen et al., 2021; Fu et al., 2021; Scheef et al., 2019; Teipel et al., 2018; Vergallo et al., 2021). One study relied exclusively on resting-state functional MRI (fMRI) to determine the functional connectivity of the cholinergic basal forebrain in SCD (Chiesa

et al., 2019). Four neuroimaging studies used combined measures (Cavedo et al., 2018; Herdick et al., 2020; Nemy et al., 2023; Teipel et al., 2022), meaning more than one neuroimaging marker (sMRI, fMRI, diffusion tensor imaging (DTI) indexes, such as fractional anisotropy (FA) and/or mean diffusivity (MD)). The remaining two studies used biofluid markers (Karami et al., 2021) (i.e., cerebrospinal fluid – CSF and plasma markers) and transcranial magnetic stimulation (Nardone et al., 2015; TMS; Table 1).

Eight studies out of the 13 included other groups (i.e. controls or clinical groups) for comparisons with the SCD group. Of those, three studies included a single control group of healthy individuals to compare with the SCD group (Chen et al., 2021; Nardone et al., 2015; Scheef et al., 2019); four studies included a control group, and clinical groups (i.e., MCI and/or AD patients) to compare with the SCD group (Fu et al., 2021; Herdick et al., 2020; Nemy et al., 2023; Teipel et al., 2022); and only one study exclusively compared the SCD group (as the reference group) vs MCI and AD patients (Karami et al., 2021).

3.2. Risk of bias in the included studies

All studies were classified as having a high methodological quality except one, which was classified as having a low quality (Nardone et al., 2015; Fig. 3). The FLC 3.0 web platform indicated that the article showed lower quality based on (1) the absence of specifications on the origin of the study data, (2) a poor description of the results (i.e., the results section did not include an explanation of the performed analyses or a table of the acquired data) and (3) the conclusions were not adequately justified based on the results of the study.

3.3. Qualitative synthesis of the data

The included studies are described below and categorized according to the type of measurement used for the cholinergic system: (1) volume of the cholinergic basal forebrain, (2) functional connectivity of the cholinergic basal forebrain, (3) cholinergic system integrity based on DTI, (4) biofluid cholinergic markers, (5) cholinergic changes on TMS and additionally, (6) other findings related to the cholinergic system. Five studies used multiple measurements of the cholinergic system and were thus described in more than one category.

3.3.1. Volume of the cholinergic basal forebrain

Six out of 10 included studies showed basal forebrain atrophy in SCD individuals. These studies are described in detail below.

The main aim of Scheef and colleagues (2019) was to investigate whether there were differences in basal forebrain volume between controls without cognitive complaints and SCD individuals. They found that the SCD group showed lower volumes in Ch1/2 and the posterior part of Ch4 (Ch4p) compared to controls. Additionally, they investigated memory performance over time and different AD biomarkers. The results showed an association between reduced volume of Ch4p and reduced hippocampal volume in both groups. Regarding memory performance, the results of the study showed lower cognitive performance at follow-up in SCD, in the absence of association with volume change in the basal forebrain.

Chen and colleagues (2021) also found lower basal forebrain volume in SCD individuals compared with controls without complaints. In addition, the authors described positive relationships between Ch4 and entorhinal cortex volumes, and between basal forebrain and hippocampal volume in SCD. Results related to spatial navigation performance in this study are discussed below.

Fu and colleagues (2021) compared the volumes of cholinergic regions and structures that are part of the default mode network, the salience network, and the executive control network, in controls without complaints, SCD, amnesic MCI, and AD. The results showed greater strength of structural covariance between the Ch4 volume and the volume of the areas belonging to the executive control network (left middle

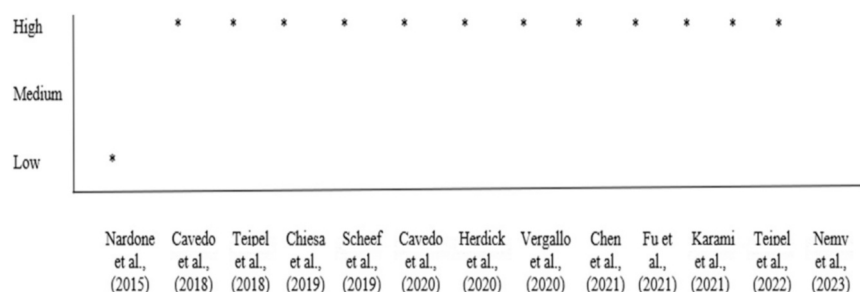


Fig. 3. Quality and risk of bias of the included studies.

temporal gyrus) in the control group compared to the SCD group. Further, greater strength of structural covariance was found between Ch1/2 vol and the volume of the areas belonging to the executive control network (left parahippocampal gyrus) in the control group compared to the SCD group.

Teipel and colleagues (2018) found an association between basal forebrain atrophy and trajectories of cognitive performance in SCD. These cognitive trajectories were assessed with a neuropsychological evaluation that included the Mini-Mental State Examination (MMSE) (Folstein et al., 1975), to measure global cognition; and the Memory Binding Test (MBT) (Buschke et al., 2017) to measure immediate (MBT-BS) and long-term (MBT List 1/2) memory performance with a two year follow-up period. The results showed that lower basal forebrain volume over time was associated with poorer trajectory (i.e. worse performance at follow-up) of the MMSE score in SCD individuals. In this regard, the study also showed that the lower the basal forebrain volume, the lower the performance trajectory in free recall long-term memory, but not in immediate recall.

Cavado and colleagues (2020) found an association between atrophy in Ch1/2 and Ch4 during a two year follow-up period and the presence of subjective memory complaints. Moreover, this longitudinal association was related to increased levels of total tau in plasma.

Vergallo and colleagues (2020) found a negative association between changes in β -site amyloid precursor protein cleaving enzyme 1 (BACE1) and lower basal forebrain volume, in individuals with SCD, within a 3-year follow-up. The authors highlighted the importance of these findings because BACE1 was elevated in the brains of individuals with AD compared to cognitively unimpaired individuals (Hampel et al., 2021).

In the study by Cavado and colleagues (2018), no sex differences were found in basal forebrain volume in SCD individuals, even after adjusting for amyloid status and APOE ϵ 4 genotype.

Teipel and colleagues (2022) investigated the influence of basal forebrain volume and functional connectivity on neuroinflammatory markers based on CSF and serum markers in AD's spectrum. However, they found no association between basal forebrain volume and neuroinflammatory markers in SCD.

Finally, Nemy and colleagues (2022) investigated whether microstructural alterations in cholinergic pathways exist in the AD continuum, including the SCD, as well as the predictive power from biomarkers vs. more conventional ones, such as forebrain volume. Regarding the latter, the results did not show an association between lower basal forebrain volume and SCD.

In summary, of the 10 included studies, six reported lower basal forebrain volumes in SCD individuals, whereas three studies did not find this association. The study focused solely on gender differences and found no differences between SCD males and females regarding basal forebrain volume.

3.3.2. Functional connectivity

From the four studies including functional connectivity measures of the cholinergic system, three compared the SCD group against controls without cognitive complaints, and another one compared females vs

males with SCD.

Chiesa and colleagues (2019) aimed to determine whether fibrillar β -amyloid burden in vivo was associated with cholinergic functional connectivity in people with SCD. The results showed that the greater the functional connectivity between the basal forebrain with the left hippocampus and thalamus, the lower the global β -amyloid load. Additionally, they measured the influence of both sex and the APOE ϵ 4 allele on this connectivity. They found that females with SCD had a stronger positive association between global β -amyloid load and basal forebrain connectivity. Also, they found that SCD individuals carrying the APOE ϵ 4 allele had weaker associations between cholinergic basal forebrain connectivity and global β -amyloid load.

Herdick and colleagues (2020) found no significant differences between the control group and the SCD group in functional connectivity. However, they found reduced connectivity in the anterior and posterior basal forebrain in SCD individuals with abnormal β -amyloid loads.

As described above, Teipel and colleagues (2022) also investigated the association of functional connectivity of the basal forebrain with neuroinflammatory markers on CSF and serum in the AD spectrum. The result from this study showed that functional connectivity of the basal forebrain was not associated with neuroinflammatory markers in SCD.

In the study by Cavado and colleagues (2018), no sex differences were found in functional connectivity, even when amyloid status and APOE ϵ 4 genotype were taken into account.

In summary, one of the studies comparing SCD vs controls found an association between lower functional connectivity and SCD, whereas two studies did not find this association. A third study did not find differences in basal forebrain functional connectivity between males and females.

3.3.3. Measures based on cholinergic system integrity

One study combined sMRI, fMRI resting state, and DTI (Herdick et al., 2020; Table 1, column "cholinergic system measure" and Fig. 2A). As explained above, no significant differences were found between the control group and SCD individuals in either sMRI or fMRI. The findings related to DTI showed that lower Ch4a (anterior part of Ch4) and Ch4p (posterior part of Ch4) integrity were associated with the clinical stage of individuals (controls, SCD, MCI, and AD). The same occurred in Ch4a when the β -amyloid state was analyzed, but not in Ch4p, where there was no significant overall effect of diagnosis.

Only one other study combined sMRI, DTI diffusivity indices and CSF biomarkers (Nemy et al., 2023; Table 1, column "cholinergic system measure" and Fig. 2A). As described above, Nemy and colleagues (2022) also studied whether microstructural alterations in cholinergic pathways exist in the AD continuum, including SCD. This study showed alterations in the white matter integrity of the cholinergic pathways and demonstrated that this biomarker was more informative than more conventional measures (i.e. basal forebrain and hippocampal volume) for distinguishing individuals with SCD from a control group.

3.3.4. CSF and plasma markers

Karami and colleagues (2021) found significant differences between

the diagnosis severity (i.e., AD > MCI > SCD) and the patterns of ChAT and AChE markers in CSF and plasma. The most relevant results related to SCD individuals are described below.

First, CSF AChE activity was positively related in all groups to t-tau and p-tau CSF levels, as well as to β -amyloid₄₂ CSF levels in the MCI group. Furthermore, in plasma, both ChAT activity and protein levels differed between AD, MCI, and SCD individuals, following the AD > MCI > SCD pattern.

3.3.5. Cholinergic changes by TMS

Nardone and colleagues (2015) aimed to assess the short-latency afferent inhibition (SAI) of some cholinergic pathways to the human motor cortex in SCD individuals. When comparing controls without complaints and SCD individuals, no significant differences were found between the groups.

3.3.6. Other findings in the cholinergic system

3.3.6.1. Spatial navigation. Chen and colleagues (2021), studied whether atrophy of the basal forebrain and entorhinal cortex contributed to spatial disorientation in SCD participants compared with a control group. Egocentric navigation occurs when the person is the reference frame for orientation while allocentric navigation occurs when the environment is the frame of reference for orientation. They found a significant negative association between basal forebrain volume and the number of allocentric errors in the SCD individuals, but not in a control group.

4. Discussion

We reviewed the existing research on the association between the degeneration of the cholinergic system and SCD. Our main aim was to investigate whether there is evidence of degeneration in the cholinergic system already in SCD. Overall, the reports indicated that the cholinergic system is affected in SCD individuals compared to individuals without cognitive complaints in cohorts aged between 55–85 years old and from various origins (i.e., from clinical and community-based samples). SCD individuals report complaints about their cognitive performance in the absence of objective cognitive impairment (Jessen et al., 2020). The reviewed studies involve a wide range of techniques and the findings of our review are in line with previous studies showing that neuroimaging and biofluid markers are more sensitive than classical neuropsychological tests to detect neurodegeneration in SCD (Cedres et al., 2019; Meiberth et al., 2015; Peter et al., 2014; Saykin et al., 2006).

The longitudinal studies showed evidence of cholinergic system atrophy in individuals who reported cognitive complaints (Cavedo et al., 2020; Scheef et al., 2019; Teipel et al., 2018; Vergallo et al., 2021). In healthy aging, there is a vulnerability of the basal forebrain to human brain neurodegenerative processes (McKinney, 2005). Thus, histopathological analysis has shown axonal, synaptic, and dendritic loss of basal forebrain neurons in older adults (Ypsilanti et al., 2008), and even in non-human primate brains (Nagahara et al., 2009). Furthermore, Contestabile and colleagues (2007) found that pathological aging is associated with neuronal loss in the basal forebrain. Previous studies found evidence of early neurodegeneration of the NBM in preclinical AD, which became more pronounced during the dementia stage (Kilimann et al., 2014; Liu et al., 2015). In fact, Teipel and colleagues (2018) demonstrated that basal forebrain atrophy was associated with poorer cognitive performance after two years of follow-up in patients with SCD. All this may suggest that the impact of cholinergic system impairment may manifest itself in the form of subjective cognitive complaints in SCD. This supports the notion that SCD individuals are at higher risk of future cognitive impairment.

In line with the longitudinal study findings, the cross-sectional studies highlight that the degeneration of the cholinergic system may

be already present in SCD individuals, as assessed by multiple methods (i.e., basal forebrain volume, functional connectivity, and CSF and plasma markers) and that this occurs independently of sex (Cavedo et al., 2018). One multimodal study reported no association between SCD and the status of the cholinergic system, using a relatively small sample and fMRI, DTI, and sMRI (Herdick et al., 2020). However, the measures used for the cholinergic system were not very restrictive, causing the possible inclusion of adjacent areas, which may also influence the results obtained (Fritz et al., 2019; Li et al., 2017). Also, different neuroimaging scanners were used to measure the cholinergic system which may have induced noise in the results, especially in functional connectivity, due to increased variance between scanners (Richter et al., 2017a; Teipel et al., 2018, 2019). Interestingly, another study using a bigger sample from the same cohort and more refined neuroimaging techniques showed that while there were no differences in the basal forebrain volume, the SCD showed poorer integrity of the cholinergic white matter pathways compared to controls (Nemy et al., 2023). Furthermore, these two cross-sectional studies operationalized SCD based on cognitive complaints in multiple cognitive domains. This may have influenced their results since it has been demonstrated that the cholinergic system is mainly related to attention and memory abilities (Ballinger et al., 2016; Haense et al., 2012; Härtig et al., 2002; Herholz et al., 2001; Nemy et al., 2020). While amnesic SCD has shown an AD-like brain atrophy pattern, non-amnesic SCD seems to be closely associated with increased underlying cerebrovascular disease (Diaz-Galvan et al., 2021). Interestingly, all the studies included defining SCD solely on memory complaints that investigated the basal forebrain volumes showed increased basal forebrain atrophy in the SCD. Thus, different definitions of SCD may be associated with different underlying pathologies and disease outcomes.

Regarding other biomarkers, our review shows evidence of an association between abnormal AD biofluid markers and the degeneration of the cholinergic system already present in SCD individuals. Notably, the studies demonstrated that this association was also related to worse memory performance in SCD, both cross-sectional and longitudinally (Karani et al., 2021; Teipel et al., 2018). Although the association between SCD and AD biomarkers is already well-established in the literature (Jessen et al., 2020), only a handful of studies are available that include associations with the cholinergic system. This, once again, highlights the necessity for future studies using combined techniques that include the relationship between SCD and both, the cholinergic system and AD biomarkers. If the association between cholinergic neurodegeneration, AD biomarkers, and SCD is strongly established, the design and implementation of clinical trials in SCD individuals using pharmacological treatments based on AChE inhibitors may be promising.

The neuroimaging approach selected to measure the cholinergic system in SCD individuals may have important implications for the results and interpretations of the included studies. Volumetric measures of the basal forebrain in SCD provide consistent insights into the size and structure of the cholinergic system and its degeneration in the preclinical stage of Alzheimer's disease. However, The single use of basal forebrain volume may be insufficient to understand the dynamics of cholinergic interactions with other brain areas. On the other hand, non-volumetric measures (i.e. DTI and fMRI) aim to assess the cholinergic activity, connectivity, or integrity, thus providing information regarding the functional role in cognitive processes. Nevertheless, these techniques may lack sensitivity and robustness due to various influencing factors. The current systematic review shows that basal forebrain atrophy is consistently associated with SCD, whereas the few studies including non-volumetric measures show conflicting results. Future research aiming to refine the sensitivity of non-volumetric measures, using more advanced techniques, or integrating both volumetric and non-volumetric approaches for a more comprehensive understanding of the cholinergic system in SCD is needed.

This review has some limitations and different aspects must be taken

into account when generalizing the results. First, most of the studies included used brief screening test such as the MMSE (Folstein et al., 1975) to assess cognitive performance. These short screening tests might not be sensitive enough to discard subtle cognitive impairment. Many studies in the review involved measuring only basal brain volume, a macrostructural measure of the cholinergic system. Therefore, we propose that future studies involve other techniques, such as tractography of the cholinergic white matter pathways or functional connectivity of the cholinergic system with the cortical mantle. Moreover, five of the eleven articles included in the review used the same cohort (INSIGHT-PreAD). Regarding the origin of the sample, most of the studies are based on clinical settings (11 clinical samples vs. two community-based samples) and some of the studies have small sample sizes (i.e. $N < 30$). The use of more heterogeneous and community-based samples, as well as larger sample sizes, would enhance the generalization of the results. On the other hand, although the FLC 3.0 platform for risk assessment (López de Argumedo González de Durana et al., 2017) is a widely accepted method to measure the quality of the studies, it involves a certain degree of subjective interpretations. Even though one of the studies was classified as having low quality, this study was not excluded because we focused on gathering all the information related to the study of the cholinergic system in SCD, including a wide set of methods and operationalization approaches. Finally, we were unable to perform a meta-analysis because only half of our studies included a control group. Nevertheless, our primary objective was to assemble the first global overview of the current evidence on the neurodegeneration of the cholinergic system in individuals with SCD as a preclinical stage of AD. In the present study, we synthesized the available data on the association between SCD and multiple markers of neurodegeneration of the cholinergic system.

5. Conclusions

In conclusion, there are changes in the cholinergic system in SCD individuals compared to controls without cognitive complaints. Future studies should focus their efforts on the use of combined techniques that include the relationship between SCD and both the cholinergic system and AD biomarkers, as well as more heterogeneous, community-based, and larger samples. We suggest that assessment of the cholinergic system in SCD could facilitate early diagnosis of preclinical stages of AD dementia, which in turn would allow for a greater therapeutic benefit.

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CRediT authorship contribution statement

Marta A. Rodríguez-Hernández; Conducted the literature search; Prepared the data base; Analyzed and interpreted the data, and drafted the manuscript for intellectual content. **Iris Alemany**; Conducted the literature search; Prepared the data base. **Jonas Olofsson**; Interpreted the data; and revised the manuscript for intellectual content. **Patricia Diaz-Galvan**; Design and conceptualized study; Interpreted the data; and revised the manuscript for intellectual content. **Milan Nemy**;

Design and conceptualized study; Interpreted the data; and revised the manuscript for intellectual content. **Eric Westman**; Interpreted the data; and revised the manuscript for intellectual content. **José Barroso**; Design and conceptualized study; Interpreted the data; and revised the manuscript for intellectual content. **Daniel Ferreira**; Design and conceptualized study; Interpreted the data; and revised the manuscript for intellectual content. **Nira Cedres**; Funding acquisition; Design and conceptualized study; Supervision of the literature search; supervision of the data base preparation; Interpreted the data; revised the article critically; and contributed to draft the manuscript for intellectual content.

Data availability

Data will be made available on request.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neubiorev.2024.105534.

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