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Is Brain Connectome Research the Future Frontier for Subjective Cognitive Decline? A Systematic Review

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Highlights

- Network disorganization in people with SCD was found in the majority of the reported studies.
- Brain Connectome in SCD is disrupted in a similar way as in MCI compared to HC.
- Small-world and Rich-club were preserved in SCDs while aberrant local connections were observed.

Abstract

Objective: We performed a systematic literature review on Subjective Cognitive Decline (SCD) in order to examine whether the resemblance of brain connectome and functional connectivity (FC) alterations in SCD with respect to MCI, AD and HC can help us draw conclusions on the progression of SCD to more advanced stages of dementia.

Methods: We searched for studies that used any neuroimaging tool to investigate potential differences/similarities of brain connectome in SCD with respect to HC, MCI, and AD.

Results: Sixteen studies were finally included in the review. Apparent FC connections and disruptions were observed in the white matter, default mode and gray matter networks in SCD with regards to HC, MCI, and AD. Interestingly, more apparent connections in SCD were located over the posterior regions, while an increase of FC over anterior regions was observed as the disease progressed.

Conclusions: Elders with SCD display a significant disruption of the brain network, which in most of the cases is worse than HC across multiple network parameters.

Significance: The present review provides comprehensive and balanced coverage of a timely target research activity around SCD with the intention to identify similarities/differences across patient groups on the basis of brain connectome properties.

Key Words: Alzheimer's Disease, Network Analysis, Subjective Cognitive Decline, Mild Cognitive Impairment, Neuroimaging

Abbreviations	
Alzheimer's Disease (AD)	Medial Temporal Memory system (MTMS)
Anterior Cingulate Cortex (ACC)	Medial Visual Network (MVN)
Anterior Ventral DMN (avDMN)	Mild Cognitive Impairment (MCI)
Caudate nucleus (CAU)	Posterior Cingulate Cortex (PCC)
Cuneus (CUN)	Posterior Default Mode Network (pDMN)
Default Mode Network (DMN)	Precuneus (PUN)
Dorsal Attention Network (DAN)	Putamen (PUT)
Functional Connectivity (FC)	Region of Interest (ROI)
Gray Matter Networks (GMN)	Retrosplenial Cortex (RSC)
Healthy Controls (HC)	Subjective Cognitive Decline (SCD)
Hippocampus (HP)	Supplementary Motor Area (SMA)
Inferior Parietal Cortex (IPC)	Synchronization Likelihood (SL)
Inferior Parietal Gyrus (IPG)	Thalamus (THA)
Inferior Parietal Lobule (IPL)	Ventral Medial Prefrontal Cortex (vmPFC)
Medial Prefrontal Cortex (mPFC)	White Matter Network (WMN)
Medial Temporal Lobe (MTL)	

1 Introduction

Alzheimer's disease (AD) is the most common type of dementia and is considered one of the most devastating neurodegenerative disorders with social, economic and clinical impact. In particular, AD has been found to change brain structure and function several years before the appearance of the first symptoms of cognitive decline and clinical deficits (Jansen et al. 2015; Busche and Konnerth 2016). Therefore, the early identification of brain dysfunctions in individuals likely to develop AD is among the greatest challenges of current research in the field of AD (Garcia-Ptacek et al. 2016; Cheng et al. 2017).

More specifically, there is a growing body of literature suggesting that Subjective Cognitive Decline (SCD) is associated with the presence of brain changes and disorganization of early cognitive decline related to AD (Reisberg and Gauthier 2008; Rodda et al. 2011; Lazarou et al. 2018; Mazzon et al. 2018). Several longitudinal studies have also underlined the important role of this stage as a precursor of future cognitive decline such as dementia (Ferris and Reisberg 1993; Geerlings et al. 1999; Jorm et al. 2001; St John and Montgomery 2002; Amariglio et al. 2018; Bessi et al. 2018; Snitz et al. 2018). In detail, SCD is specified as a perceived self-reported impairment of cognition in an absence of any objective abnormal clinical and neuropsychological evidence (Jessen et al. 2014; Tales et al. 2015) and it has been recently characterized by a set of criteria suggested by Subjective Cognitive Decline – International Working Group (SCD-IWG) (Rabin et al. 2018). Nevertheless, despite the fact that SCD can actually be considered as a clinical stage with high predictive value to the future development of cognitive decline or dementia (Sperling et al. 2011), until now, the diagnosis of SCD is largely based on self-reported symptoms and absence of any clinical sign (Rabin et al. 2018). A recent meta-analysis has found that people with SCD are more susceptible on developing Mild Cognitive Impairment (MCI) and subsequently AD compared to elders without the self-awareness feeling of memory decline. SCD conversion rate per year to more advanced stages such as MCI and dementia is approximately 6.6% and 2.3% respectively during a 5 year follow-up period (Mitchell et al. 2014). Similar longitudinal approaches (Snitz et al. 2018) with 3-year follow-up, concluded that the annual conversation rate for SCD to MCI is approximately 16% when the subjects decide to visit a memory clinic, and 1.2 % when the subjects decide not to further inquire this feeling of forgetfulness. This fact highlights that the feeling of memory disturbances has great value as a prediction factor to subsequent cognitive decline. Consequently, there is 4.5 - 6.5 times greater risk for people with SCD to shift from SCD to the later stages of MCI or AD than for people without cognitive complaints (Schmand et al. 1996; Smith et al. 1996; Geerlings et al. 1999; Reisberg et al. 2010). The relationship between SCD and objective performance in neuropsychological tests has been extensively investigated (Ferris and Reisberg 1993; Geerlings et al. 1999; Jonker et al. 2000; Jorm et al. 2001; St John and Montgomery 2002; Elfgren et al. 2003, 2010; Amariglio et al. 2018; Bessi et al. 2018) with controversial findings. In addition to neuropsychological differences among SCD and other patient groups, several studies have found volumetric differences between SCD and healthy elders (van der Flier et al. 2004; Striepens et al. 2011; Hays et al. 2018b) while the structural changes observed in SCD exhibit similarities with the later stages of the AD continuum, showing the potential link of this preclinical stage to cognitive decline due to AD. Additionally, in our previous electrophysiological cross-sectional study (Lazarou et al. 2018), we have observed also significant differences between SCD and healthy elders with regards to brain activation, while the SCD showed several commonalities with MCI with respect to reduced activated brain regions after the presentation of visual ERPs.

On the other hand, MCI is a widely-known preclinical stage of the AD continuum and holds a great risk on developing AD. It is characterized by well-established criteria (Petersen et al. 2001) and has been

found to manifest particular brain changes and cognitive limitations relevant to AD (Storandt et al. 2006; Palmer et al. 2008; Reisberg et al. 2008; Bennys et al. 2011; Liu et al. 2011; Dimitriadis et al. 2018a). More specifically, a great body of literature proposes that the MCI stage and in particular the amnestic subtype can be considered as a harbinger of future cognitive decline of AD (Ganguli et al. 2004; Drzezga et al. 2005; Fischer et al. 2007; Olichney et al. 2008; Palmer et al. 2008; Nordlund et al. 2010; Brown et al. 2011; Yang et al. 2014; Verfaillie et al. 2018b). In general, the annual conversion rate from a healthy aging population to AD ranges from 0.17% to 3.86% (Petersen et al. 2001), whereas in MCI these rates are around 6 and 40% (Geslani et al. 2005).

Finally, normal aging, according to (Harada et al. 2013), "is associated with declines in certain cognitive abilities, such as processing speed and certain memory, language, visuospatial, and executive function abilities. However, these changes are small and should not result in impairment in function". In research around brain disorders when we conduct cross-sectional studies about normal or cognitively intact elders, we suggest that these participants do not meet the inclusion criteria of pathologies that may contribute to cognitive decline and they do not have a self-perceived feeling of forgetfulness or any other impairment in any cognitive function. Additionally, their cut-off scores in the standardized and validated neuropsychological tests, as well as respective screening tools (i.e., Global Deterioration Scale, CDR, etc.) are within the normal range. In a nutshell, the only differentiation between SCD and normal aging is that the SCD have a consistent feeling of gradual subtle cognitive memory worsening compared to the past, but with no objective decline as measured by neuropsychological tests compared to MCI or AD. However, to the best of our knowledge, there is no commonly acceptable definition or any consensus about the normal aging process exists so far. Figure 1 illustrates the different cognitive stages of elderly population, ranging from cognitive healthy aging to AD.

{Figure 1 about here}

Although SCD might be considered as a prior stage of MCI, until now it is unclear which of the SCD elders will probably convert to MCI and subsequently AD (Mitchell et al. 2014; Moreno-Grau and Ruiz 2016). Nevertheless, people with SCD have been found to exhibit neurodegenerative changes in their brain (Elfgren et al. 2003; Babiloni et al. 2010; Li et al. 2016; Hays et al. 2018a; Lazarou et al. 2018; Li et al. 2018a) in similar regional patterns with people in more advanced stages of the AD continuum (van der Flier et al. 2004; Rodda et al. 2011; López-Sanz et al. 2017a, 2017b; Shu et al. 2017). Several studies have examined the volumetric differences and brain activity among SCD people (Jessen et al. 2006; Babiloni et al. 2010; van Rooden et al. 2014; Hayes et al. 2017), while others have investigated connectivity and communication between brain regions of people with SCD (Bajo et al. 2012; Hafkemeijer et al. 2013; Wang et al. 2013; López-Sanz et al. 2017b; Yan et al. 2018) by investigating brain connectome and network properties through graph theoretical approaches (Broyd et al. 2009; van den Heuvel and Hulshoff Pol 2010; Mevel et al. 2011; Sexton et al. 2011; Badhwar et al. 2017; Contreras et al. 2017; Hayes et al. 2017; López-Sanz et al. 2017b; Shu et al. 2017; Verfaillie et al. 2018a, 2018b). All the above highlight the importance of investigating the brain alterations of people with SCD by using graph network properties.

In general, graph theory in brain research presents “a network as a set of nodes, which are the components of a system (represented in the brain network perspective as a region of interest - ROI, and a number of edges, representing the connection (functional connectivity - FC) between each pair of nodes” (Sanz-Arigita et al. 2010; Eid and Saleh 2013; Gits 2016). Several neuroimaging tools (e.g., MRI, EEG, etc) have been extensively used in order to extract different network properties. A framework of brain network analysis with the most frequent network properties studied is illustrated in Figure 2. The hypo-synchronization between two nodes could entail difficulties in the successful communication between

brain regions which decreases the potential of effective information transfer, which in turn leads to memory disturbances. Over the last decade more and more studies have suggested that the human brain can be depicted as a network, showing the brain connectivity among multiple brain regions, the so-called "brain connectome" (Sporns et al. 2005). Brain connectome "provides a more holistic view by assessing and modeling the entire human brain as a set of several networks and assessing the whole-brain organization, widespread changes or disruptions as an entity" (Dickerson and Sperling 2009; Brier et al. 2014; Kim et al. 2016). Several studies have suggested that apparent connections in brain networks appear both in early stages such as SCD and MCI as well as in later ones such as AD (Stam et al. 2005; Knyazeva et al. 2010; Tahaei et al. 2012; Wang et al. 2013, 2016; Xu et al. 2014; Hu et al. 2016; Contreras et al. 2017; López-Sanz et al. 2017a, 2017b; Shu et al. 2017; Zheng et al. 2018). Investigating the changes in preclinical stages of the AD continuum, from a brain connectome perspective, may give an insight into new hypotheses on the pathophysiology of the disease that cannot be ascertained with information from current neuropsychological and clinical assessment or by investigating isolated brain regions (Papaliagkas et al. 2008; Rossion and Caharel 2011; Smart et al. 2014). The most common network measurements which are being extensively used in brain connectome studies and which will be discussed in sections 6.1.1 - 6.1.2.2 are presented in Table 1.

{Figure 2 about here}

Table 1 Commonly Studied Network Modalities of Brain Connectome Studies

Network Modalities	Meaning
Small World	The small-world measure is defined as the clustering coefficient divided by the path length, and a network is considered "small-world" if this measure is greater than 1
Functional Connectivity	Functional connectivity is determined as the connection among multiple brain structures that have similar functional properties (i.e., nodes of DMN)
Rich Club	The extent to which central or well-connected nodes also interconnect to each other
Path Length	The minimum number of edges that must be traversed to reach from one node of interest to another
Clustering Coefficient	The number of connections between the nearest neighbors of a node proportional to the maximum number of connections
Transitivity	The transitivity is based on the relative number of triangles in the graph, compared to the total number of connected triples of nodes
Modularity	Modularity shows the strength of division of a network into modules (clusters)
Degree Centrality	The number of connections from the node of interest to other nodes of the network
Eigenvector Centrality	The connections of a node to other nodes which have also high scores in the network
Betweenness	The proportion of shortest paths between any two nodes that pass through this node
Global/ Local Efficiency	The average global or local efficiency of subgraphs for each node containing the neighbors of that node

More specifically, it has been suggested that FC alterations in people at risk of shifting to more advanced stages of cognitive impairment after some time, may happen before severe brain damage and volumetric changes, objective neuropsychological deficits and severe clinical manifestations take place (Wang et al. 2007; Dickerson and Sperling 2009; Rodda et al. 2010; Mevel et al. 2011; Hafkemeijer et al. 2013; Badhwar et al. 2017; Li et al. 2018b). Several studies proposed that potential AD individuals, from the preclinical to dementia stages, have severe network distributions leading to more apparent connections

between hub regions (Daianu et al. 2013, 2014). In particular, alterations in the precuneus (PUN), which is considered as a main component of the Default Mode Network (DMN), have been suggested to begin more than 15 years before the manifestation of dementia-related signs (Bateman et al. 2012). Moreover, several regions vulnerable and disrupted due to AD pathology coincide with the key regions (hubs) of the DMN (Sanz-Arigita et al. 2010; Zanchi et al. 2018) and SCD (Hafkemeijer et al. 2013; Verfaillie et al. 2018a). Furthermore, disrupted connectivity over brain regions of the DMN demanding encoding tasks has also been exhibited in individuals who are prone to develop AD due to genetic profiles, showing widely interruptions over the medial temporal lobe (MTL), PUN and cingulate gyrus (Bookheimer et al. 2000; Bondi et al. 2005; Han et al. 2007; Borghesani et al. 2008). There are also several studies which have demonstrated that FC disruption involves the posterior DMN (pDMN), comprising largely the posterior cingulate cortex (PCC), which is considered as a key hub region of the DMN since it is the only hub directly connected to the rest DMN nodes (Dillen et al. 2017). These disruptions in the pDMN are evident in the earliest stages of AD and MCI (Wang et al. 2006; Zhang et al. 2009; Cai et al. 2017; Zanchi et al. 2018), showing decreased FC between parietal and occipital regions.

Therefore, disruptions of network properties associated with SCD could provide insightful suggestions as regards the diagnosis and treatment planning; by showing whether the resemblance of brain connectome and FC alterations of SCD with respect to MCI, AD and HC may constitute precursors of SCD progression into more severe AD stages. Although three recent systematic reviews have investigated FC alterations in the AD spectrum and brain connectome (Broyd et al. 2009; van den Heuvel and Hulshoff Pol 2010; Badhwar et al. 2017), none of them have used the term of "Subjective Cognitive Decline (SCD)" in their research criteria. More specifically, in (Badhwar et al. 2017), the authors only searched for resting state fMRI studies with AD or MCI and age-matched healthy controls participants, leaving outside studies which explored the potential disrupted network properties investigated with other neuroimaging tools, such as MEG. In another systematic review (Broyd et al. 2009), the authors conducted a precise and thorough literature search solely for DMN dysfunction in a wide variety of mental disorders, leaving outside the SCD population since the first reported study which examined brain network properties in SCD subjects was published in 2012 (Bajo et al. 2012). Other researchers (van den Heuvel and Hulshoff Pol 2010) reported several neuroimaging studies, which had explored FC by investigating the level of co-activation of resting-state fMRI among several brain regions by using new methods of human brain analysis. This particular review did not explore potential findings of brain connectome from other studies which observed brain network alterations with other neuroimaging tools, such as MEG. As a result, the existing reviews are mostly composed of studies focusing on comparing cognitively healthy elders with people at more advanced stages such as MCI and/or AD or other neurological disorders; additionally, there are studies investigating properties of a particular network (i.e., the DMN) by using a specific neuroimaging tool (i.e. fMRI). There are only a few existing studies reporting brain network disturbances and apparent connections in people at earlier stages of the AD continuum, which indicates that research on SCD using the brain connectome is really in its infancy. To the best of our knowledge, no existing review study summarizes and explores the findings of all studies in the field of brain connectome in SCD population. The present systematic review is the first combined approach to explore the potential disruption of brain connectivity and topologic alterations in people with SCD, by reviewing and reporting studies which have explored the whole-brain connectome or a specific network such as the DMN, the Gray Matter Network (GMN) and the White Matter Network (WMN), with a wide variety of neuroimaging tools.

2 Objective

This systematic review focuses on brain connectome studies which explored whether FC alterations of individuals with SCD compared to MCI, AD and HC can help us drive conclusions on the potential progression of SCD into more advanced stages of cognitive impairment related to AD pathology. Cognitive decline in people with AD and MCI is not only caused by the damage of a single or local brain region but also results from changes in several brain areas. Thus, the connections across brain areas along with the investigation of brain connectome of pre-dementia stages could be insightful. Therefore, we present a number of studies with the intention to provide a better understanding of brain connectome in people with SCD and highlight its importance in the early detection of cognitive decline, as well as its potential predictive value on the progress of the disease. The discussed studies demonstrate the brain connectome and the network-based current research on SCD in order to facilitate the detection of the affected brain regions as well as FC interruptions. Graph theory approaches have been used in order to explore the topologic alterations of the brain connectome in people with SCD. The analysis and comparison of SCD with healthy controls and other patient groups (e.g., MCI or AD) may highlight the underlying pathological mechanisms of AD from the early preclinical to more advanced stages which entails better prospects for future treatment or cognitive decline forestallment. This systematic review has a three-fold goal: a) to highlight which connections between specific brain regions (nodes) are commonly affected in the earliest stages of cognitive decline such as SCD; b) to examine the connectivity abnormalities (hub alterations) and network properties (e.g. small world, rich club, etc) in the SCD population compared to other people with cognitive impairment and healthy elders; c) to summarize the current state of brain network research with emphasis on its application to SCD.

3 Review Question

In order to answer our review question and summarize the review objectives, we adopted the “Population, intervention, comparison, and outcomes (PICO)” framework, which is presented in Table 2.

Table 2 Review Question (PICO)

Population	Intervention	Comparison	Outcome
People with SCD of no other medical etiology except cognitive impairment possibly related to future AD progression	Neuroimaging tools (MRI, EEG, PET, MEG, DTI) and brain connectome (e.g., DMN, GMN, WMN, etc)	Healthy controls or other patient groups (e.g., MCI, AD)	Functional Connectivity, Communication of brain regions, Topological alternation of brain connectome, Synchronization, Hub regions

4 Methods

4.1 Search Strategy

We have searched the following electronic databases for any study related to the review question: EMBASE, Scopus, IEEExplore, MEDLINE / PubMed, Research Gate, and Google Scholar. The focus of our search was brain connectome and brain networks based on graph theory as measured by any neuroimaging tool (MRI, EEG, and MEG) in people with SCD. Studies related to cognitive decline due to other medical reasons such as Multiple Sclerosis, epilepsy, Parkinson's disease, stroke, etc., or studies with cognitively intact participants only were excluded from our review. We searched the databases using the following keywords, either separately or combined: “subjective cognitive decline” or “SCD” or “subjective cognitive impairment” or “SCI” or “subjective memory complaints” or “SMC” or “subjective

cognitive complaints" or "SCC" or "cognitive complaints" or "cognitive impairment" or "elders" or "Alzheimer's Disease" or "AD" or "mild cognitive impairment" or "MCI" or "cognitive decline" or "dementia" or "brain imaging" or "Magnetic Resonance Imaging" or "MRI" or "neurophysiology" or "neuroimaging" or "Magnetoencephalography" or "electroencephalography" "EEG" or "Diffusion Tensor Imaging" or "DTI" or "brain networks" or "network" or "default mode network" or "DMN" or "executive control network" or "salience network" or "sensorimotor network" or "auditory network" or "visual network" or "gray matter network" or "white matter network" or "functional connectivity" or "connectome" or "resting state networks" or "functionality" or "synchronization likelihood" and "connectivity".

We have considered only English-language articles that directly analyzed network properties in participants with SCD. We conducted the systematic review with journal papers and conference articles up to 30 December 2018, following the instructions of the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA)" (Liberati et al. 2009).

4.2 Study Selection

We screened both the title and the abstract of the identified studies for relation to the objective of our review. Studies which were considered unsuitable for the review topic were removed. Also, studies relevant to the review question, but probably not very suitable on the grounds of study participants or brain network analysis were examined by the authoring team and then excluded or qualitatively analyzed. Finally, only full text/papers, which matched the inclusion and the selection criteria, were evaluated for this review. The flow chart of Figure 3 was used to facilitate the selection process of our study.

4.2.1 Methodological Quality Assessment of the final included Studies

In order to assess the quality and methodology of each included study individually, we used the "Critical Appraisal Checklists for an Article (CASP)".The majority of the criteria in the CASP checklist consists of general features and fundamental elements of building research protocols (e.g. clear research statements, recruitment strategy). Every author assessed the methodological quality of the final included publications individually. In detail, the authors assessed all selected studies which met the checklist quality criteria and any diverging ones were discussed until we reach a consensus.

4.3 Data Extraction

Our search identified 2,102 potentially relevant papers. We further examined if there were any duplicates of the retrieved articles (23 duplicates identified and removed). Of the remaining 2,079 articles, 1,536 studies were removed after title screening. Five hundred and forty-three (543) articles were screened thoroughly, based on both title and abstract, to only include studies involving individuals with SCD related to AD and brain network analysis. The process of title, abstract, and whole text screening yielded a total of 38 publications that met the inclusion criteria. Further screening of the 38 studies focused on brain connectome, and the existence of network analysis based on graph theory in the target population (SCD). As a result of this process, the sample was further reduced to 16 articles (Figure 3) published between 2012 and 2018 (Figure 4). In the following sections, we appraise these articles with respect to participant characteristics, the neuroimaging tool used, the utilized network-based analysis, the clinical findings, and outcomes.

{Figure 3 about here}

{Figure 4 about here}

5 Eligibility criteria for this review

5.1 Participant Types and Model Systems

The studies that have been finally selected should definitely include participants with SCD of no other medical etiology except for its potential link to AD. Some studies involved both cognitively intact (Healthy Controls) and individuals with cognitive decline within the AD spectrum (e.g., MCI and/or AD). Specifically, participant types included: Healthy Controls (HC), Subjective Cognitive Decline (SCD), Mild Cognitive Impairment (MCI) and Alzheimer' Disease (AD).

5.2 Selecting Eligible Studies

- ***Population****:* We excluded studies if they only included HC or only MCI and AD. Furthermore, we excluded studies on the basis of subject age (elderly population only). However, we did not exclude studies on the basis of gender or education.

- ***Interventions****:* We chose studies which only used EEG, MRI (structural MRI, functional MRI and MRI using the DTI method) and MEG with representative subjects (e.g. people with SCD). We opted for studies that demonstrated, explored the usability or compared implementations of network properties (e.g., FC, network properties like small world, path length, etc) or other connectome analysis with the aforementioned mechanisms. Moreover, we selected studies that demonstrated or compared network properties with other well-established clinical or neuropsychological measurements or biomarkers (e.g., APOE, CSF) between different groups. We excluded studies the main focus of which was to compare different algorithms on the grounds of network analysis.

- ***Comparators****:* We decided on studies with a design that also included HC or people of advanced stages such as MCI and AD or other patient groups or studies which deployed interventions so as to provide a comparison between different SCD groups (i.e. intervention vs. no-intervention group).

- ***Outcomes****:* We picked studies that reported differences among different groups (observational studies) or studies which explored participants' FC improvement after an intervention (clinical studies) or studies that examined participants longitudinally (longitudinal prospective studies).

- ***Study designs****:* Given the nature of neuroimaging studies, there was a wide range of different study designs. The following study types were included: Randomized controlled trials, Controlled trials, Cross-sectional, Observational studies with a comparison group and Prospective longitudinal studies.

6 Data Synthesis- (Results)

6.1 Description of Studies-Target Population Characteristics

From the 16 selected studies, only two investigated brain connectome including an SCD group without other groups as comparators. In the first study, a clinical trial was conducted with Ganglioside administered to SCD patients, while the other examined the SCD cohort longitudinally. A total of 13 studies involved both HC and SCD participants. The majority of studies also included participants with MCI (nine studies); while some included participants at different stages of AD (four studies). Among the selected ones, seven used fMRI, four used MEG, three applied the DTI method and two used structural MRI as neuroimaging tool. Although we searched for studies using EEG to study brain connectome in SCD population, we did not find any published study which met our research criteria (e.g., EEG related studies only included MCI or AD). All aforementioned studies are presented in detail in Table 3. The majority of these studies examined the participants for general cognitive function and reported their

demographic characteristics. The mean values of the Mini-Mental State Examination (MMSE) across groups (HC, SCI, MCI, and AD) are illustrated in Figure 5, while age and gender mean values of the final selected studies are depicted in Figure 6 and Figure 7 respectively.

6.1.1 Studies which used Magnetoencephalography (MEG) for Brain Connectome in SCD

Magnetoencephalography (MEG), as a neuroimaging tool, has been extensively "used to capture pieces of information about how local and long-range oscillatory patterns change across brain regions in people with a wide variety of disorders" (Stam 2010; Alamian et al. 2017). Table 4 presents a more detailed description of the main methodology adopted by the authors of MEG studies.

However, the first ever study which deployed MEG in order to measure synchronization of different bands (alpha, beta, and gamma) and FC of different brain regions in people with SCD was conducted almost seven years ago (Bajo et al. 2012). Authors adopted a whole brain static FC approach on the sensor level employing Synchronization Likelihood (SL) as a proper FC estimator. By comparing the SL of different bands among SCD, MCI, and HC during a memory task, the study proved that the SCD group presented several commonalities as regards brain connectivity to HC, but in general, they presented a lower SL value. When comparing HC and SCD, the HC showed statistically significant higher SL values over the *left temporal lobe, anterior brain areas* and *posterior regions* in frequencies between *alpha1* (8–11 Hz) and *beta2* (25–35 Hz). On the other hand, MCI exhibited higher SL values in almost all regions of *anterior, frontal, posterior* and *central* areas in almost every frequency band (except band *alpha2*) compared to HC. This finding paved the way to suggest that when memory deficits become severe enough to be identified by clinical and neuropsychological assessment, people at MCI stage tend to combine information between both frontal lobes and establish better cognitive strategies while achieving a common performance pattern compared to other earlier stage groups. The increased SL in MCI compared to HC is in alignment with other studies suggesting that MCI causes hyperactivity of specific brain regions so as to compensate for their cognitive impairment and widely apparent connections between brain areas as a result of cognitive dysfunction (Cabeza et al. 2002; O'Brien et al. 2010; Kim et al. 2012; Chechko et al. 2014). Finally, decreased SL in the SCD compared to HC could implicate memory disturbances commonly occurring in daily living activities.

Along the same line, another milestone study used MEG to investigate whole-brain FC resting state networks on the source level using an Oxford - Harvard atlas of 64 ROIs, which were further integrated in well-known sub-networks such as the dorsal attention network (DAN) and the DMN in alpha band among HC, SCD and MCI (López-Sanz et al. 2017a). In particular, they observed higher FC over the anterior network both in MCI and SCD participants in comparison with HC. The interrupted connections over anterior regions were basically located in the *left Amygdala, right Frontal Medial Cortex and left Anterior Inferior Temporal Gyrus with left Anterior Cingulate Gyrus and left Paracingulate gyrus.* The posterior network presented lower FC in the MCI group and comprised 14 connections between posterior cortical brain areas, such as: "*temporal medial structures* (both *hippocampi* and *right parahippocampus*), *parietal* (*left Postcentral Gyrus, both Supramarginal Gyri*), and *occipital* areas (*left Frontal Pole, both Superior Occipital cortices, right Inferior Occipital Cortex, right Lingual Cortex*)". All connections over anterior regions which had increased FC in both SCD and MCI exhibited significant negative correlation with neuropsychological tests assessing language; this meant that participants with higher FC hyper-synchronization in the particular connections of the abovementioned brain regions showed worse performance in tests assessing cognitive functions such as language and complex executive functioning. SCD also showed decreased FC in several connections between *posterior regions* of both hemispheres. In the SCD group, the neuropsychological tests and the abovementioned brain areas were negatively correlated. Most importantly, almost all disrupted connections observed in the SCD participants were

similarly affected in the MCI group. Finally, the statistical analysis also showed a significant decrease of FC with regards to DAN both for SCD and MCI compared to HC.

A pioneering study investigated network properties by using graph theoretical models in order to examine resting state activity brain network in theta (4–8Hz), alpha (8–12Hz), and beta (12–30Hz) bands (López-Sanz et al. 2017b). In total 52 ROIs were extracted from homogeneous resting state networks. A static functional connectivity graph was constructed per subject and frequency band by applying the Pearson correlation coefficient estimator over orthogonalized envelopes of pairs of time series. Both functional brain networks and structural MRI were compared across the three groups. In order to avoid the bias of network analysis due to the arbitrary selection of a proper thresholding scheme, the authors demonstrated global network metrics over a range of density values [0.05, 0.35]. Density denotes the percentage of the strongest connections over the whole set of functional connections. They found that all three groups (HC, SCD and MCI) showed small-world brain network properties since values were 1 in all matrices. However, concerning the global network clustering, MCI and SCD exhibited a decrease in beta and theta band compared to HC. Similarly, as regards local clustering and modularity in SCD, both properties were found to be somehow between HC and MCI in the density range matrix, whereas MCI exhibited modularity increases in the theta band. With respect to transitivity in the theta band, they observed a progressive and consistent decrease from HC to the rest of the groups. Nevertheless, transitivity was much more increased in the alpha band for the SCD compared to both HC and MCI. Moreover, SCD and MCI exhibited a "*posterior degree decreases"* in the theta band, while MCI also exhibited an increase over *anterior* regions in theta and beta band. More specifically, the nodes of posterior areas which were affected by this degree decrease involved the "*bilateral occipital, middle temporal lobe and parietal areas including two nodes located in the left precuneus"*. Brain regions with increased nodal degree included the "*bilateral middle and superior frontal gyrus, left hippocampus, anterior cingulate cortex,* and the *insula"*. Additionally, SCD showed a nodal degree increase over the *left postcentral node* compared to HC in the beta band and nodal decrease in the *left superior occipital lobe* compared to MCI in the alpha band. These results show a similar pattern with reference to FC both for MCI and SCD, exhibiting anterior hyper-synchronization with an FC decrease over identical posterior brain areas. Interestingly, the authors did not find a pattern in the nodal degree of the SCD group, suggesting that despite the significant synchronization alterations widely observed in SCD participants, many network properties seem to be preserved, compared to the advanced MCI stage.

Another study employed a more combined approach using MEG and compared their results with hippocampal volumes in structural MRI to seek for any FC disruption of the alpha band and structural differences among people with SCD, HC and MCI [74]. Despite the fact that SCD had a within the normal range neuropsychological profile and no differences were observed in the hippocampal volume of SCD with regard to HC, significant differences were found in alpha band between HC and SCD under the framework of spectral analysis. Specifically, SCD presented decreased alpha relative power in several brain regions. The most significant differences were basically located over the "*bilateral prefrontal areas, bilateral middle* and *superior temporal lobe* and also *bilaterally over calcarine fissure* and *cuneus (CUN)* in the *occipital lobe"*. The regions which showed significant low FC were highly overlapped with core brain areas of the DMN (e.g., *medial prefrontal areas, parietal areas, etc)*. MCI showed a common pattern of reduction as SCD in alpha band activity over "bilateral occipital areas *(Inferior occipital, calcarine, lingual gyrus,* and *CUN),* bilateral prefrontal areas (*orbitofrontal cortex, middle* and *superior frontal gyri*) and small portions of the *bilateral temporal poles"* compared to HC.

The findings of the abovementioned MEG studies prove that disrupted connectivity of brain connectome would start in the preclinical stages of the AD continuum, such as the SCD stage. This is indicated by an

initial increase of FC over the anterior region and decreases over posterior areas, while in more advanced stages, this pattern is more obvious followed by further posterior decreases of FC. Therefore, the difficulties in bringing about a successful connection among different brain areas reduce the potential of ~~a~~ successful information transmission leading to memory difficulties frequently observed in SCD.

6.1.2 Studies which used Magnetic Resonance Imaging (MRI) for Brain Connectome in SCD

Not only can MEG-based resting-state functional neuroimaging show FC alteration in elderly with SCD, but also MRI has been considered as a powerful neuroimaging tool for brain connectome investigation (Hafkemeijer et al. 2013). There are several studies which have provided valuable insights for the brain FC of SCD population (Hafkemeijer et al. 2013; Jeon et al. 2016; Verfaillie et al. 2018a), MCI (Contreras et al. 2017) and AD (Dillen et al. 2016; Contreras et al. 2017; Franzmeier et al. 2018). A great body of literature with MRI studies has suggested that AD affects specific distributed brain networks (Badhwar et al. 2017). Since FC at resting state condition is considered as a reflection of the link between neuronal activities of several brain regions separated anatomically, the investigation of the structural connectivity (SC) between brain regions using MRI has gained interest. In particular, brain connectome through fMRI has been extensively explored in several studies which have produced valuable results of brain connectivity in people within the AD spectrum (Borghesani et al. 2008; Afshari and Jalili 2017; Badhwar et al. 2017). In the next section, we demonstrate and analyze the studies which have deployed functional MRI (fMRI), structural MRI (sMRI) or the Diffusion Tensor Imaging - Tractography (DTI) method to study brain connectome and network properties in people with SCD. Table 3 summarizes the basic information of the selected studies including demographics, modality, brain areas and results.

6.1.2.1 Structural Magnetic Resonance Imaging (sMRI)

To the best of our knowledge, there is only one study which has so far investigated explicitly brain network changes (Gray Matter Network - GMN) of an SCD cohort (*n*= 231) longitudinally (3 years) and by using sMRI (Verfaillie et al. 2018b). Their findings suggested that lower values of path length in *PUN* as well as in *fronto - temporal - occipital* cortices with lower values at baseline of clustering coefficient, betweenness centrality, and small-world properties were generally linked with a gradual lower performance in language and global cognition, as measured by neuropsychological assessment. Lower values as regards the path length in the "*left superior and inferior frontal, right middle frontal and superior occipital, left CUN and middle occipital, left PUN and right transverse temporal gyri* were correlated with worse performance in global cognitive function. Conversely, hippocampi volumes did not substantially play a pivotal role in these results, showing that GMN alterations and changes could be considered as additional informative measures over the volumetric values. These converging pieces of evidence imply that GMN could underlie very discreet structural brain alterations predicting the future decline of cognitive performance associated with AD over time.

6.1.2.2 Diffusion Tensor Imaging – Tractography (DTI)

Three DTI studies met our eligibility criteria and all of them have explicitly examined White Matter Network (WMN) properties among SCD and other groups such as HC, MCI and AD. One of the studies used DTI in order to investigate brain connectome and more specifically the organization of WMN in people with SCD compared with amnestic MCI (aMCI) and HC (Wang et al. 2016). They constructed fully-weighted structural brain networks by employing the product of fiber number and mean fractional anisotropy of the connecting fiber. They adopted the Automated Anatomical Labelling (AAL) template with 90 ROIs. By estimating nodal betweenness centrality and applying a 10% threshold on the top-ranked values, nine hub areas were revealed per group. By examining those nine hubs, they found that all groups presented a small-world organization. However, they found differences among the different groups relating to the values of the characteristic path length, global and local efficiency. Their results showed statistically significant decreased global and local efficiency and at the same time increased

characteristic path length only between aMCI and HC, and not in other cross-sectional comparisons between groups. The right *PUN* was found to have reduced centrality, whereas increased centrality was found in *CAL* and *PUT* in the aMCI group compared to HC. Decreased centrality was also observed in *PUN*, while increased centrality was basically located over the *Anterior Cingulate Gyrus* (*ACG)* and Putamen (*PUT)* in aMCI as to SCD elders. Brain areas with significant diversities of betweenness centrality among the participants of the three groups were found in the right *PUN*, *PUT*, *calcarine fissure* and surrounding cortex (*CAL*) and *left ACG*. Consequently, SCD participants were found to have values intermediate to aMCI and HC, implying a common dysfunctional motive but more preserved as regards aMCI.

Similarly, a recent study examined the organization of brain structural connectome in SCD compared to HC (Shu et al. 2017). Their findings suggest that, compared to HC, SCD had longer shortest path length, lower strength of the rich-club, less connection strength, global as well as local efficiency, which was mainly located over the *bilateral prefrontal regions* and *left thalamus*. Although both HC and SCD showed organization of WMN small-world, less nodal efficiency in the SCD group was found in the "*bilateral orbital* part of *middle frontal gyrus, the bilateral orbital* part of the *superior frontal gyrus, the right anterior cingulate* and *paracingulate gyrus, the left temporal pole* of *superior temporal gyrus, the left thalamus, the left superior occipital gyrus,* and the *right CUN"*. The disrupted SC was generally located in the *bilateral frontal, temporal, parietal,* and *occipital* areas, including both long and short range connections. Disrupted nodal efficiency was widely located in the "*bilateral orbital frontal cortex, left thalamus, left temporal pole* of *superior temporal gyrus, right anterior cingulate* and *paracingulate gyrus,* and *several occipital regions"*. With respect to SCD, there was a strong positive correlation between the rich-club and local connections and the total scores in the delayed recall of the auditory verbal learning test. Evidently, disrupted brain network properties are commonly observed both in functional integration and segregation in the SCD.

Finally, a recent study tested WMN rich-club among SCD, HC, aMCI and AD (Yan et al. 2018). They constructed a fully-weighted structural brain network by adopting the AAL template with 90 ROIs and a weighting strategy for every existing connection. The "fractional anisotropy based inter-regional connection (FABIRC)" was calculated as the mean of the FC values of all the detecting streamlines that formed the connection between two regions. Their results suggest that the rich club organization was interrupted, since decreased connectivity across rich-club nodes was found in MCI and AD, but was relatively preserved in SCD compared to HC. In detail, the SCD, MCI, and AD exhibited common patterns of disconnected peripheral brain areas and decreased connectivity in these brain regions, underlying their role and involvement in cognitive impairment as a preclinical manifestation of SCD. In particular, the strength of connectivity was tested by investigating three types of connections, i.e. a) local connections of nodes in peripheral regions, b) feeder connections among nodes of both peripheral areas and rich-club, and c) connections among key nodes of the rich-club. Strength of local connectivity was significantly decreased in the patient groups compared to HC, suggesting that these three groups had aberrant connections among peripheral brain areas. Despite the fact that cross-sectional statistical analysis revealed no significant difference between SCD and MCI, MCI exhibited lower values compared to SCD. Apparent feeder connections between peripheral and rich-club nodes were found in all groups compared to HC, following gradual disruption in SCD, MCI and finally in AD. Significant clustering coefficient decrease was found in the three groups compared to HC. More specifically, characteristic path length was significantly higher in SCD with regards to HC and in AD compared to MCI, but no significant difference was observed between SCD and MCI. For SCD, three nodes demonstrated the most apparent connections compared to HC, including two peripheral nodes, the "*left caudate nucleus* (CAU.L) and the *left middle*

frontal gyrus, *orbital part* (ORBmid.L), and one rich-club node, the *right caudate nucleus* (CAU.R)". Also, the nodal efficiency of the *CAU.L* and *ORBmid.L was* found to have surprisingly common patterns as the disease progresses. It would seem that in SCD connectivity disruptions are basically located over local connections, while in MCI and AD it affects the whole network organization.

6.1.2.3 Functional Magnetic Resonance Imaging (fMRI)

A milestone study (Hafkemeijer et al. 2013) tested resting state FC of DMN and MVN among SCD and HC by using fMRI. The findings showed that participants with SCD exhibited reduced volumes of the *right hippocampus* and *amygdala, mPFC, bilateral ACC, CUN, PUN,* and *precentral gyrus* compared to HC. Moreover, a positive correlation was observed between *inferior and middle temporal gyrus* and the neuropsychological scores on visuospatial function tests. A positive correlation was also found between the neuropsychological tests assessing attention and the *frontal pole*. In contrast to the majority of brain connectome studies, this particular study found increased FC in the two resting-state networks in SCD compared to HC (the DMN and the MVN). Regions showing increased FC in the DMN included the "*right hippocampus, bilateral thalamus, PCC, CUN, left precuneus,* and *right superior temporal gyrus*, while structures with increased FC included the *bilateral ACC, CUN, PCC* and *PUN"*. However, the authors adopted an indirect way of assessing FC following resting-state network-based parcellation of the brain into eight templates. Then, by applying a dual-regression approach, individual time series were first extracted from the eight templates including the white matter and cerebrospinal fluid maps in spatial regression manner against individual fMRI map (first regression). Derived matrices – 3D maps described individualized temporal dynamics for every layout. At long last, the "ten regressors (eight from the layouts and two from the noise regressors) were entered in a linear model fit against individual brain maps (second regressor)" for defining unique fMRI per subject. The authors practically analyzed brain activity and not connectivity and this is a major drawback presented in the literature especially with fMRI modality.

Similar research examined brain alterations of DMN among HC, SCD, and MCI (Wang et al. 2013). The authors applied a group independent component analysis (ICA) and dual regression, as in (Hafkemeijer et al. 2013). The outcome of this preprocessing analysis of fMRI activity revealed that the SCD exhibited enhanced DMN activity in *right hippocampus PUN* compared to the MCI group, but showed significantly reduced DMN activity in the *right hippocampus* compared to the HC. Additionally, significantly reduced activity of DMN in the *right hippocampus* and *parahippocampal gyrus, right PUN,* and *thalamus* were widely demonstrated in the MCI compared to the HC. Although MCI exhibited lower activity than HC and SCD in key hubs of DMN, including *the right hippocampus, PUN,* and *right thalamus*, the SCD presented intermediate alterations and disruptions of DMN activity with MCI and HC in the *right hippocampus*. Moreover, positive correlations between DMN activity and neuropsychological tests were most obvious in the *right hippocampal gyrus, hippocampus,* and *thalamus*, whereas negative correlations were demonstrated between values of *the right hippocampus* and the CDR global score. The authors misinterpreted the results discussing their shreds of evidence under the umbrella of FC even though they analyzed brain activity via group ICA which yields a summarization of spatiotemporal brain activity (Hafkemeijer et al. 2013).

Likewise, another study examined the potential FC differences of DMN among SCD, HC and prodromal AD (Dillen et al. 2017). Specifically, the authors restricted their FC analysis between five nodes within the DMN by employing Pearson's Correlation Coefficient. Functional strength was investigated across *ventral medial prefrontal cortex (vmPFC), hippocampus, PCC, retrosplenial cortex (RSC)* and *inferior parietal lobule*. They observed apparent connections between anterior and posterior brain regions and disconnection of hippocampi and nodes of the posterior DMN as the disease progresses. As regards the

prodromal AD group, the authors observed aberrant connections between *frontal* and *parietal regions*. However, no significant difference was found between HC and SCD between the abovementioned regions, suggesting that either a limited number of SCD participants could possibly have subtle AD-pathology or those brain abnormalities were too sparse and difficult to locate. Moreover, in HC, all nodes from both lobes were part of a particular cluster which follows a unique order; it originates in the *PCC* and *RSC*, which are linked to the *IPL* and the *vmPFC*, and ends up in the *hippocampus*. With respect to SCD and AD participants, the DMN is organized in two basic arrays: a) in SCD, one cluster consists of *the PCC, the IPL,* and *the vmPFC*, whereas the second one includes the *RSC* and the *hippocampus*; b) in the AD group, the first array consists of the *PCC, IPL,* and *RSC*, while the second one the *vmPFC* and the *hippocampus*. These findings suggest that bilateral hippocampi are basically connected with the brain areas of the posterior DMN and are secluded from the DMN while the disease progresses.

Recent research also examined the DMN properties of a cohort of 124 elderly people with and without SCD longitudinally (for one year) by using resting-state fMRI (Verfaillie et al. 2018a). The authors adopted a framework with 122 segments which were afterwards placed on an AAL brain atlas in order to choose the predefined ROIs. Static FC graph was estimated by applying "Fisher *Z*-transformed Pearson correlation values", were calculated from the average starting and ending time sequences of every voxel between each combination of ROIs. SCD participants exhibited enhanced connectivity over posterior areas of the DMN with respect to the "*bilateral middle cingulate* and *left inferior parietal cortices"* and apparent connections of the medial temporal memory system (*MTMS)* as regards *PUN, middle* and *posterior cingulate, inferior occipital* and *left inferior parietal* lobes. Moreover, SCD exhibited a common connectivity pattern among the *posterior and anterior DMN, MTMS* and the rest of the brain regions. The FC among *dorsomedial prefrontal cortex*, the ROIs and the rest of the brain regions were equal among participants who showed the subjective feeling of memory difficulties and those who did not. No statistically significant differences of the volumetric values were found between the two groups since no connections were observed between *MTMS* and *anterior* or *posterior DMN* or between the other brain regions and baseline or follow-up cognitive tests. However, increased FC between *MTMS* and *posterior DMN* in SCD participants was correlated with worse performance in immediate recall neuropsychological tests in the follow-up.

A recent study tested whole brain network properties and several resting state networks (three patterns: RSN, VIS, FP-DMN) from 278 brain regions of SCD, MCI, AD and HC participants (Contreras et al. 2017). The authors estimated individual FC matrices by adopting Pearson's Correlation Coefficient as a proper connectivity estimator. Then, they concatenated the individual FC matrices into a group where every row represents the FC matrix of each individual, while columns correspond to the items of an FC matrix (upper triangular elements of a 2D matrix representation of the FCG). Applying FastICA onto this group graph, components and FC patterns associated with the cohort were extracted with relative weights across subjects. Their findings suggested that higher subjective awareness of memory problems, as revealed by the cognitive complaint questionnaire, was highly correlated with a decreased individual weight of both the RSN-pattern and VIS-pattern (visual network). Consequently, better episodic memory performance, as measured by relevant neuropsychological tests, was associated with increased connectivity between regions of FP and DMN. In a nutshell, increased levels of subjective feeling of cognitive impairment are highly correlated with decreased FC in the VIS network. Thus, the impairment in brain areas which have a pivotal role in the visual cognitive function might be linked with cognitive impairment at the preclinical stages of the AD continuum.

Another research group employed a combined approach to testing the potential of FC at a local and global level by measuring Degree and Eigenvector centrality respectively (Li et al. 2018a). They came into the

conclusion that SCD exhibit a generally disrupted local functional network which may not be observable at a global level. This disconnection basically compromises of the DMN nodes. By correlating their results with CSF, they found strong correlations between the FC and Tau values over the temporal brain areas. They noted that the functional disconnection in SCD may be due to the tau-related accumulation. Moreover, they found that SCD showed higher disconnection over the *MTL*, the *hippocampi* and the *fusiform gyrus*, whereas lower aberrant connections were located in the *inferior parietal gyrus (IPG)*, revealing disrupted connectivity at a local level of the DMN. However, they did not find any differences in FC between HC and SCD, which suggests that the SCD have relatively preserved global connectivity.

Comparably, another study examined the general left frontal (gLFC) seed-based connectivity among HC, SCI, MCI, and AD, some of which were Aβ positive and some were not (Franzmeier et al. 2018). Among the 40 SCD participants, 23 were Aβ positive whereas 17 were not. The gLFC was estimated among the *LFC* and the other brain regions, using Pearson's Correlation Coefficient. A higher concentration of CSF-tau with a simultaneous lower accumulation of Aβ42/40 ratio and hippocampal volume indicated an advanced level of AD pathology. Moreover, participants with increased gLFC connectivity tended to decline later on the total MMSE score instead of individuals with decreased gLFC connectivity and tau-related concentration as regards the SCD - Aβ positive group.

To best of our knowledge, there is only one study that has so far investigated the effects of a clinical compound in a randomized, double-blind, placebo-controlled trial of SCD people, by studying brain alterations in DMN (Jeon et al. 2016). The authors investigated whether FC between brain areas located within DMN and working memory change in SCD people following a ganglioside treatment. Three different groups of SCD were allocated to low, high dose ganglioside or placebo group, respectively. The results showed that volumetric properties of the *mPFC*, *PCC*, *PUN*, and *IPC* significantly increased in the ganglioside groups, particularly in the high-dose group. FC alterations of the *PCC/PUN* were increased more in both ganglioside groups (low and high-dose) than in the placebo group, while a significant correlation was also found with improvement in neuropsychological tests assessing memory. Their findings suggested that *PCC* and *PUN* are key regions highly correlated with working memory deficits, despite the fact that the SCD total scores fell within the normal range in the neuropsychological tests.

Table 3 Summary of brain network studies of SCD (2012-2018.

Authors	N of subjects	Network	Network Measure	Gender (M: F)	MMSE M (SD)	Age M (SD)	Neuroimaging Tool	Type of Study	Regions tested	Main Outcome
(Bajo et al. 2012)	25 HC 12 SCD 19 MCI	FC of alpha, beta and gamma bands	SL in alpha, beta, gamma bands	NA 3:9 NA	29.5 (0.7) 29 (1) 28 (1)	72 (8) 72 (6) 75 (3)	MEG	Cross-Sectional Study	whole brain analysis - sensor level	SCD and MCI showed lower SL in anterior, temporal and posterior areas compared to HC.
(López-Sanz et al. 2017a)	39 HC 41 SCD 51 MCI	DMN and DAN in the alpha band	FC	NA	29.0 (1.1) 28.9 (1.1) 27.4 (2.0)	70.4 (3.7) 71.6 (4.5) 73.0 (3.7)	MEG	Cross-Sectional Study	source level, 60 ROIs within DAN and DMN	SCD and MCI exhibited lower FC over posterior brain regions and higher FC over anterior areas compared to HC.
(López-Sanz et al. 2017b)	63 HC 55 SCD 69 MCI	resting state activity brain network in theta, alpha and beta bands	Small-world, Local and Global Clustering Coefficient, Transitivity, Modularity, Degree Centrality	24:39 13:42 22:47	28.9 (1.2) 29 (1) 26.8 (2.4)	70.7 (4.5) 71 (5) 71.9 (4.2)	MEG	Cross-Sectional Study	52 ROIs	MCI showed decreased small-world, local and global clustering coefficient, nodal degree and transitivity and increased modularity in theta and beta bands. SCD presented common disrupted patterns except for modularity, nodal degree, and transitivity.
(López-Sanz et al. 2016)	39 HC 41 SCD 51 MCI	alpha band patterns	FC	12:27 9:32 22:29	29 (1.1) 28.9 (1.1) 27.4 (2.2)	70.4 (3.7) 71.6 (4.5) 73 (3.7)	MEG and sMRI	Cross-Sectional Study	whole brain spectral analysis - source level	SCD and MCI exhibited a common pattern of disruption in the alpha band activity compared to HC.
(Verfaillie et al. 2018b)	231 SCD	GMN	Degree, Small- World Network Size, Path length, Connectivity	126:105	28.35 (1.56)	62.95 (9.25)	sMRI	Longitudinal Study	whole gray matter regions	Lower baseline values in Clustering Coefficient, Path Length and network size were correlated with linear

			Density, Clustering Coefficient, Betweenness Centrality							and worse performance in neuropsychological annual assessment (language and global cognition).
(Hafkemeijer et al. 2013)	29 HC 25 SCD	DMN	FC	17:12 14:11	27.9 (0.2) 27.2 (0.4)	71.3 (3.4) 71.4 (9.2)	fMRI	Cross-Sectional Study	mPFC, PUN, hippocampus, MVN, PCC, ACC, CUN, parietal cortex, and THA	SCD showed reduced volumes in several brain structures and enhanced FC in DMN compared with HC.
(Wang et al. 2013)	16 HC 23 SCD 18 MCI	DMN	FC	4:12 8:15 8:10	28.9 (0.9) 29.2 (1.0) 27.9 (1.2)	70.7 (6.0) 70.1 (7.3) 73.7 (9.1)	fMRI	Cross-Sectional Study	PCC, PUN, dorsal and ventral mFC, the lateral inferior parietal cortex and the medial temporal lobes	SCD and MCI presented decreased FC over DMN regions compared to HC.
(Jeon et al. 2016)	75 SCD -30 High-dose ganglioside group -30 Low-dose ganglioside group -15 Placebo group	DMN	FC	**High-dose** 7:23 **Low-dose** 7:23 **Placebo** 4:11	**High-dose** 27.4 (1.2) **Low-dose** 28.0 (1.2) **Placebo** 27.7 (0.9)	**High-dose** 53.4 (6.4) **Low-dose** 54.2 (5.4) **Placebo** 53.6 (5.2)	fMRI	Randomized Longitudinal Controlled Study	mPFC, IPC, PCC, and PUN	Increased FC over DMN hubs in ganglioside group.
(Contrer	13 HC	RSN	FC	1:12	NA	67.15	fMRI	Cross-	278 ROIs -	SCD showed a

as et al. 2017)	16 SCD 21 aMCI 8 AD	VIS FP-DMN		8:8 9:13 2:6		(5.50) 73.38 (7.95) 73.33 (8.98) 76.38 (8.89)		Sectional Study	three patterns	significant correlation between decreased FC in RSN and VIS and steeper cognitive decline in neuropsychological tests.
(Dillen et al. 2017)	25 HC 28 SCD 25 prodromal AD	DMN	FC	15:10 13:15 15:10	29.2 (1.3) 28.9 (1.8) 25.0 (2.2)	62.4 (7.0) 65.8 (7.8) 70.8 (6.2)	fMRI	Cross-Sectional Study	vmPFC, RSC, PCC, IPL and HP	SCD and prodromal AD had HP disconnected from posterior DMN regions. Prodromal AD showed disrupted connections of the vmPFC and PCC.
(Franzmeier et al. 2018)	**Aβ +** 25 HC 23 SCD 14 MCI 13 AD **Aβ -** 24 HC 17 SCD	gLFC-connectivity	FC	**Aβ +** 9:16 13:10 9:5 4:9 **Aβ –** 9:15 8:9	**Aβ +** 29.20 (0.96) 29.39 (0.78) 27.71 (1.68) 23.85 (2.82) **Aβ –** 29.67 (0.76) 29.06 (0.9)	**Aβ +** 67.76 (5.23) 72.26 (4.16) 74.64 (5.34) 71.31 (6.18) **Aβ –** 67.29 (4.6) 71.06 (5.53)	fMRI	Cross-Sectional Study	gLFC	Aβ+ participants showed increased FC of gLFC. Later onset of cognitive of AD in participants with higher levels of left frontal cortex connectivity.
(Verfaillie et al. 2018a)	56 HC 68 SCD	DMN	FC	16:40 26:42	NA	64 (5) 64 (5)	fMRI	Longitudinal Study	pDMN, avDMN, MTMS, and the connectivity of each with the rest of the brain and interconnectivity	SCD showed higher FC among regions of the pDMN and the MTMS, which was significantly correlated with cognitive decline over time.

									among regions of each network	
(Li et al. 2018a)	40 HC 44 SCD	Whole brain	Degree and Eigenvector Centrality	22:18 24:20	29.05 (1.18) 29.36 (0.75)	75.10 (5.39) 73.38 (5.81)	fMRI	Cross-Sectional Study	Bilateral hippocampus (HP), MTL, Fusiform gyrus, Inferior Parietal regions, and DMN regions	SCD showed higher degree in both HP and left fusiform gyrus and decreased degree in the inferior parietal region compared to HC. No difference was found between SCD and HC with regards to Eigenvector centrality.
(Wang et al. 2016)	36 HC 21 SCD 33 aMCI	WMN	Small-World, Path length, Degree, Strength, Global and Local efficiency, Betweenness Centrality	12:24 6:15 16:17	28.1 (1.9) 27.9 (1.5) 25.0 (3.0)	61.8 (7.5) 62.9 (9.2) 64.3 (9.7)	DTI	Cross-Sectional Study	SMA, PUT, THA, right PUN, CUN, left superior parietal gyrus (SPG), superior frontal gyrus and dorsolateral (SFGdor), caudate nucleus (CAU) and the right gyrus rectus (REC)	All groups showed small-world characteristics. SCD and aMCI showed lower efficiency and increased characteristic path length compared to HC. aMC showed decreased nodal strength of PUN and strong correlation between neuropsychological performance and betweenness centrality.

(Shu et al. 2017)	51 HC 36 SCD	WMN	Small-World, Path Length, Global and Local efficiency, Nodal Degree, Network Strength, Rich-club	18:33 15:21	28.1 (2.0) 27.5 (1.7)	62.2 (9.1) 63.5 (8.7)	DTI	Cross-Sectional Study	90 ROIs	Both HC and SCD had preserved small-world properties. SCD showed less network strength, rich-club organization, global and local efficiency, and longer path length compared to HC.
(Yan et al. 2018)	62 HC 47 SCD 60 aMCI 55 AD	WMN	Rich-Club, Clustering Coefficient, Path Length, Connectivity Strength	39:23 21:26 31:29 35:20	27.78 (2.25) 27.98 (1.72) 24.74 (4.12) 16.96 (6.33)	63.27 (8.11) 65.34 (8.35) 67.27 (9.39) 70.93 (9.80)	DTI	Cross-Sectional Study	90 ROIs - The rich club regions were: the left and right PUN, right and the left lenticular nucleus, PUT, left calcarine fissure and surrounding cortex (CAL.L), superior temporal gyrus (TPOsup.L), left THA, left and right CUN, left and right MTG, right CAU, right HP and the	The rich-club at low-degree regions and local connectivity strength were significantly decreased in SCD, aMCI, and AD compared to HC. Rich club nodes were relatively preserved in SCD compared to HC, while aberrant connections are observed in peripheral regions such as CAU.L and ORBmid.L.

									left temporal pole	

Table 4 Summarization of MEG-based studies in terms of basic preprocessing steps and adaptation of data brain network analytic pathways

Studies	Resting-State	Task	Template/Sources	Sensor Level	Whole-Brain Analysis	Sub-Graph-Analysis	Connectivity Estimator	Power Analysis	Topological Filtering	Network Analysis	Frequencies	Main Outcome
(Bajo et al. 2012)		Memory Task		✓	✓		Synchronization Likelihood				Alpha (1 & 2), Beta (1 & 2) and Gamma band	A statistically significant decrease of SL of SCD and MCI was found in the a2 frequency
(López-Sanz et al. 2016)	Eyes-Open & Eyes-closed		2459 sources placed in a homogeneous grid of 1 cm in MNI template		✓			Alpha			Alpha band	A statistically significant difference in alpha peak and relative power
(López-Sanz et al. 2017a)	Eyes-closed		64 areas of the reduced Harvard-Oxford atlas			DAN and DMN	Phase Locking Value				Alpha band	A similar decrease of FC in SCD and MCI in the a band
(López-Sanz et al. 2017b)	Eyes-Closed		60 ROIs extracted through spatially constrained spectral clustering, generating spatially coherent regions of		✓		Pearson Correlation Coefficient between the orthogonalized envelopes of		Density over a range of values	Small-worldness, clustering, modularity, and	Alpha, Beta and Theta band	Statistically significant decreased was found in beta and theta

			the homogeneous resting state. Finally, 52 cortical areas were selected.				two-time series			transitivity		frequency

{Figure 5 about here}

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7 Discussion

It has been proposed that SCD may precede MCI, which many times progresses to the later stages of AD (Glodzik-Sobanska et al. 2007; Reisberg and Gauthier 2008; Reisberg et al. 2010). Whether there is a possible relation between pathological interruptions and brain connectome disruption demands further investigation. Our systematic review summarizes the main findings in brain connectome and SCD while underlying the added value of connectome-based metrics to draw conclusions on the progression of SCD into more advanced stages of the AD spectrum. Our study confirms and unveils the disrupted mechanisms of brain connectome of people at the preclinical stage of cognitive impairment, the so-called SCD, and highlights the potential of future connectome-based biomarkers for the detection of early cognitive deficits. Additionally, it suggests that disrupted brain functions, which are basically defined by apparent connections between specific nodes, may be related to SCD. This implies that SCD can be considered as an intermediate stage between the two stages, healthy aging and MCI. The reported studies explored how structural and functional connectome is altered in SCD adapting global and local network properties. However, there is no study that attempted to fuse connectomic meta-analytics across different modalities. Additionally, the most heterogeneous pre-processing step in the reported studies was the adaptation of a different anatomical parcellation scheme. This diversity prevented the integration of current findings from different modalities into certain well-known networks.

The majority of resting state studies mainly examined the connectivity between DMN nodes and found disrupted lesions and aberrant connections in SCD with regards to HC (Wang et al. 2013; Contreras et al. 2017; Dillen et al. 2017; López-Sanz et al. 2017a); some reported conflicting results, showing increased FC in SCD with respect to HC (Hafkemeijer et al. 2013; Verfaillie et al. 2018a). More precisely, the results of most studies denote that SCD exhibited significantly less DMN connectivity, which was basically located over the right hippocampus when compared to HC (Wang et al. 2013). Decrease of functional coupling of the vmPFC to left-sided PCC and the IPL was found in SCD (Dillen et al. 2017), as well as in connections between posterior cortical brain areas (medial structures, parietal and occipital areas) compared to the HC group (López-Sanz et al. 2017a). Possibly, there is mutual information transfer and bilateral activity between DMN and parietal areas of the brain strongly involved in memory retrieval (Wagner et al. 2005) and widely interrupted in AD. Thus, these findings imply that interdependent and forceful connections among the brain regions which are part of the frontoparietal network and play a key role in the DMN, are crucial both for memory and for the general cognitive functioning. Additionally, in the majority of studies, SCD and MCI exhibited higher FC than HC over anterior regions such as left Paracingulate Gyrus, Inferior Temporal Gyrus, and ACC. This suggests that all the connections, which are disrupted in SCD, were similarly affected in MCI, while both groups present a common functional coupling pattern, suggesting that SCD exhibit intermediate changes of DMN connectivity over specific posterior regions between MCI and HC. The PCC/RSC, the hippocampus, a crucial brain structure for memory and structurally connected to the RSC, as well as the PUN consistently displayed pathological changes in the SCD (Wang et al. 2013; Dillen et al. 2017). In the few studies where increased FC of SCD with respect to HC was found, FC was basically located over PUN (Hafkemeijer et al. 2013; Verfaillie et al. 2018a), a key region of DMN, which has demonstrated interrupted connections as the disease progresses (Rombouts et al. 2005; Zhang et al. 2009; Agosta et al. 2012). These inconsistencies in study findings may be due to the diversity of the disease stages of SCD participants and the inclusion criteria during recruitment. SCD participant selection was conducted without taking into account the latest proposed SCD-I WG criteria, since the SCD group had an MMSE total score *M* (SD)= 27.2 ± 0.4), including participants even with 26.8, a total score of global cognitive function more suitable for MCI

(Hafkemeijer et al. 2013). Additionally, participants younger than 60 (range 55 – 77) were also recruited for the study of (Verfaillie et al. 2018a), a selection criterion which does not conform either to the SCD-I WG guidelines (Molinuevo et al. 2017).

Disruptions of FC in SCD were observed not only in DMN but also in other tested networks. More specifically, higher levels of subjective cognitive complaints were related with decreased within-network FC among brain regions of the visual network (VIS) (Contreras et al. 2017). Presumably, dysfunction in brain areas responsible for visual cognition may be related with early manifestations of cognitive disorder related to AD (Contreras et al. 2017). This assumption has corroborated previous research which reported similar connections between visual impairment and early signs of cognitive disturbances (Risacher et al. 2013). Network properties, such as shortest path length of GMN, emerging from the PUN, which is one of the brain regions basically involved in the early "amyloid deposition" (Villeneuve et al. 2015) and links fronto-temporal-occipital cortices, had lower values in SCD (Verfaillie et al. 2018b). Additionally, lower clustering coefficient values in SCD indicated a more randomly organized GMN suggesting a rapid decline in overall cognitive performance especially in the language (Verfaillie et al. 2018b). Decreased values of path length and clustering coefficient have also been related with a subsequent future impairment in language, which is usually deteriorated in AD, as longitudinal studies have shown (Brier et al. 2014; Tijms et al. 2014; Mårtensson et al. 2018).

In MEG studies, SCD had a general hypo-synchronization compared to HC (Bajo et al. 2012). These pieces of evidence suggest that the feeling of subjective cognitive impairment without any objective cognitive dysfunction could be an early sign of pathological brain function related to future progression to AD. When FC alterations were compared between SCD and HC, the HC had higher synchronization values, while in SCD a posterior disrupted connection basically located over the medial temporal - occipital area and lateral inferior parietal region was found with an anterior hyper-synchronization deteriorating similar brain areas as in MCI participants (López-Sanz et al. 2017a). Thus, SCD elders exhibited disruptions in the brain connectome in a similar manner as those observed in MCI. However, a growing body of literature has suggested a robust decrease of transitivity in AD networks compared to HC (Pereira et al. 2016; Mårtensson et al. 2018). The majority of MEG studies showed that changes in SCD as regards transitivity and modularity in the alpha band are different compared to those observed in MCI, which could be described as a "compensatory mechanism" (López-Sanz et al. 2017b). With respect to nodal clustering changes, it is worth mentioning that significant differences were found solely among the groups of HC and MCI participants. MCI exhibited extensive clustering decreases, denoting apparent connections of these particular nodes at a local level. On the other hand, local clustering in SCD did not differ significantly from HC and MCI (López-Sanz et al. 2017b).

The impaired capacity of information transfer due to the early WMN degeneration in SCD has been examined in DTI reported studies (Selnes et al. 2012; Li et al. 2016; Wang et al. 2016; Yan et al. 2018). Disrupted connectivity and nodal efficiency of WMN was widely observed in the bilateral frontal, parietal, temporal and occipital brain areas, including the bilateral orbital frontal cortex as well as the bilateral orbital area of the middle frontal gyrus and the superior frontal gyrus, the left thalamus, the left and the right anterior cingulate and the paracingulate gyrus, the left temporal region of the superior temporal gyrus, the PUN, the PUT, the left temporal pole of superior temporal gyrus, the left superior occipital gyrus, the right cuneus, the calcarine fissure and the surrounding cortex (CAL), and several occipital regions (Wang et al. 2016; Shu et al. 2017; Yan et al. 2018). In addition, despite the fact that rich-club regions (CAU.R) of the WMN are generally preserved in SCD and are gradually disrupted as the disease progresses in later stages (MCI and AD), the surrounding brain regions (CAU.L and ORBmid.L) are more likely to show aberrant connections in predementia stages, before obvious symptoms appear in the neuropsychological assessment (Yan et al. 2018). In sum, SCD has shown

remarkably limited strength of the rich-club, lower local as well as global efficiency of the WMN links compared to HC, which suggests that there is brain interruption of both functional integration and segregation. In all abovementioned studies which investigated WMN, SCD presented values between MCI and HC, implying a common disrupted profile of brain network for the SCD participants more moderate than the MCI ones.

In the majority of the studies, brain connections were interrupted in SCD group compared to HC; however, small-world properties were mostly preserved in SCD, implying that the brain has not undergone such damage as to demonstrate a randomized network. Although SCD preserved some network properties, they exhibited common network disrupted connections (node degree, path length, etc) comparable to those observed in MCI, but at a lower degree. In detail, the reviewed studies showed that by assessing different network properties (i.e., small-world, degree, path length, etc), someone can extract valuable results for brain connectome of people with SCD or later stages of the AD continuum. In the present systematic review, we observed that the majority of the reported studies found aberrant connections and disruptions at local level (i.e., local efficiency, nodal strength, etc) instead of global metrics (i.e., small-world) or interruptions of higher-up nodes (i.e., rich-club nodes) which tend to remain persistent in SCD and are disrupted gradually as the disease progresses. This review of several neuroimaging studies supports and enhances the hypothesis of SCD as a predementia with no objective clinical manifestation stage of the AD continuum and with potential future progression in more advanced stages. MCI and AD suffer severe network damages in the connections of rich-club brain areas and exhibit a more random brain network instead of a small-world organization. On the other hand, SCD have relatively stable connections as far as small-world and rich-club properties are concerned compared to HC, but exhibit lower values in connections between specific regions over posterior brain structures. These findings underline that lower nodal strength of DMN nodes over posterior brain areas as well as temporal brain regions and higher strength of anterior regions is evident among SCD as in MCI and AD, respectively. This localized disconnection has been proposed also in previous works demonstrating that posterior DMN subsystem connectivity declines within the AD spectrum (Jones et al. 2016).

Concerning the type of the final included studies, we included both longitudinal as well as cross-sectional ones in order to investigate whether brain connectome could show potential causality of SCD. It is widely known that longitudinal studies provide strong pieces of evidence around aging process, since they manifest the brain changes and brain connectome alterations of a particular population over time, while it has been suggested that critical differences of brain functionality have been found between cross-sectional and longitudinal studies regarding brain functionality of elderly population (Nyberg et al. 2010). From the final list of studies included in our review, only three can be considered as longitudinal. In detail, the longitudinal study of (Verfaillie et al. 2018b) investigated whether network parameters such as local and global degree, clustering coefficient, path length and betweenness centrality as measured in individuals by using sMRI at the baseline, could be possibly correlated with the total values of the longitudinal (follow-up) annual neuropsychological assessment of an SCD cohort. Even though they did not include longitudinal data of the MRI in order to seek for potential network changes over time in SCD, they found that GMN disruptions (i.e., longer clustering coefficient and path length), which are indicative of random network in specific brain regions (i.e., PUN, frontal areas, etc) at the baseline sMRI, were highly correlated with decline in the language and the global cognition neuropsychological tests in one year follow-up. In addition to their previous seminal work, the same research group (Verfaillie et al. 2018a) examined the potential disrupted connectivity of DMN regions among participants with and without SCD with a family history of AD (APOE genotype) over time. Again, they tested potential comparisons solely between follow-up neuropsychological performance and baseline resting state fMRI network connectivity. Similarly, the authors demonstrated that increased connectivity in the DMN was highly correlated with better baseline performance both in the global cognition as well as the language, whilst

increased connectivity between temporal regions (MTMS) and the rest brain areas as well as DMN found to be significantly correlated with worse performance in the neuropsychological tests over time. Last but not least, the only longitudinal study which has examined so far the potential changes of the brain connectome in the SCD, is the clinical interventional study of (Jeon et al. 2016), showing that the SCD participants who received the Ganglioside showed increased grey matter volumetric properties, exhibited higher functional connectivity over the DMN regions (i.e., PCC, PUN, etc) and demonstrated better neuropsychological performance in the follow-up assessment, whereas the placebo SCD group presented no difference in the above-mentioned metrics. However, this study examined the potential changes in functional connectivity within two months duration, which is considered a very short timeframe to observe any differences at functional or volumetric level in people with cognitive impairment due to AD, since the majority of SCD people shift to more advanced stages into one year (Snitz et al. 2018). Consequently, there is no single reported study which has so far examined the baseline and follow-up network properties among SCD participants.

Preclinical symptoms in prodromal AD are accompanied with pathophysiological changes that cause disruption in resting-state functional brain networks. A consistent outcome across neuroimaging studies is an increased interaction pattern between FP-DMN which was positively correlated with verbal episodic memory (Contreras et al. 2017). However, the majority of the presented studies adopted a different algorithmic pipeline which makes their direct comparison almost impossible. In order to integrate scientific results from different studies, a series of algorithmic steps should be aligned. Some alternative strategic choices and basic preprocessing steps which could alter the final scientific results would be as follows: a) the denoising of recordings with e.g. independent component analysis etc.), b) the adopted source-localization algorithm for electro and magneto-encephalography (e.g. sLORETA (Lazarou et al., 2018) and LCMV (Dimitriadis et al. 2018b, 2018c) etc.), c) the selection of anatomical Templates (e.g. AAL (Dimitriadis et al. 2018b, 2018c), OXFORD-HARVARD (Desikan et al. 2006) etc.) for functional neuroimaging modalities, d) the ROI representation that produces a representative time series per ROI (e.g. principal component analysis, centroid (Dimitriadis et al. 2018b, 2019) etc.), functional interpolation of ROI-oriented virtual time-series (Dimitriadis et al., 2018c), e) the selected functional connectivity estimator that quantifies the inter-relationship between two or more brain areas oscillating on the same or different frequency (cross-frequency coupling) (e.g. “imaginary part of phase locking value” (Dimitriadis et al. 2018b, 2018c), correlation of the envelope (Dimitriadis et al. 2018b, 2018c) etc.) including the adaptation of a proper statistical filtering with surrogates analysis, f) the data-driven Topological filtering of the FCG (e.g. “Orthogonal Minimal Spanning Trees (OMST)” (Dimitriadis et al. 2017a, 2017b, 2018c, 2018b) etc.). In a recent study, we showed how ROI representation and connectivity estimator altered the classification performance on the prediction of MCI using “MEG-beam formed resting-state recordings” (Dimitriadis et al. 2018b). Patterns of SC and FC were associated in a different manner with the various neuro-cognitive variables assuming to alter early in the time-course of AD-like in SCD. An integrated approach of unfolding the complex inter-relation of SC with FC and cognitive variables may support the elucidation of the complex relationship between objective and subjective parameters of cognitive decline. More research effort is needed through the evaluation of the most informative algorithmic pipeline based on its sensitivity to the prediction of subjective cognitive decline.

Different neuroimaging analysis pipelines can produce significantly different results, raising uncertainties and inconsistencies about the reliability and replicability of brain imaging findings. Sharing of analysis pipelines and neuroimaging datasets will allow a researcher to select a different set of preprocessing and analysis options exploring the impact of particular preprocessing decisions to the final outcome. The most widely known tool for studying human brain organization in vivo is functional and structural magnetic resonance imaging (MRI) (Eickhoff et al. 2016) as well as High density EEG. Moreover, open data repositories can be classified into many categories. Either these are tailored to specific modality (Niso et

al. 2016), or they target a particular population like MCI and AD (Jack et al. 2008). Repeat-scans open cohorts attract neuroscientists to test the reliability and reproducibility of the proposed biomarkers (Zuo et al. 2014). Neuroimaging competitions are a prerequisite for pushing the machine and deep learning over its limits towards the optimization of automatic classification of target groups (Schizophrenia: (Salman et al. 2019) MCI-AD: (Dimitriadis et al. 2018a)) over HC.

8 Conclusion

Our review adds to the growing body of literature that SCD may actually exhibit changes in the brain at a network level and implies that brain connectome could be considered as a potential biomarker of subsequent cognitive deterioration associated with AD. Several studies which have used neuroimaging tools have pinpointed AD-related brain interruptions, such as whole-brain GMN or WMN or DMN that also occur in SCD before cognitive deficits are detected during neuropsychological assessment. At the global network level, rich-club network property and small-worldness have been observed and preserved in SCD subjects. In contrast, local network properties like degree, shortest path length, clustering coefficient, etc revealed in an aggregated fashion the aberrant spatial, functional and structural brain connections between specific brain areas observed in SCD compared to HC. However, more research with longitudinal studies is needed in order to further replicate, expand and explore the possible pathophysiological mechanisms that are linked with the abovementioned brain network changes in SCD. In general, SCD exhibited lower values of global and local efficiency, network strength and longer shortest path length but preserved general network properties such as small-world and rich-club. Therefore, research around brain connectome holds great interest for the investigation of the complex brain mechanisms of SCD who will eventually shift to more advanced stages such as AD with common FC patterns. However, a more consistent analytic procedure should be adopted across research groups in order to integrate the findings of several studies.

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Conflicts of Interest

The authors declare no conflicts of interest.

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Figure 7 Mean values of gender (female and male) across different groups of participants (HC, SCI, MCI and AD) of the final included studies

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