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Functional connectivity and cognitive decline: a review of rs-fMRI, EEG, MEG, and graph theory approaches in aging and dementia

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Abstract

Age-related changes in the brain cause cognitive decline and dementia. In recent year's researchers' extensively studied the relationship between age related changes in functional connectivity (FC) in dementia. Those studies explore the alterations in FC patterns observed in aging and neurodegenerative disorders using techniques such as resting-state functional magnetic resonance imaging (rs-fMRI), electroencephalography (EEG) coherence analysis, and graph theory approaches. The current review summarizes the findings, which highlight the impact of FC changes on cognitive decline and neurodegenerative disease progression using these techniques and emphasize the importance of understanding neural alterations for early detection and intervention. The findings underscore the complexity of cognitive aging and the need for further research to differentiate normal aging from pathological conditions. rs-fMRI is essential for studying brain changes associated with aging and pathology by capturing coherent fluctuations in brain activity during rest, providing insights into FC without task-related confounds. Key networks such as the default mode network and front parietal control network are crucial in revealing age-related connectivity changes. Despite challenges like neurovascular uncoupling and data complexity, ongoing advancements promise improved clinical applications of rs-fMRI in understanding cognitive decline across the lifespan. EEG and magnetoencephalography (MEG) are cost-effective techniques with high temporal resolution, allowing detailed study of brain rhythms and FC. Recent studies highlight EEG/MEG's potential in early Alzheimer's disease detection by identifying changes in brain connectivity patterns. Integration of machine learning techniques enhances diagnostic accuracy, although further validation and research are necessary. Graph theory offers a quantitative framework to analyze cognitive networks, identifying distinct topological differences between healthy aging and pathological conditions. Future research should expand exploration into diverse neurodegenerative disorders beyond mild cognitive impairment, integrating neuroimaging techniques to refine diagnostic precision and deepen insights into brain function and connectivity.

Keywords

Aging, dementia, functional connectivity, resting state, electroencephalography, coherence analysis, graph theory approaches

Introduction

With advancing age, crystallized cognitive abilities, such as accumulated knowledge and vocabulary, tend to be preserved or even improve, while fluid cognitive abilities, including abstract thinking, reasoning, and decision-making, decline in older adults, independent of pathology [1–3]. These declines in fluid abilities are associated with age-related deficits in processing speed, attention, memory, and executive function, collectively known as cognitive aging [1, 2]. Cognitive aging is linked to functional impairments in managing new information, adapting to the environment, and problem-solving, impacting older adults' independence in society and at home [4, 5]. Extensive evidence suggests that cognitive decline in older adults is associated with changes in brain structure and function, emphasizing the importance of identifying brain-based factors contributing to cognitive aging [3, 6–8]. Understanding age-related neural alterations in cognitive aging may aid in differentiating normal aging from disease states and identifying brain areas for intervention [3].

Concerning individuals, aging correlates with cognitive decline, even among those who maintain normal daily activities [9]. Research indicates widespread changes in the brain, including reductions in grey matter, disruptions in anatomical connections, and diminished functional connectivity (FC). These findings underscore the complexity of cognitive aging and emphasize the necessity of exploring its neural underpinnings for better understanding and potential intervention [9].

The natural decline in cognitive abilities during healthy aging, even without pathology, significantly impacts daily activities, quality of life, and has psychological and socio-economic consequences. Differentiating between normal cognitive decline and early signs of dementia or mild cognitive impairment (MCI) remains challenging, making early detection crucial for effective intervention [10].

Though the numerous studies have established that functional networks in the aging brain differ from those in younger individuals [10], the exact nature and extent of these changes remain incompletely understood. They are believed to result from a combination of cell loss, functional decline, and emerging compensatory mechanisms. Additionally, associations have been found between these altered resting-state FC patterns and cognitive performance in older adults [3, 11]. Moreover, FC disruptions are evident in clinical conditions prevalent among the elderly, such as Alzheimer's disease (AD), Parkinson's disease, and MCI, with the severity of symptoms correlating with connectivity metrics [10, 12].

Even though "age" significantly impacts functional and anatomical brain connectivity, more research is needed to understand these changes fully due to inconsistent findings. While most studies report decreased FC, some find increased between-network connectivity. Onoda et al. [11] and Huang et al. [13] found no age-related association. These inconsistencies may be due to differences in study designs and methodologies, highlighting the need for further investigation [9].

The United Nations World Population Prospects predict that the number of people over 80 will triple by 2050, with the group 65 or older is experiencing the fastest growth rates worldwide. However, significant regional disparities exist in these demographic trends [14]. These demographic shifts pose challenges for healthcare management of age-associated diseases like cancer, neurodegenerative disorders, and dementia. Addressing these challenges requires a multidisciplinary approach spanning various scientific fields [15].

Recent advances in techniques such as magnetic resonance imaging (MRI), magnetoencephalography (MEG), and electroencephalography (EEG) have significantly enhanced our ability to analyze brain networks, providing deeper insights into the complex relationships between aging and dementia. These neuroimaging tools have made it easier to study changes in FC that are linked to cognitive decline. This has

led to a better understanding of how brain networks are affected by both normal aging and neurodegenerative diseases. In this review, we aim to summarize recent findings derived from these three techniques, highlighting their contributions to the ongoing exploration of FC in aging and dementia.

FC and cognitive decline

Understanding and introducing MCI and FC is crucial in the study of cognitive decline and neurodegenerative diseases. MCI serves as an intermediate stage between normal cognitive aging and conditions like AD, making it a key focus for early detection and intervention strategies. Recognizing the patterns of cognitive decline in MCI allows researchers to differentiate between normal aging and pathological processes, aiding in timely diagnosis.

FC, which refers to the coordinated activity between different brain regions, offers valuable insights into how brain networks change with age. Both cognitive performance and the progression of neurodegenerative diseases are associated with alteration in FC. By studying FC in individuals with MCI, leading to understand the neural mechanisms underlying cognitive decline with more effective treatments and interventions aimed at slowing disease progression.

MCI is characterized by self- and hetero-reported cognitive complaints, objective cognitive impairment, and preserved independence in daily activities without meeting the criteria for dementia [16]. MCI often represents a transitional state from healthy aging to AD or other forms of clinical dementia. However, it is crucial to recognize that not all MCI cases progress to dementia [15].

In recent research, there has been a growing focus on understanding the functional and structural impacts of MCI in comparison to healthy aging and AD. Studies utilizing blood oxygen level dependent (BOLD) contrast have extensively analyzed differences in FC or coactivation patterns between brain areas in both task-based and resting-state designs [15].

People who have MCI often have cortical atrophy, less activity in certain part of the brain, and more activity in the default mode network (DMN) when they are at rest [17]. Furthermore, researchers observe a more severe decrease in FC in MCI patients who eventually transition to AD [18]. For example, Sullivan et al. [19] found that cognitive preservation in healthy older adults is associated with higher interactivity across brain regions, while MCI participants show lower interactivity, which correlates with lower Mini Mental State Examination scores. According to Zhao et al. [20], MCI patients have lower global and local efficiency in whole-brain FC networks compare to healthy controls [15].

Recent studies have also highlighted the heterogeneity within MCI subtypes and their distinct implications for FC changes. For instance, research has identified different MCI subtypes based on patterns of cognitive decline and progression risk, such as low-, medium-, and high-risk subtypes. Each subtype demonstrates unique FC profiles, which may have significant implications for understanding disease mechanisms and tailoring interventions. High-risk MCI subtypes often exhibit more pronounced disruptions in FC and greater cortical atrophy compared to low-risk subtypes. This variability underscores the importance of differentiating between MCI subtypes to better understand their specific neural signatures and progression trajectories.

Addressing these findings, it is evident that MCI is not a homogeneous condition and that FC changes may vary significantly among subtypes. This heterogeneity in MCI subtypes emphasizes the need for more refined and individualized approaches in both research and clinical practice to enhance early diagnosis and treatment strategies for dementia [21].

In addition, it is mentioned that the two highly prevalent subtypes of MCI are amnestic MCI and vascular MCI. Both subtypes exhibit widespread structural and functional brain alterations, yet the patterns of FC strength (FCS) alterations remain inadequately explored. A study examining resting-state FC changes among individuals with amnestic MCI, amyloid beta, and healthy controls found significant reductions in FCS in the left middle temporal gyrus for both groups compared to healthy controls. The study revealed a significant reduction in FC between the left middle temporal gyrus and various frontal brain regions,

particularly in participants with vascular MCI. Furthermore, a partial correlation analysis revealed a positive correlation between the FC values of the left middle temporal gyrus and the left inferior frontal gyrus with episodic memory performance, and a negative correlation with living status. These findings provide new insights into the pathophysiological mechanisms underlying different MCI subtypes [22].

FC of the brain network, defined as the temporal correlation between activity measures from distributed brain regions, is analyzed using various metrics focusing on synchronization of different brain rhythms. These networks' topology changes with human activity, offering insights into cognitive load, working memory, and skill acquisition. Alterations in motor cortex connectivity reflect motor learning and are vital for brain computer interface development. FC serves as a diagnostic tool for neurological disorders like autism spectrum disorder, AD, depression, and multiple sclerosis, indicating atypical FC networks. Moreover, FC networks are sensitive to age-related brain changes and provide valuable insights into physical and cognitive health in late life [9].

FC between distinct brain regions offers important information on how different brain regions cooperate to support different types of behaviors and cognitive tasks. As mentioned above, FC represents the temporal correlations in neural activity among different brain regions, suggesting that these regions are interacting or collaborating to process information. The coordination of various brain regions for tasks like problem-solving and decision-making is known as cognitive integration, and it depends on this communication. Additionally, it makes sure that various cognitive processes—like memory and attention—align and coordinate when doing challenging tasks [23].

Large-scale networks in the brain interact to support various functions. Key networks involved in introspective thinking, cognitive control, and relevance detection are the DMN, executive control network (ECN), and salience network (SN), in order. FC between these networks is vital for balancing between internal thoughts and external stimuli. Disruptions in FC within and across these networks can cause cognitive deficits and are common in neurodegenerative diseases. This show how important these connections are for keeping your brain healthy.

FC also provides insight on the relative contributions of certain brain regions to particular cognitive functions. For example, connections between the prefrontal cortex and parietal regions promote attention and working memory activities, whereas coordination between the hippocampus and cortical areas is essential for memory encoding and retrieval. The limbic system and prefrontal cortex's connectivity influence emotional regulation. Therefore, the FC patterns show how different brain regions work together to promote emotional and cognitive tasks [23].

Variations in FC can indicate pathogenic conditions as well as adaptive mechanisms. In aging or neurodegenerative diseases, the brain may enhance connectivity in certain regions to compensate for losses in others. A number of neurological disorders, including AD, are frequently characterized by abnormal FC patterns. The altered connection between the DMN, ECN, and SN in AD reflects both the disease's development and cognitive loss. These alterations may function as biomarkers for methods of early detection and intervention [23].

On a more granular level, FC relates to synaptic and cellular mechanisms. It reflects the effectiveness of synaptic connection, which is essential for efficient neuronal transmission between various brain regions. Disruptions in this connection frequently correlated with cognitive declines and illness states. Further evidence that changes in neurotransmission may impact cognitive performance comes from FC's connection to neurotransmitter systems that regulate brain activity [23, 24].

Understanding the biological implications of FC helps explain how neural networks integrate to support cognitive functions and how disruptions in these connections can signal normal developmental changes or pathological conditions. This knowledge is crucial for developing targeted interventions to address cognitive decline and neurodegenerative diseases, as it sheds light on the underlying mechanisms contributing to these conditions [23, 24].

Impact of FC changes on the mesoscopic level

At the mesoscopic level, FC is often considered in terms of the interactions between clusters of neurons, columns, or localized circuits. This level of analysis helps to understand how groups of neurons in different brain regions synchronize their activity to support cognitive processes and behaviors. Changes in FC at this level can shed light on the following:

Network integration and segregation: Mesoscopic-level changes in FC are crucial for understanding how the brain integrates information across various regions while maintaining the specialization of localized circuits. For example, disruptions in segregation and increased integration between brain areas have been linked to neurodegenerative conditions like AD and aging. Studies have shown that age-related decline in FC results in reduced network efficiency and may lead to functional impairments [25].

Synaptic connectivity and plasticity: FC at the mesoscopic scale reflects the underlying synaptic connectivity and plasticity between brain regions. Changes in these connections can indicate the brain's adaptive responses to learning, injury, or disease. In disorders like AD, synaptic dysfunction leads to aberrant FC, particularly in key networks like the DMN. Understanding how these alterations occur can help in identifying early biomarkers for cognitive decline [25].

Coordination of brain rhythms: At this scale, FC changes reflect how brain regions coordinate rhythms such as theta, alpha, beta, and gamma oscillations. These rhythms support different cognitive functions, such as working memory and attention. Alterations in these rhythmic patterns can indicate dysfunction in neurocircuitry. For example, disruptions in alpha and beta band synchronization have been associated with reduced cognitive control in aging populations and patients with AD [25].

Glial cells and extracellular space in FC

The extracellular space and glial cells play a crucial role in determining the functional connection of neurons. Astrocytes, a type of glial cell, are pivotal in regulating synaptic activity by managing neurotransmitter uptake and maintaining ion balance in the extracellular space. By releasing gliotransmitters and modulating the extracellular environment, they contribute to synaptic transmission strength and efficiency and contribute to synaptic plasticity.

Another class of glial cells called microglia is crucial for synaptic pruning, which affects the FC and overall structure of the network. By removing or modifying synapses, microglia play a key role in determining the connectivity patterns within neural networks [26].

The extracellular matrix also plays a significant role in neuronal connectivity. It provides structural support and influences synaptic formation and plasticity. Alterations in the extracellular matrix can affect how neurons establish and maintain connections, further highlighting the extracellular matrixe's impact on network dynamics. Overall, the intricacy of neural networks is revealed by the participation of glial cells and the extracellular matrix in functional connection, underscoring the need for incorporating these components in research on brain function and pathology [26].

Relationship between cerebral blood flow, FC, and pathology

Recent studies have underscored the critical role of cerebral blood flow (CBF) in modulating FC, particularly in the context of aging and dementia. Neurovascular coupling—the process that links neural activity to changes in blood flow heavily influences FC, often measured by resting-state functional magnetic resonance imaging (rs-fMRI). Efficient neurovascular coupling ensures active brain regions receive sufficient oxygen and nutrients to maintain normal function. Variations in CBF can significantly impact FC measurements, particularly in aging populations where compensatory mechanisms may initially maintain connectivity despite neural decline. However, as pathology progresses, diminished CBF leads to weakened FC networks, contributing to cognitive impairments commonly seen in AD and vascular dementia [27].

Researchers have linked the development and progression of cognitive decline to chronic reductions in CBF, also known as cerebral hypoperfusion. Hypoperfusion deprives brain cells of essential nutrients and oxygen, promoting amyloid-beta accumulation and impairing waste clearance, processes that exacerbate

neurodegeneration in conditions like AD. This relationship is bidirectional: as neural networks deteriorate, CBF further declines, disrupting neurovascular coupling and impairing FC. The role of vascular abnormalities in cognitive decline, collectively termed vascular contributions to cognitive impairment and dementia, highlights the importance of addressing blood flow deficits in understanding and managing dementia.

Researchers have used several imaging techniques, including arterial spin labeling MRI, positron emission tomography (PET), and dynamic susceptibility contrast (DSC) MRI, to measure CBF in aging populations and individuals with dementia. Studies employing these techniques show how cerebral hypoperfusion correlates with altered connectivity patterns in patients with cognitive decline. Arterial spin labeling MRI, a non-invasive method, provides direct quantification of CBF and has been instrumental in showing reduced blood flow in AD [28, 29]. On the other hand, PET scans, which often use radiotracers, gives us more information about both blood flow and metabolic changes. This shows how problems with FC are connected to vascular issues in dementia.

There is growing evidence suggesting that CBF can serve as a biomarker for early stage cognitive decline. Longitudinal studies that combine CBF measurements with FC analysis provide strong predictors of cognitive decline, particularly in individuals at risk for AD. These multimodal approaches can improve diagnostic accuracy, identifying subtle changes in blood flow and network connectivity that precede the onset of clinical symptoms. Additionally, researchers have used graph theoretical analyses to study the topological changes in brain networks associated with both CBF and FC in dementia, revealing how vascular health influences the efficiency and integration of neural networks.

Incorporating CBF into the understanding of FC changes in aging and dementia also opens potential avenues for therapeutic interventions. Restoring or maintaining healthy blood flow to the brain may stabilize FC networks and slow cognitive decline. For instance, treatments targeting vascular risk factors such as hypertension and atherosclerosis may have the dual benefit of preserving both CBF and FC. Future research should focus on exploring how interventions designed to improve CBF, either pharmacologically or through lifestyle changes, could potentially influence FC and slow the progression of neurodegenerative diseases [28–30].

As per the recent findings, in diagnostics, there's notable focus on large-scale brain networks. These networks reflect neural responses to cognitive and motor-related activities, with interactions between distant brain regions playing a crucial role. For instance, processes such as working memory, attention, and cognitive control involve the fronto-parietal area, and the sensorimotor system associates with motor related activities [30]. Neurological disorders commonly show disruptions in the typical large-scale FC pattern [9].

Recent studies have observed alterations in dynamic functional network connectivity (DFNC) across the AD spectrum, from subjective cognitive decline to dementia. Notably, the DMN, SN, and ECN are key brain networks implicated in cognitive functions and are particularly vulnerable to Alzheimer's dementia. However, it remains uncertain whether dementia risk and protective factors are associated with changes in DFNC. Investigating the relationships between DFNC within these networks and dementia risk and protective factors offers a promising approach to understanding whether variations in functional brain organization may be linked to dementia risk [31].

Studies highlight significant brain changes during aging, with neural systems vulnerable to age also being susceptible to AD and other neurodegenerative conditions. Studies suggest that accelerated biological aging, as predicted by these models, may serve as a biomarker for neurodegenerative diseases, with faster aging seen in individuals developing AD dementia, including those with MCI. Lifestyle and genetics link variations between predicted biological and chronological age, but it's unclear if accelerated brain aging precedes cognitive decline, detectable in pre-clinical AD phases [32].

AD dementia symptoms appear after significant brain changes, emphasizing prevention efforts' importance. Understanding AD's preclinical phase is crucial but challenging due to uncertain dementia development. Autosomal dominant AD (ADAD), caused by *APP*, *PSEN1*, or *PSEN2* gene mutations, provides

insight into this phase due to its predictable progression, making ADAD an ideal model for studying preclinical AD [22, 23].

Certain factors increase sporadic AD (sAD) dementia risk, such as the *ε4* allele at the APOE locus, which affects Aβ clearance, and a strong family history of sAD dementia [33]. Individuals with Aβ pathology, even without symptoms, are in the pre-clinical phase and at higher dementia risk if carrying *APOE ε4* or other genetic risk factors or having a family history. Studies investigate if those in pre-clinical ADAD or at risk for pre-clinical sAD show accelerated brain aging before expected symptom onset based on genetic risk or Aβ status [32].

As mentioned above, aging is closely linked to neurodegeneration, making it difficult to distinguish between normal and pathological aging due to ongoing brain changes. Neuropathologically, aging involves reductions in grey and white matter, synaptic loss, and amyloid deposition, even in non-demented individuals. Research aims to correlate cognitive decline with structural neuronal changes, and shifts in functional connections have been observed, indicating that functional changes might precede structural reorganization. FC measures the temporal relationship between neurophysiological processes, forming networks like the cognitive control network (CCN), dorsal attention network (DAN), DMN, and SN. Researchers have found differences in FC have been found between individuals with MCI or AD and healthy controls, linking dysfunction in the CCN and DAN to psychiatric disorders such as depression and AD. Age-related changes in FC include decreased connectivity within resting-state networks, increased connectivity between different networks, and reduced global efficiency and modularity. Esposito et al. [34] noted a reduction in anticorrelation activity between the DMN and DAN in MCI during rest. Clinical settings often derive these findings from resting-state measurements [35].

Recent findings of resting-state functional MRI (rs-fMRI)

rs-fMRI has become increasingly popular for studying age and pathology-related changes in the brain. It detects coherent fluctuations in brain activity when individuals are not actively engaging in cognitive tasks [3].

rs-fMRI offers significant advantages for studying aging populations. It enables the examination of FC without the need for a task, mitigating potential confounds from cognitive or motor impairments. Moreover, the relatively short scan times (5–15 min) are beneficial for older adults who may struggle with prolonged periods of lying on their back or have psychological concerns about the scanning environment [3].

rs-fMRI has revealed low-frequency resting-state networks across the lifespan, delineating the brain's functional architecture. These networks cover attention, memory, cognitive control, default mode, motor, and sensory systems [36]. They were further derived by Yeo et al. [37] further categorized them into seven major resting-state networks. These are the DMN, DAN, frontoparietal control network (FPCN), cingulo-opercular network (CON), limbic network, visual network, and somatomotor network [3].

Investigators have used rs-fMRI techniques to examine how the above patterns of resting-state network FC change with age [8]. While it is evident that healthy older adults disrupt resting-state network connectivity, the contribution of these age-related changes to the cognitive aging process remains unclear. Researchers looking into the link between network connectivity and cognition in older adults have used a variety of cognitive tasks and resting-state methods. The results have been inconsistent, suggesting that future research should include all networks in analyses instead of just a few and incorporate sensitive cognitive measures that reflect the cognitive aging process [3].

One recent study has been conducted to identify a relationship between resting-state network connectivity and the overall cognitive aging process (Table 1). In this study, the NIH Toolbox Cognition battery [38] and the rs-fMRI data were used to look at how the four higher-order cognitive networks (DMN, DAN, FPCN, CON) affected the fluid cognition composite scores in a large sample of healthy older adults. This study provides important insights into inter-individual differences in resting-state network connectivity and the cognitive aging process. Specifically, it identifies CON coherence as a potential marker

for fluid cognitive performance in nonpathological aging. Among the four higher-order cognitive networks mentioned above, CON connectivity showed the strongest relationship with general fluid cognitive ability in a large sample of healthy older adults. CON connectivity explained more variance in fluid cognitive performance than age and education, affecting three out of five fluid cognitive subtests, indicating a global influence on cognitive aging. These findings suggest that CON connectivity is a key factor in cognitive aging and should be a focus in future research on neural substrates of age-related cognitive decline.

Table 1. Summary of key findings on resting-state FC in healthy cognitive aging and dementia

Network/Measure	Healthy cognitive aging	Dementia	Differential diagnosis potential
DMN	Reduced within-network connectivity with age, particularly in the anterior and posterior regions.	More pronounced disruption in connectivity, especially in hubs like the posterior cingulate cortex, which may be indicative of early-stage Alzheimer's disease.	High: Significant disruption in DMN can help distinguish between normal aging and dementia.
FPCN	Decline in connectivity, linked with reduced cognitive control and flexibility.	Greater decline, impacting cognitive flexibility and executive function more severely than in healthy aging.	Moderate to high: Changes in FPCN connectivity can signal cognitive decline progression.
CON	Some age-related changes, but generally maintains connectivity; strong relationship with fluid cognition.	Severely disrupted in dementia, affecting global cognitive functions.	High: Strong potential as a biomarker for cognitive performance in aging populations.
Hippocampal connectivity	Age and cognitive effort change the connection between intra-HC and inter-HC RSFC; predictive of future memory decline.	Disruptions in hippocampal connectivity are more severe and widespread, particularly affecting memory-related networks.	High: Alterations in HC connectivity post-cognitive effort can predict future cognitive decline.
CAPs	Reduced interactions between the frontoparietal network and DMN with age; increased dominance of DPN and attentional networks as compensation.	Lower cognitive flexibility; reduced dominance of higher-order cognitive networks, while primary sensory functions remain more intact.	Moderate: CAP changes may indicate reduced cognitive flexibility in aging, and compensatory mechanisms.
General resting-state network connectivity	Decline in connectivity across multiple networks; networks less segregated, more integrated; reduced modularity and efficiency.	More pronounced decline in higher-order networks, particularly those involving cognitive control and memory; greater impact on rich club network hubs, leading to inefficient communication between brain regions.	High: Overall network efficiency decline can indicate early stages of cognitive decline and dementia.
Metabolic brain networks (glucose metabolism)	Changes in metabolic connectivity with age; small world properties maintained but with decreased efficiency.	Greater disruption in metabolic networks, correlated with more severe cognitive decline; glucose metabolism closely linked with connectivity changes, particularly in hubs with high between-network connectivity.	Moderate: Metabolic connectivity changes offer additional insights but require further research.

CAPs: coactivation patterns; CON: cingulo-opercular network; DMN: default mode network; FPCN: frontoparietal control network; RSFC: resting-state functional connectivity

The study has performed by aiming to examine the effects of age and cognitive effort on resting-state FC (RSFC) of the hippocampus (HC) in older adults. It involved fMRI scans and seed-based RSFC analysis. The researchers also aimed to examine the correlations between RSFC before and after cognitive effort for distinct HC connections and whether these associations changed with age. The study also aimed to determine if changes in intra-HC RSFC following effort may predict future memory decline in older adults [39].

The findings indicated that for younger persons, increases in RSFC between the DMN hubs and the left anterior hippocampus (laHC) were associated with post-effort increases in laHC-pHC RSFC. On the other hand, in older people, reductions in the RSFC of the right precentral gyrus and laHC were associated with post-effort increases in the RSFC of laHC-pHC. Thus, age and cognitive exertion changed the connection between intra-HC and inter-HC RSFC. Crucially, two years later, older persons with decreased post-effort

RSFC between the laHC and the posterior hippocampi (pHC) showed a deterioration in episodic memory. Therefore, according to this study, the alteration in intra-HC RSFC after cognitive activity was able to predict memory function later in life [39].

A recent study by Liu et al. [40] in radiology compared fMRI scans in 614 healthy individuals aged 18–88 years to understand how brain function evolves over the human lifespan. This research contributes to the clinical practice of radiologists by examining the inner workings of the brain [41].

Studying brain network coactivation patterns (CAPs) can help explain how, when, and where brain networks coactivate. Liu et al. [40] identified six CAPs between brain networks, with three correlated with age. They calculated dwell time and transition time, finding that one dwell time and three transitions correlated with age. This study helps understand how brain networks coactivate and correlate with each other. The authors found a reduction in interactions between the frontoparietal network and the DPN with older age, possibly due to lower cognitive flexibility. Primary sensory functions remain intact. They also found evidence of cortical plasticity in the brains of older people. The DPN and attentional network CAPs became dominance with age, making up for the primary sensory network and frontoparietal network CAP becoming weaker [41].

Deery et al. [42] have summarized that the brain undergoes significant structural, functional, and metabolic changes with age, leading to alterations in cognition and behavior. In the early years, functional networks are rapidly organized and refined until around the third and fourth decade. These changes can lead to various expressions of cognition and behavior. Older adults display lower within-network connectivity and higher between-network connectivity than younger adults. The trajectory of alterations varies by network. Some networks may remain relatively stable (e.g., primary sensory and motor) and others may vary substantially (e.g., associative regions) [42].

The typology of functional networks influences age-related changes and their functions. Older adults have a less segregated, modular, and integrated system of networks than younger adults. They have lower efficiency in higher-order networks. Alterations to a "rich club" network hub reduce communication between brain regions, impacting efficient higher-order cognitive functions. These functional network changes are likely driving aging in higher-order cognitive processes [42].

Functional networks based on glucose metabolism show covariance differences across adult life, but evidence is limited. The "small world" properties of metabolic brain networks show strong correlation between brain glucose metabolism and local and global connectivity, especially for hubs with high between-network connectivity. This suggests brain glucose is a key contributor to age-related changes in connectivity and cognitive performance [42].

Recent MR-PET measurements show synchrony between hemodynamic processes and glucose uptake, offering high sensitivity and regional specificity for functional and multimodal brain imaging. However, their application in aging and cognitive decline has not been widespread. In cognitive aging, there is a well-documented complex interaction between brain glucose, age, and peripheral physiology, including cardiovascular and metabolic factors. Future research will need to characterize these peripheral factors [42].

Limitations of resting-state functional MRI (rs-fMRI)

The technique of "resting state" is not truly "at rest", as our brains are never actually at rest. Comparing scans of fearful subjects to comfortable ones and using a large number of subjects to compensate remains a challenge [41].

The second limitation involves neurovascular uncoupling (NVU), where fMRI scans measure the vascular response to neuronal activity rather than the activity itself. Abnormal blood vessels, such as those found in tumors or due to conditions like diabetes or hypertension, show a reduced response, leading to NVU. This issue has been documented to weaken the blood oxygen level-dependent fMRI response in brain tumors [43] and aging brains [44], potentially affecting study results. NVU also impacts rsfMRI [45]. Efforts are being made to mitigate the NVU issue [46].

The rapid increase in research using rs-fMRI to study clinical diseases has brought attention to several controversial issues related to the technique, particularly concerning noise from human physiological factors. Notable sources of noise include head motion, respiratory motion, arterial CO_2 concentration, blood pressure, cerebral autoregulation, and vasomotion. Head motion is particularly problematic as it causes changes in the content of each voxel, altering the uniformity of the magnetic field, which has been calibrated for a specific head position. During scanning, any head movement can disrupt the steady-state magnetization by changing the timing between excitations in the tissues that have moved from one slice to another [47].

Respiratory motion also introduces challenges by causing shifts in the magnetic field due to breathing, which can result in image shifts in the phase-encoding direction and alter the spin history in a spatially dependent manner. A different source of noise is the amount of CO_2 in the arteries. CO_2 is a potent vasodilator that increases CBF, reducing deoxyhemoglobin concentration and leading to changes in the BOLD signal. Other physiological factors such as blood pressure, cerebral autoregulation, and vasomotion can further complicate rs-fMRI data interpretation.

Previous studies have demonstrated that differences in head motion between control and patient groups can lead to apparent group differences in resting-state networks, which may be erroneously attributed to neuronal effects. Van Dijk et al.'s research highlighted the influence of head motion on rs-fMRI estimates, demonstrating that minor variation in head motion can generate difference maps that might be misinterpreted as reflecting true neuronal activity [47]. Researchers have found that head motion decrease long-distance correlations and increase local correlations, leading to potential biases in the data. Furthermore, group differences in head motion have been observed, with elderly individuals, younger children, individuals with attention deficit hyperactivity disorder (ADHD), and various patient populations showing significantly more motion compared to their respective control groups.

Given the potential for motion artifacts to overshadow true brain activity in rs-fMRI studies, it is critical to carefully review the impact of head motion, evaluate differences across individual and patient populations, and explore effective correction methods to mitigate these artifacts [47].

Differences in brain anatomy and functional organization across individuals can lead to variability in rs-fMRI results, making it challenging to generalize findings across populations. The inherently low signal-to-noise ratio (SNR) of rs-fMRI makes it susceptible to noise and artifacts, which can obscure true connectivity patterns [48].

Several techniques can be used to lessen the difficulties posed by rs-fMRI as mentioned above. Though they can't completely remove it, advanced preprocessing methods like motion correction algorithms can greatly lessen the effect of head motion. We can achieve motion reduction during scans by ensuring participants compliance and providing clear instructions. Techniques like physiological noise modeling and RETROICOR can be used to control physiological noise, which is produced by processes like breathing and heartbeat. However, these methods necessitate additional data and careful processing. Group-level analysis and normalization techniques can be used to address subject-specific variability, but individual differences still present difficulties, especially in clinical investigations that need tailored procedures. Increasing the number of scans and utilizing high-field MRI systems is critical for improving the SNR. Increasing the number of scans, using high-field MRI systems, and applying advanced noise reduction techniques can enhance the SNR, but these methods often come with trade-offs such as increased scan time and potential subject discomfort [48].

Another challenge for clinical radiology is to utilize fMRI in cognitive analysis, an area where researchers are already making significant progress. For instance, researchers have used rsfMRI to predict an individual's likelihood of remission or treatment failure with first-line treatments for major depression [49]. Unlike motor function, cognition is more complex and involves greater variability in brain regions associated with it compared to motor areas. Therefore, it is crucial to first understand what constitutes "normal" before tackling pathological conditions like AD.

Looking ahead, it's likely that routine brain MRI exams will include an fMRI sequence with a connectivity map within the next decade. However, two key developments are necessary first. Radiologists must gain a deeper understanding of neuroanatomy, including the interactions between various brain areas and their changes in disease states. For example, while many know the function of the precentral gyrus, fewer are aware of the functions of the right anterior cingulate gyrus, which is involved in moral reasoning and conflict resolution [50]. Additionally, Liu et al.'s study [40] underscores the need for radiology to lead scientific advancements and foster industry collaboration. While rsfMRI data are simple to acquire, they are challenging to analyze due to the complexity of the required mathematical models and software, which are not typically available in radiology departments. Although there are FDA-approved software solutions for task-based fMRI data, similar tools for rsfMRI data are lacking. Collaboration is needed to develop robust, clinically practical methods for analyzing and interpreting rsfMRI data. Liu et al.'s study [40] emphasizes the opportunity for radiologists to lead this effort for the benefit of patients, though significant work remains. Many, including the author, are eager to contribute to this important endeavor.

Recent findings of EEG and MEG

EEG and MEG are non-invasive neurophysiological techniques that record electromagnetic signals from the ionic currents created by cerebral activity at the microscale. Comparing EEG to other neuroimaging technologies, it is also more affordable and adaptable. With a high temporal resolution (a few milliseconds), neurophysiological techniques allow the study of brain rhythms produced by the rhythmic activity of huge groups of cortical neurons (mesoscale) [51]. Five primary frequency bands allow brain areas to communicate: beta (12–30 Hz), alpha (8–12 Hz), theta (4–8 Hz), delta (0.5–4 Hz), and gamma (35–100 Hz). Electrophysiological signals reflect the functional synchronization (or desynchronization) produced by the oscillation of large groups of cortical neurons of several neural systems (macro-scale) supporting alertness, motivation, and several cognitive processes [52].

The interactions between inputs and outputs of neural systems can be represented by various dimensions, including deterministic-stochastic, complexity-simplicity, linear nonlinear, stationary-nonstationary, and phase-non phase locking [51].

There are several methods to evaluate FC between brain areas based on signal synchronization and coupling (Table 2) [52].

Table 2. Indexes that evaluate FC based on signal synchronization and coupling

Connectivity index	Description
Coherence (Coh)	A measure of the covariance of the frequency components of two signals. In EEG studies, COh typically corresponds to the covariance of spectral activity between two electrode locations.
Imaginary part of coherency (iCOh)	Coherency is the imaginary part of the Fourier-transformed coherency and measures the linear relationship between two EEG signals at a specific frequency. It shows how the phases of signals in channels i and j are linked, assuming the signals are stable over time.
Phase locking value (PLV)	PLV measures how consistent the phase differences are between two brain regions. When PLV is close to 1, it means the regions are highly synchronized. If PLV is close to zero, it indicates large variability in phase differences.
Phase lag index (PLI)	PLI measures the asymmetry in the phase difference between two EEG signals. It shows how consistently one signal leads or lags behind the other.
Synchronization likelihood (SL)	This measure calculates the likelihood that two signals are in the same "dynamical state". These states are defined by the time-delay embedded vectors of the signals.
Phase amplitude coupling (PAC)	This measure examines the relationship between the phase of a low-frequency oscillation and the amplitude of a higher-frequency oscillation, either within the same brain region or between different regions (e.g., the low-frequency phase in region A influencing the high-frequency amplitude in region B).
Amplitude envelope correlation (AEC)	AEC measures the correlation between the amplitude envelopes of two signals at each frequency. It uses Pearson's *r* to compare the log-transformed power envelopes of the signals.

EEG: electroencephalography

These measures can detect neuropathophysiological processes before clinical symptoms and structural alterations, proving valuable for clinical applications and new theoretical considerations [51]. Studies have shown high accuracy in distinguishing MCI from healthy controls using machine learning (ML) and synchrony measures at resting state, sensitive to early AD changes [53]. For example, Dauwels and Vialatte [54] achieved 80–85% accuracy in classifying HC and MCI using resting-state EEG (rsEEG) measures. Musaeus et al. [55] achieved 95% diagnostic accuracy in distinguishing HC, MCI, and AD patients using coherence, imaginary part of coherency (iCOh), and weighted phase lag index (PLI), noting decreased alpha coherence in AD patients. These findings highlight the potential of these methods in early AD diagnosis [52].

However, findings on FC changes in MCI are inconsistent. Studies have reported both global hyper synchronization and hypo synchronization in various EEG bands compared to healthy controls. Many studies observed a slowdown of EEG activity in MCI, with a significant reduction in alpha activity at rest noted as a potential AD biomarker. Local activity alone might not fully explain the temporal dynamics of neurodegenerative diseases as "disconnection syndromes". Understanding this intermediate stage is crucial for finding neurofunctional biomarkers, as the boundaries between aging and MCI blur. A systematic review of brain connectivity alterations in MCI is necessary [52].

A recently conducted meta-analysis [52] aimed to identify early signs of connectivity changes in MCI by quantitatively analyzing previous findings on synchrony alterations in MCI patients compared to healthy controls at resting state. They have calculated the standardized mean difference (SMD) of effect sizes from studies found through systematic literature research up to June 2023. Additionally, they have employed a novel random-effects analysis method, "MetaNSUE", which includes non-statistically significant unreported effect sizes. This is the first study to use this innovative approach in a meta-analysis of synchrony changes in pathological aging. Identifying an electrophysiological biomarker of AD could facilitate early and accessible diagnosis, improving disease management. The study reveals a global reduction in functional integration between cortical areas, indicating a "disconnection syndrome" that could be observed even at the MCI stage in specific brain sites. The electrophysiological assessment of temporo-parietal functional synchronization in the alpha band is used to detect neurodegenerative processes, such as gray matter atrophy and temporo-parietal hypometabolism, which are well-established neuropathological biomarkers of AD. ML studies show that alpha 1 sources in parietal and temporal areas are stronger in MCI converters than stable subjects.

Several previous studies of resting and task-related EEG coherence in AD patients have demonstrated reduced synchronization within and between hemispheres. A recent study group hypothesized that if synaptic disconnection as the neuropathology of AD is responsible for the failure of the brain to integrate various regions into effective networks, then electroencephalographic evidence of the disruption of FC might be used to diagnose AD. They have explored the relationship between EEG coherence and executive function in patients with MCI, AD, and healthy controls. The study's general goal was to identify potential AD markers that could facilitate early recognition of neural functional deficiency and reduce the time needed to diagnose major neurocognitive disorders in primary care [56].

The above study found reduced FC in all studied networks in AD patients, with frontotemporal and parietal beta wave coherence significantly lower in the AD group. The study suggests that task-related EEG coherence in the AD group was modulated by cognitive performance demands. The most notable changes were found in frontal EEG coherence during the visual-spatial task challenge, parietal EEG coherence during the writing task, and temporal EEG coherence during the speech understanding task. The results suggest that changes in spontaneous EEG coherence of the frontoparietal region in the AD group can be detected in a clinical setting, potentially serving as a marker of neuronal disconnection. The MCI group demonstrated a paradoxical increase in task-related EEG coherence in temporal lobes, suggesting high neurocognitive reserve and increased compensatory activities or an alternative to AD neurodegenerative processes. The sensitivity of EEG coherence as a marker of neuronal disconnection needs to be explored, and the specificity of EEG coherence markers is another challenge to be addressed [56].

A study examined group differences in EEG coherence within global cortical networks at rest and during executive challenges among patients with AD, individuals with MCI, and healthy controls. Results showed decreased EEG coherence in cross-hemisphere frontal, temporal, parietal, and occipital pairs in the AD group both at rest and during tasks requiring comprehension, analysis, perceptual-motor response, and executive functioning. Overall, the results from our study support the disconnection hypothesis of AD, which proposes that cognitive deficits may be due to the diffuse disconnection process in neurocognitive dementias rather than isolated changes in specific areas. The difference in EEG coherence between healthy and AD patients could play an important role in clinical practice. As neurodegeneration starts long before clinical manifestations of AD, detecting neuronal disconnection across hemispheres with EEG might be possible even in the pre-clinical stage. Further evaluation of the markers' sensitivity and specificity to the neurodegenerative process in the brain needs to be conducted [57].

Another recent study group has mentioned that understanding how MCI affects global neural networks may explain changes in brain electrophysiology. By using graph theory (GT) and the visual oddball paradigm, they have evaluated the FC of neuronal networks in brain lobes. The study has involved 30 participants: 14 with MCI and 16 healthy control participants. They have conducted an examination using the visual oddball paradigm, focusing on EEG signals with targeted stimuli. Their analysis employed FC utilizing the change point detection method. Additionally, they have implemented training for linear discriminant analysis, K-nearest neighbor, and decision tree techniques to classify brain activity, distinguishing between subjects with MCI and those in the healthy control group. The results demonstrate the efficacy of combining FC measurements derived from EEG with ML for cognitive impairment classification. This research opens avenues for further exploration, including the potential for real-time detection of cognitive decline in complex real-world scenarios [58].

Quantitative EEG (QEEG) is useful for predicting treatment responses, but no study has looked at changes in FC using QEEG after a lifestyle intervention. A research group investigated neurophysiological changes in QEEG after a 24-week multidomain lifestyle intervention in the South Korean SUPERBRAIN study. The study involved participants aged 60–79 without dementia but with at least one dementia risk factor. They were randomly assigned to a facility-based intervention (FMI) (n = 51), a home-based intervention (HMI) (n = 51), or a control group (n = 50). Data from 44 FMI, 49 HMI, and 34 control participants who underwent EEG at baseline and study end were analyzed [59].

The study found that participants who received the intervention showed increases in the power of the beta1 and beta3 bands and the iCoh of the alpha1 band compared to the control group. They also showed decreases in the characteristic path lengths of the alpha1 band in specific brain regions, indicating improved functional brain networks and higher global efficiency. This is the first study to demonstrate positive functional brain changes using QEEG after a 24-week lifestyle intervention to prevent dementia. The results suggest increased FC and higher global efficiency in the intervention group. More studies with larger sample sizes and longer intervention periods are needed to confirm these findings. Quantitative EEG helps understand brain health in aging people. Studies on EEG coherence and power in specific brain areas have had mixed results. Another study has measured EEG coherence and power across the entire scalp and a wide frequency range to find global EEG markers for cognition in people at risk for dementia. Global markers are more reliable and less error-prone than specific ones, which could help resolve past inconsistencies. The study has looked at global EEG coherence (1–30 Hz) and an EEG slowing score, which is low-frequency power (1–8 Hz) divided by high-frequency power (9–30 Hz). It also has examined how these EEG measures predicted cognition and cognitive decline over 5 years [59].

The results have shown that baseline global coherence was linked to better cognition at the start but not to cognitive decline or cognition after 5 years. There was no correlation between the EEG slowing score and either cognitive decline or cognition. This suggests that resting state global EEG coherence might be a useful marker for brain health in older adults at risk for dementia. However, the small sample size of study hindered its ability to determine the predictive value of global coherence, a topic that requires further exploration in larger studies [59].

Limitations and future perspectives of M/EEG

Buzi et al. [52] chose different electrode pairs for each brain area due to differences in electrode placement and density in M/EEG setups. To maintain consistent spatial references across studies, they only selected articles analyzing data in the sensor space, which limits spatial resolution. Despite these differences, the heterogeneity index for their meta-analysis was low.

They concluded that further research is necessary to ascertain whether tempo-parietal and fronto-parietal coupling in particular frequency bands can predict the progression of neuropathology. Identifying functional biomarkers for AD, such as phase-coupling changes, could help develop new therapies and stimulation protocols targeting specific brain areas. Neurostimulation might enhance plasticity and connectivity in areas with weak coupling [52].

When conducting EEG studies with young participants, researchers face specific challenges related to data quality due to the unpredictable behaviors of infants. Movement artifacts are prevalent, especially as children become more active around 12 months of age. Factors such as the child's age, the type of EEG device, the experimental setup, and the child's general state (e.g., time of day, emotional state, recent feeding) can influence data quality [60]. Vigilance and sleep stages are particularly critical in newborns, as the neonatal brain's activity varies significantly between active and quiet sleep, impacting EEG recordings [61].

Minimizing artifacts requires careful preparation, such as acclimating children to the experimental environment, using skilled staff, and considering the timing of the experiment. Despite efforts to reduce artifacts, some are inevitable, including eye movements, facial muscle activity, and cardiac activity. While adults can control some of these movements, infants cannot, leading to frequent artifacts in their EEG data. Techniques like using pacifiers can help calm infants and improve data quality, despite the potential for low-frequency EEG artifacts [62].

Artifacts often lead to data loss when removed, affecting the SNR. Recent studies highlight variability in data editing methods and their impact on the quality of infant EEG data. Using video-EEG synchronization can help monitor and reduce artifacts by providing real-time feedback during data acquisition [63]. Despite its common use in adult studies, independent component analysis (ICA) effectively correct artifacts. However, successful application of ICA to infant EEG data suggest its viability for this population as well [64].

Accurate source localization in infant EEG studies is challenging due to structural differences between infant and adult brains. These analyses can be more accurate with high-density EEG systems and age-appropriate MRI templates, but individual MRI scans are still the best way to get a precise anatomical localization [64].

In the field of MEG, spatial resolution presents notable challenges and limitations, particularly when comparing high-density and low-density systems. The smoothness of the magnetic field constrains spatial resolution in the high-density MEG regime, causing a slow, logarithmic divergence in resolution limits as sensor density increases. Conversely, in the low-density MEG regime, the sensor density itself limits spatial resolution, leading to a faster resolution increase that follows a square-root law. These constraints highlight the difficulty of achieving optimal spatial resolution solely through increasing sensor density.

Another significant limitation arises from the sensor-to-brain distance. The placement of traditional cryogenic MEG systems using superconducting quantum interference devices (SQUIDs) 2–4 cm above the scalp can impact spatial resolution. Scalp optically pumped magnetometers (OPMs) offer a potential solution by reducing this distance, potentially providing higher spatial resolution. This closer proximity of scalp OPMs to neural sources addresses the limitations associated with greater distances in traditional cryogenic systems.

The type of sensors used in MEG systems also affects spatial resolution. Magnetometers, gradiometers, and various sensor configurations each have distinct impacts on resolution and SNR. Multi-component sensors, for instance, can offer enhanced resolution and sensitivity but introduce complexity in sensor

design and data interpretation. Balancing the benefits of advanced sensor designs with practical considerations is crucial for improving MEG performance.

SNR is another critical factor influencing spatial resolution. Variations in SNR can complicate the clarity and precision of spatial measurements, making it essential to employ advanced signal processing techniques to enhance the SNR. Improved signal processing can lead to better spatial resolution and more accurate mapping of neural activity.

This new analytical theory and multipolar expansions can help solve these problems by giving us a good way to compare and the design of future OPM-based scalp MEG systems. This theoretical framework helps to find the limits of spatial resolution by integrating ideas from both high-density and low-density regimes [65]. It also gives a way to improve the design of MEG system.

General recommendations for methodology of FC resting state EEG and MEG research

In EEG and MEG resting-state research, subject-related methodology should focus on reducing heterogeneity by defining resting-state instructions a priori. Controlling for confounding factors like time of day, caffeine intake, and vigilance level is crucial to minimizing data variability.

For measurement-related issues, selecting the right reference montage, such as reference-free or common average, is important as it affects connectivity outcomes. An independent researcher should re-inspect consistent artifact-free epochs. Filtering should avoid phase shifts and artifacts, and epoch length and frequency should be consistent across the study. Analyzed each frequency bands separately, particularly avoiding the gamma band if myogenic artifacts are present.

Regarding connectivity measures, avoid those susceptible to volume conduction and compute connectivity values per epoch, averaging them to enhance stability. Weighted networks or the minimum spanning tree approach should be used to account for network density and reduce subjectivity in network analysis [65].

Recent findings of GT approaches

GT, a mathematical tool for quantifying networks, has been used to study cognitive systems where nodes represent tasks and edges represent correlations between performances. Research by Garcia-Ramos et al. [66] and Kellermann et al. [67] on epilepsy demonstrates its utility in identifying neuropsychological differences [68]. Tosi et al. [69] found qualitative differences in cognitive networks between healthy individuals and those with neurological diseases but lacked quantitative differentiation. Ferguson [70] confirmed network reorganization in early Alzheimer's stages by comparing the cognitive networks of healthy older adults with early Alzheimer's type dementia and amnestic MCI. However, research on cognitive network changes during healthy aging is limited, which is crucial for detecting topological deviations indicating neuropathology. Different cognitive impairments likely show unique network topologies, as seen in AD versus vascular encephalopathy [69].

Wright et al. [68] have applied GT to compare cognitive network structures among healthy individuals of different ages and patients with varying cognitive impairments. They used six network metrics to assess integration, segregation, and modularity. They then tested to see if differences in neural networks in AD show up similarly in cognition. They were expecting distinct network topologies between healthy aging and pathological cognitive decline. The study hypothesized that older, healthy adults rely more on semantic memory within their cognitive networks, whereas individuals with AD, even at prodromal stages, would show reduced influence of semantic processing. For Alzheimer's patients, network differences have been anticipated in semantic processing and memory functions. In healthy aging, older adults' networks have expected to emphasize crystallized abilities with notable differences in executive function tests due to age-related declines. Additionally, individuals with amnestic MCI have expected to have network compositions similar to those with Alzheimer's dementia, aligning with Ferguson [70] and other neuroimaging studies [68].

Finally, the study demonstrated that cognitive networks change with aging and are differentially affected by cognitive impairments, with specific alterations potentially serving as early indicators of AD. These findings could help develop better diagnostic tools for neurodegenerative diseases [68].

According to Bateman et al. [71], AD has a long preclinical phase where brain changes occur without obvious cognitive symptoms. Changes begin 25 years before symptoms show up in familial AD. They start with less amyloid in the cerebrospinal fluid, then amyloid deposition, increase tau protein, brain atrophy, and hypometabolism [72]. Vermunt et al. [73] have studied a large cohort from the Dominantly Inherited Alzheimer Network (DIAN) using structural MRI and GT. They have found that brain connectivity changes begin as early as 13 years before symptoms, particularly in the precuneus. The correlation between these changes and biomarkers such as amyloid accumulation, brain metabolism, cortical thickness, and cognition suggest the potential use of brain connectivity measures for early diagnosis and tracking AD progression [72].

Cognitive functions depend on communication between interconnected brain regions, not isolated areas. Recent brain network studies use GT, representing the brain as nodes connected by edges, to assess its topological architecture. Vermunt et al. [73] have used this approach to study brain network topology in familial AD mutation carriers. They found network changes 13 years before disease onset, showing shorter network paths or more direct links between brain areas. These changes, most prominent in the precuneus—a crucial brain hub and early amyloid accumulation site Palmqvist et al. [74], confirm previous findings in sporadic AD. The shorter paths in the precuneus might be a compensatory mechanism, increasing connections to counteract pathology, similar to changes seen in individuals at higher genetic risk for sporadic AD [72].

The study by Vermunt et al. [73] has found that, in individuals who will develop AD, brain network paths shorten, followed by a loss of small-world organization and reduced local clusters of connections. This indicates that brain networks become more random over time, losing the balance between global and local connectivity. These changes in network topology precede simpler measures such as degree and density, suggesting that complex measures that combine clusters and paths undergo earlier changes and are associate with amyloid deposition, brain hypometabolism, and cognitive deficits. Thus, network topology alterations could be an important AD biomarker, helping to understand cognitive decline mechanisms. It is still unclear what exactly structural correlations in grey matter reflect; they might be linked to physical white matter tracts or FC. Previous studies show overlap between structural correlations and white matter tracts and between clusters from structural and FC. Identifying these network abnormalities may help understand how amyloid and tau pathology spread, causing cognitive decline. They have mentioned that future research should explore the neurobiological factors driving these changes and replicate findings in other samples [72].

A recent study has RSFC in 772 older adults (55–85 years, 421 males) using a graph-theoretical approach. The results show age-related increases in between-network RSFC and decreases in within-network RSFC, indicating a reorganization towards more pronounced functional network integration. This reorganization particularly affects early sensory networks, such as the visual and sensorimotor networks, and correlates with age-related cognitive performance differences. Additionally, lower RSFC within primary processing networks correlates with lower cognitive performance, while increased RSFC between higher-order networks and the sensorimotor network suggests a compensatory mechanism to maintain cognitive functions. However, this increased between-network RSFC often correlates with worse cognitive performance, supporting the dedifferentiation theory, where less specialized networks lead to cognitive decline [75].

The study also found systematic sex-related network differences: females show more segregation in networks like the default mode and ventral attention network, while males show a more integrated network system, particularly in the sensorimotor network. These findings highlight sex-related connectivity differences, possibly influencing sex-related behavioral functioning. The study emphasizes the importance of sex-stratified analyses, as RSFC patterns differ significantly between older males and females, indicating different reorganizational processes with aging [75].

Limitations of GT approaches

GT provides a robust framework for analyzing the topological features of functional and structural networks derived from neuroimaging data. However, this approach is not without its limitations (Table 3). A significant issue arises from the frequent occurrence of false positive (FP) connections, which can substantially influence the inferred network topology. The common practice of thresholding to mitigate the impact of FPs often introduces its own challenges. Typically, a priori assumptions guide thresholding, altering the inferred network structures and causing biases in the results.

Table 3. Major challenges in graph-theoretic studies of FC in the brain

Challenge	Recommendation
Brain parcellations vary substantially across studies	In the absence of a standard for brain parcellations, the following minimum requirements are recommended:
	• Ensure comprehensive coverage of functional regions throughout the brain, including cortical, subcortical structures, and the cerebellum.
	• Divide the brain into at least 200 functional regions.
	• Base the delineation of regions on FC, potentially combined with multimodal imaging.
	• Ensure regions exhibit high FC homogeneity.
	• Provide clear guidance on the modular structure of regions within the parcellation, discouraging researchers from identifying functional modules when a published modular structure is available.
The quality of RSFC data varies over time	• Longer resting-state acquisitions improve the stability and test-retest reliability of FC estimates.
	• Clinical researchers should collect resting-state data for at least 9 min.
	• Faster temporal sampling (e.g., 1-second TR) should be used, when possible, potentially utilizing multiband imaging.
Edge definition	• The reliability of FC based on partial correlation decreases with an increasing number of nodes or fewer measurements, requiring longer scan times.
	• Bivariate correlations are more stable, typically reaching consistency after 250 measurements, regardless of node count.
	• For conventional resting-state data (e.g., 180 volumes, 2-second TR), using a shrinkage estimator of marginal correlation is recommended over conditional association measures.
	• Proportional thresholding should be avoided in case-control studies as it can obscure or distort results.
	• Researchers should clearly describe how negative FC estimates are handled, as deleting negative edges is an untested assumption. If many negative edges are present, they should be reported and possibly analyzed using a separate graph.
Graph metrics varied across studies	To promote formal comparisons across studies, researchers are encouraged to report a standard set of graph metrics. A minimal set includes:
	• Global clustering coefficient.
	• Average path length.
	• Modularity.
	• Degree.
	• Eigenvector centrality.
	• Summary statistics of edge strength.
Need to align neurobiology and the network representation	• Researchers should conceptualize and report graph analyses across different levels of analysis, from global to specific.
	• Global metrics may overlook regional effects of pathology or neurodevelopment, so careful consideration is needed.
	• Researchers should ensure alignment between the graph analysis level and the biological understanding of neuropathology.
	• The relevance of certain graph metrics, like small-worldness, to understanding brain disorders is still unclear [77].

FC: functional connectivity; RSFC: resting-state functional connectivity

The analysis of four common network metrics—global efficiency, mean clustering coefficient, mean betweenness, and small-worldness—using a model tractography dataset revealed that even a single FP

connection could significantly affect these metrics. While thresholding helps dampen the impact of FPs, it comes at the cost of introducing substantial bias. This bias complicates the accurate assessment of network properties.

Further investigation into a larger set of tractography datasets (n = 248) demonstrated that network metrics exhibited significantly more variability than non-network metrics (such as the number of streamlines and edges) when subjected to random group permutations across various thresholds. To assess sensitivity to genuine group differences, artificial network atrophy was introduced to half of the datasets. This atrophy was detected as significant ($P < 0.05$, using permutation testing) only within a limited range of thresholds for certain network metrics.

To address these limitations, we propose a multi-threshold permutation correction (MTPC) method. This approach builds upon the cluster-enhanced permutation correction technique to identify sustained significant effects across clusters of thresholds. The MTPC method reduces the necessity of selecting a single threshold a priori, thereby minimizing bias and improving sensitivity to genuine group effects. We showed that MTPC works better than traditional methods at finding real differences between groups by using network analyses of clinical tractography data that had already been published.

In summary, while thresholding introduces significant biases and instability into network metrics, the MTPC method offers a promising solution by evaluating effects across multiple thresholds. This approach enhances the robustness of network analysis and facilitates more accurate identification of genuine differences in network topology [76].

There is significant heterogeneity in how nodes and edges of graphs are defined across resting-state studies, which complicates quantitative comparisons and meta-analyses. Key sources of variability include differences in brain parcellations, the FC metrics used (e.g., full vs. partial correlation), the handling of negative FC estimates, and various preprocessing decisions, such as global signal regression. Additionally, few graph metrics are consistently reported across studies, further hindering efforts to identify commonalities across different studies and disorders.

One common approach, proportional thresholding, converts continuous FC metrics (e.g., Pearson correlation) into binary edges while maintaining a constant number of edges across all subjects. However, this method can obscure the effects of brain pathology in case-control studies, where clinical groups may experience changes in both the number and strength of functional connections. Proportional thresholding can also produce spurious group differences when groups differ in the connectivity strength of certain brain regions.

Furthermore, concepts like neural efficiency often presumed rather than empirically establish the relationship between many graph metrics and neurobiology. Many studies fail to consider how findings at one level of analysis (e.g., global topology) influence or contextualize within other levels (e.g., modular structure). This misalignment can limit the interpretability and relevance of the results [77].

Future directions

Echeverri-Ocampo et al. [58] study has highlighted the complex relationship between MCI and FC, opening new avenues for future research in neurodegenerative disorders and brain function assessment. As they mention, future research should expand beyond MCI to include other neurodegenerative conditions such as AD, Parkinson's disease, and other forms of dementia. This broader focus can help identify common and unique FC patterns across different disorders, providing deeper insights into their mechanisms. Additionally, integrating other neuroimaging techniques like fMRI and MEG with EEG could offer a more comprehensive view of brain function and connectivity. Future studies should explore the benefits of combining multiple modalities to improve diagnostic accuracy.

Conclusions

The review article summarizes current research on cognitive aging and neurodegenerative disorders through the lenses of FC studies using rs-fMRI, EEG/MEG, and GT approaches. Age-related changes in cognitive abilities, characterized by preserved crystallized skills and declining fluid abilities, underscore the importance of understanding neural alterations in brain structure and function. FC studies, particularly using rs-fMRI, have illuminated disruptions in resting-state networks like the default mode and FPCNs, offering insights into cognitive aging processes and their implications for neurodegenerative diseases such as AD and MCI.

Moreover, advances in rs-fMRI have revealed FC deficits in AD and MCI, particularly in critical networks like the DMN, highlighting its potential as a diagnostic tool. Despite challenges such as NVU and variability in resting-state conditions, rs-fMRI remains integral to studying brain function across the lifespan and in pathological conditions.

EEG and MEG complement rs-fMRI by providing high temporal resolution for studying brain rhythms and FC. These techniques, combined with ML, show promise in enhancing early diagnosis and understanding connectivity changes in neurodegenerative diseases.

GT, another essential tool, quantifies cognitive networks and reveals topological changes associated with AD and MCI. By elucidating network reorganization and connectivity alterations, GT offers insights into early biomarkers and potential diagnostic strategies.

Future directions include integrating multimodal neuroimaging techniques to improve diagnostic precision and therapeutic interventions for neurodegenerative disorders. This review shows how important it is to use methods from different field in neuroscience research to better understand how cognitive networks change during healthy aging and pathological conditions. This is important for finding good solutions to health problems that come with getting older.

Abbreviations

AD: Alzheimer's disease

ADAD: autosomal dominant Alzheimer's disease

BOLD: blood oxygen level dependent

CAPs: coactivation patterns

CBF: cerebral blood flow

CON: cingulo-opercular network

DAN: dorsal attention network

DFNC: dynamic functional network connectivity

DMN: default mode network

ECN: executive control network

EEG: electroencephalography

FC: functional connectivity

FP: false positive

FPCN: frontoparietal control network

GT: Graph theory

HC: hippocampus

iCOh: imaginary part of coherency

laHC: left anterior hippocampus

MCI: mild cognitive impairment

MEG: magnetoencephalography

ML: machine learning

MRI: magnetic resonance imaging

MTPC: multi-threshold permutation correction

NVU: neurovascular uncoupling

OPMs: optically pumped magnetometers

PET: positron emission tomography

pHC: posterior hippocampi

PLI: phase lag index

QEEG: quantitative electroencephalography

RSFC: resting-state functional connectivity

rs-fMRI: resting-state functional magnetic resonance imaging

sAD: sporadic Alzheimer's disease

SL: Synchronization Likelihood

SMD: standardized mean difference

SN: salience network

SNR: signal-to-noise ratio

Declarations

Author contributions

PVNNR: Investigation, Writing—original draft, Writing—review & editing. MSTM: Conceptualization, Investigation, Writing—review & editing, Supervision. Both authors read and approved the submitted version.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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