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MINI - REVIEW

Metabolic connectivity in Alzheimer's diseases

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Abstract
Multiple studies have investigated the disruptions in structural and functional connectivity in aging, dementia and Alzheimer's disease (AD). The study of metabolic connectivity between brain regions using fluorodeoxyglucose positron emission tomography (FDG-PET) however, is a new focus of interest. Several methodological approaches, including seed-based correlation, independent and principal component analysis, and graph-theoretical approaches have been employed to study the metabolic disconnectivity in AD. We conducted a systematic search of the literature using the keywords metabolic connectivity and Alzheimer disease, up to the date of last submission and included 15 original articles as relevant. Existing literature implies a generalized metabolic disconnectivity in the brain which closely follow findings from functional studies. In the following review, we introduce the concept of metabolic disconnectivity and discuss the alterations in metabolic connectivity in AD and the potential underlying mechanisms. We find it imperative for future studies to investigate alterations in metabolic and functional connectome of AD and mild cognitive disorder through simultaneous acquisition of FDD-PET, functional and structural scans.

Keywords Alzheimer's disease · Metabolic connectivity · Amyloid beta · Network analysis · Positron emission tomography

Introduction on FDG-PET network analyses and methodology

Synaptic signal transmission is a major function of neurons, consuming some 90% of the neurons energy expenditure, which in turn comprises about 80% of total energy spent in the brain tissue [1]. Unlike astrocytes and other glial cells, neurons rely almost exclusively on oxidative glycolysis to generate ATP, resulting in a one-on-one, direct relationship between synaptic activity, glucose consumption in neurons [2]. It is, therefore, plausible to deduce that changes in neuronal activity alter neuronal glucose consumption and hence glucose uptake, a physiologic reflex called neurometabolic coupling [2]. Neurometabolic coupling is the underlying notion in fluorodeoxyglucose-positron emission tomography (FDG-PET), offering a unique potential to measure the rate of cerebral glucose uptake (cerebral metabolic rate of glucose: CMRglc), as a proxy for regional neuronal activity [3, 4]. This description implicates that conditions which reduce aerobic glycolysis in neurons, such as aging or malignant transformation, can decouple glucose uptake from oxygen consumption, leaving measurements based on oxygen consumption with less accuracy [5].

Study of connectivity patterns, or connectomics, has found its place in clinical neuroimaging. Given its multivariate nature, connectomics gives additional value over simple univariate analyses as it generates new and neurobiologically meaningful variables to quantify properties of the "whole brain" as a complex network [6]. Studies have demonstrated alterations in metabolic connectivity in different dementia disorders [7, 8], as well as its association with cognitive reserve [9], and with clinical outcome of temporal lobe epilepsy following vagal nerve stimulation [10]. Moreover, integrated acquisition of functional MR/PET is now used as a measure to compensate for high intrinsic fluctuations in CMRglc signal intensity and enable fully quantitative analyses of metabolic connectivity alongside functional data. Importantly, the correlation between functional connectivity (FC) measures and regional CMRglc of the major brain

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networks has been reported as either week or non-existent in a healthy population [11, 12]. This provides proof that changes in intrinsic CMRglc during tasks, i.e. univariate or intensity-based FDG-PET measurements, have little to reflect from FC architecture of the brain and FC changes during tasks [12]. The idea of connectivity analysis was first implemented in functional imaging data, generating the concept of FC, which can be simply defined as the magnitude of functional co-activation between distinct brain regions [13]. Metabolic connectivity can be similarly defined based on FDG-PET data as the strength of co-activation or -deactivation between two regions based on a conjugate increase or decrease in the cerebral metabolic rate of glucose) in those regions [6].

FC maps have helped unravel important facts about the pathobiology of brain in health and disease. These maps illustrate the coordinated fluctuations in blood oxygenation levels in different brain regions as a result of increased neuronal activity and hence glucose and oxygen uptake, a phenomenon called "neurovascular coupling" [14]. It is important to note that neurometabolic coupling itself, which is the bases for CMRglc measurement in FDG-PET partly relies on neurovascular coupling to deliver sufficient amounts of glucose to the site of activation. This implies that alterations in FDG-PET signal capture neural hyperactivity closer to its source, and depends less on the neurovascular response, compared to the blood oxygen level-dependent (BOLD) signal, which relies on real-time fluctuations in regional blood flow and oxygen saturation [15, 16]. This can explain the superiority of FDG-PET in identifying patterns of altered cortical metabolic connectivity in various neurobiological disorders, compared to multivariate FC measurements, despite the inherent inter and intra-individual variability in univariate CMRglc fluctuations [17]. Nevertheless, when comparing the correlation between metabolic covariance maps with FC and volumetric connectivity maps, a strong correlation is identified between FGD-PET and BOLD connectivity matrices in that metabolic correlations partially mediates the correlation between resting-state functional connectivity and volumetric connectivity in healthy individuals [18]. Although, metabolic covariance maps show the highest correlation with FC maps, the overall overlap between networks is less than 40% meaning that more than half of significant metabolic connectomes cannot be explained by functional connectivity [18]. This also suggests that multivariate metabolic maps might represent pathologically distinct features from functional or structural connectomes.

We conducted a systematic search of the literature using the following keywords in the PubMed and Scopus search engines: ("metabolic connectivity" OR "metabolic network" OR "metabolic connectome") AND ("Alzheimer disease" OR Alzheimer OR "Alzheimer's disease"). The search was updated to the date of the last revision. Two authors, FR and HSM separately reviewed the resulting 123 records and excluded results in the form of review articles, book chapters, and conference proceedings, as well as studies using non-FDG PET tracers. We then screened the articles based on title and abstract to identify original articles which had addressed the concept of metabolic connectivity. Full text of potential articles of interest (#63) was then reviewed by two independent authors and finally 15 articles were included as relevant if they were original articles investigating changes in brains metabolic connectivity using FDG-PET in patients with AD, mild cognitive impairment (MCI) or both (Table 1).

Logic for metabolic network (connectomics) and methodology

Region-based FDG-PET evaluation of brain cortex has long been used to differentiate patterns of hypo- or hypermetabolism, with the goal to identify disease-specific patterns of altered cortical activity. As mentioned in the previous section, alterations in interregional FDG-PET signal has its benefits over resting-state fMRI data in identifying disease-specific patterns in dementia [6]. This owes to higher signal-to-noise ratio in univariate CMRglc values, which result from the inherently stable nature of neurometabolic coupling patterns, as well as higher variance, i.e. inter and intra-subject variability of CMRglc values, which ultimately confers higher reproducibility of multivariate connectivity maps built based on interregional covariance of CMRglc signals [6].

Numerous statistical approaches have been implemented to capture multivariate metabolic connectivity, including methods of modelling both single-subject and group-based data [6, 25]. These include: first, seed correlation analyses which have been widely implemented in the voxel-wise interregional correlation analysis (IRCA). This method is based on picking a reference region and quantifying the correlation of its strength with all other voxels in the brain. Second is the independent and principal component analyses (ICA and PCA), which put additional constraints, such as statistical independence and multivariate decomposition to identify significant metabolic covariance's [33]. The third model leverage from graph theory principals to identify the underlying connectivity matrix using sparse inverse covariance estimation (SICE) [34, 35]. None of these approaches have shown inherent superiority over others, and all three have been used by the relatively sparse literature to study characteristics of metabolic connectivity maps. As mentioned in the previous section, the overlap between multivariate metabolic and functional connectivity maps is as low as 40% in healthy individuals [18], and the even higher

Table 1 Summary of included articles and methods used for metabolic network construction

First author	Year	Method for network construction	Citation
Kerrouche	2006	PCA	[19]
Markiewicz	2009	PCA and FDA	[20]
Markiewicz	2011	PCA	[21]
Toussaint	2012	Voxel-based group analysis and ICA	[22]
Sanabria-Diaz	2013	Graph theory	[23]
Carbonell	2014	MCS	[24]
Carbonell	2014	HMC	[25]
Carbonell	2016	Modulated seed-based metabolic correlation analysis	[26]
Yao	2015	Graph theory	[27]
Chung	2016	Graph theory	[28]
Titov	2017	SICE and SICS	[7]
Li	2018	Gaussian kernel function and lattice-close-degree	[29]
Yao	2018	Graph theory	[30]
Huang	2018	Graph theory	[31]
Chang	2018	ICA	[32]

PCA principal component analysis, *FDA* fisher discriminant analysis, *ICA* independent component analysis, *SICE and SICS* sparse inverse covariance estimation and selection, *EAD* early-onset AD, *LOAD* late-onset AD, *MCS* metabolic correlation strength analysis, *HMC* hierarchical multivariate covariance analysis

discrepancy has been reported in AD patients [36]. Indeed, one study implemented spatial ICA on resting state BOLD images and FDG-PET of AD patients identified several metabolic networks similar to resting FC networks including those originating from sensory-motor cortices, cerebellum and basal ganglia [36]. However, the substantial discrepancy was identified between FDG-PET and BOLD covariance maps in large-scale anteroposterior, signature AD networks, including the loss of metabolic, but not functional, connectivity between DMN and frontoparietal network with the medial prefrontal cortex, in AD patients [36]. This suggests that impairments in some covariance maps of signature AD regions occur earlier and are specific to metabolic level, a feature that was not detected by BOLD ICA or univariate FDG-PET analyses.

Network characterization of connectivity maps using graph theory has been a popular approach in the characterization of both functional and metabolic networks, as demonstrated among the literature discussed in this manuscript. When trying to implement the graph theory in metabolic connectivity maps, each brain region can be considered a "node" of the network and the significant metabolic covariance between the two regions as the "edges" of the network [37]. Graph theory analysis provides the additional benefit of generating the so-called network topological metrics, which can be used to quantify the strength of centrality/importance of individual nodes in the network, as well as connectivity of the network as a whole [37]. Unlike IRCA, ICA, or PCA, graph theory enables defining anatomical, functional, and metabolic connections on the same map, hence exploring structure/function/metabolism connectivity relationships [38]. Among the most common network topological metrics in the literature are: (1) measures of segregation, the most important being clustering coefficient, (2) measures of integration including the characteristic path length and global efficacy, (3) measures of centrality including degree centrality and betweenness centrality, and finally (4) measures of network resilience such as degree distribution [37].

In the following sections, we introduce Alzheimer disease (AD) as one of the most commonly studied types of dementia and will move forward to discuss the alterations in metabolic connectomics in AD and their potential relevance to the underlying AD pathology.

Metabolic network disruption in AD

AD is characterized by distinct patterns of reduced cortical FDG-PET uptake, revealing hypometabolism in the posterior associational areas, including the lateral temporal, angular, posterior cingulate (PCC) and precuneal cortices [39]. Many of these AD signature regions, in terms of Aβ deposition, hypometabolism and atrophy, are spatially located in the default mode network (DMN) of the brain. Cortical patterns of hypometabolism have been long used to classify AD and differentiate it from other types of dementia [40].

Despite the above-mentioned evidence, however, the mechanistic justification for the observed correlated glucose metabolic activity in remote brain regions remains elusive. Indeed, besides anatomic connectivity, which relies upon actual white matter tracts connecting different regions in the brain, cortical connectivity maps based on functional,

metabolic, or amyloid beta (Aβ) and tau deposition, are all fictional in nature. There are, however, evidence using voxel-based PCA on FDG-PET data highlighted the presence of metabolic networks, independent of resting-state functional networks that could differentiate AD from vascular dementia, as an example [19]. PCA was shown to offer higher accuracy in describing the portion of the population variance, compared to univariate Pearson's correlations, and has a significant correlation with dementia severity scores in patients with AD [20, 21]. Using voxel-based ICA, FDG-PET connectivity patterns were able to differentiate patients with MCI and carriers of apolipoprotein E4 gene (ApoE4) gene, who have a higher risk for progression to AD [22]. SICE analysis of metabolic connectivity was able to discriminate patients with AD from frontotemporal dementia with almost 83% accuracy [7]. In the later, the authors compared the accuracy of univariate versus multivariate metabolic connectivity analyses (using SICS) in differentiating between AD, frontotemporal dementia and healthy controls [7]. Their results showed a uniformly higher sensitivity and specificity of SICS in the differential diagnosis of different types of dementia, compared to univariate analysis and existing literature. An indirect relation-based network of metabolic connectivity was recently used to correctly identify MCI from AD patients and healthy controls [29]. The diagnostic value of metabolic connectivity was further exemplified using graph theory and SICE method multivariate FDG-PET analyses in a group of patients with dementia of lewy body, where metabolic dysconnectivity closely followed the suggested pathological trajectory for alpha-synuclein deposition, showing alterations in the striato-cortical structural network that shows early evidence of synucleinopathy [8].

Figure 1 illustrates brain regions with altered metabolic connectivity in MCI and AD based on the existing literature. Although the idea of network-patterned clustering of CMRglc dating back to 1984 [41], Sanabria-Diaz and her colleagues were the first group to implement graph theory analysis to CMRglc values derived from a FDG-PET study of patients with AD and MCI [23]. They identified lower numbers of significant metabolic covariance "hubs" in AD patients that were predominantly located in the lateral and medial occipital surfaces. They also demonstrated a lower local and global network efficacy along the clinical trajectory of AD, while moving from cognitively normal elderly patients to MCI and AD patients [23]. Global network efficacy is a measure of networks integration, i.e. how well the network can combine information from dispersed nodes [37]. In metabolic networks, global efficacy can be better interpreted based on the "characteristic path length", which is the average shortest path length between all nodes of a network and bears an inverse relationship with global network efficacy [37]. If metabolic covariances corroborate to the organization of functional covariances in the brain, the above findings can be interpreted as low efficacy and disconnection in functional networks in the posterior associational regions in AD patients, in line with the existing literature [42]. The fact that MCI patients had intermediate topological metrics and lower number of significant metabolic hub, corroborates the role of AD pathology in disruption of metabolic covariance's between regions.

Another important finding of this seminal study was the altered patterns of "betweenness centrality" in patients with AD and MCI [23]. Betweenness centrality is a measure to identify central or hub nodes in the network, which are important nodes within a network that can facilitate networks integrity by interacting with many other nodes in the network [43]. Unlike global or local efficacy, betweenness centrality attributes to single nodes, but not the network as a whole. Meanwhile higher average betweenness centrality in a network can be interpreted as a higher number of central nodes in the network that results in networks resilience to insults, such as degeneration and functional exclusion [44]. Normalized average global betweenness centrality as well as region-specific betweenness centrality, in signature AD regions in middle temporal and hippocampal gyri, were all found to be reduced in AD patients [23]. Meanwhile, a concurrent increase in univariate CMRglc as well as network centrality metrics were found in the frontal and occipital lobes, consistent with a compensatory increase in local efficacy of FC networks in these regions in MCI or early AD described in the literature [45]. The "small world" properties of metabolic connectivity networks were first investigated in 2011, and were later confirmed in larger populations [46, 47]. Small-worldness of networks is by definition a property in the networks design, where functional segregation and global integration of different nodes in the network are both optimized. Small-world networks are, therefore, significantly clustered without increasing the path lengths and reducing their global efficacy [48].

A distinct pattern of progressive disconnection in FC networks is seen along the clinical trajectory of AD, starting from carriers of *APOE4*, who have a high risk of developing dementia, to patients with an amnestic form of MCI, and to clinical AD [49–53]. A similar pattern can be identified in metabolic dysconnectivity, starting with disruption of small-worldness, clustering coefficient, and nodal centrality in metabolic networks of *APOE4* carriers [27, 32], continued with reduced global and local efficacy and clustering coefficient in multivariate cortical CMRglc networks in MCI [23], and finally, profound disruption of metabolic correlation patterns in patients with AD dementia [30]. As a result of these changes, there is an overall lower number of inter and intrahemispheric connections (i.e. edges) in metabolic connectivity networks of AD patients compared MCI patients, and in MCI patients compared to controls, starting from metabolic connections of the frontal lobe [26, 31]. Some studies have

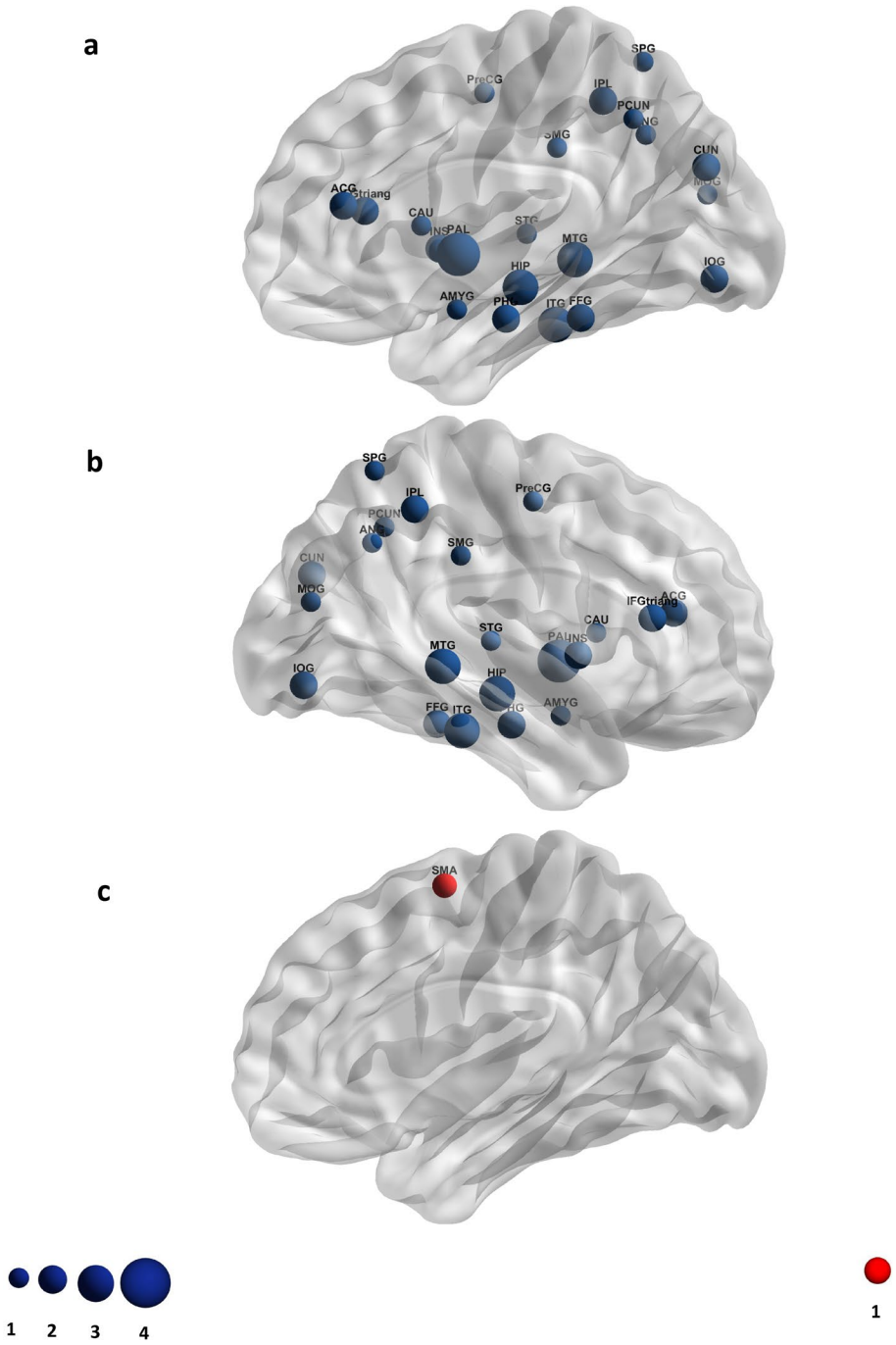

Fig. 1 Visual overview of anatomical regions found to have decreased (blue nodes) and increased (red nodes) metabolic connectivity in MCI or AD compared to normal controls. Node diameter is proportional to the number of studies, which reported the region to have altered metabolic connectivity. *SPG* superior parietal gyrus, *IPL* inferior parietal lobe, *SMG* supramarginal gyrus, *PCUN* precuneus, *CUN* cuneus, *MOG* middle occipital gyrus, *IOG* inferior occipital gyrus, *STG* superior temporal gyrus, *MTG* middle temporal gyrus, *ITG* inferior temporal gyrus, *HIP* hippocampus, *PHG* parahippocampal gyrus, *AMGY* amygdala, *PAL* pallidum, *INS* insula, *CAU* caudate nucleus, *ACG* anterior cingulate gyrus, *IFGtriang* inferior frontal gyrus, triangular, *FFG* fusiform gyrus, *preCG* precentral gyrus, *SMA* supplementary motor area

failed to demonstrate any difference in metabolic connectivity between *ApoE4* carriers and non-carriers, suggesting that *ApoE4* carrier status predisposes to a coordinated decrease in metabolic activity as opposed to inter-regional metabolic disconnectivity [24, 26]. Nevertheless, these results further imply that a common neural substrate might underlie the functional and metabolic connectivity of the healthy brain and their disruption in AD [17, 54].

Metabolic connectivity maps can even differentiate between early-onset and late-onset subtypes of AD. Early-onset AD is characterized by loss of small-worldness of metabolic connectivity in the occipital and temporal regions, in terms of reduced global efficacy and clustering coefficient, which also correlate with the severity of dementia [28]. Metabolic dysconnectivity in late-onset AD is however more confined to the cingulate: occipital regions [28]. Similarly, loss of metabolic connectivity between PCC and hippocampus could identify patients with amnestic mild AD patients among other AD subtypes [55]. Hypometabolism in the PCC and hippocampus is a prominent feature of AD

dementia [39]. This is while univariate FDG-PET measures have failed to identify differentiating patterns in CMRglc maps between early and late-onset AD [56], in line with the fact that metabolic connectome alterations exceed regional metabolic impairments in early AD.

Amyloid-beta pathology and metabolic dysconnectivity in AD

Wu and his colleague were the first group to introduce the idea of resting-state networks to CMRglc and investigate their association with resting-state FC networks in a healthy population [57]. Metabolic connectivity networks spatially overlapped with a visual, default-mode network (DMN), and hippocampus functional networks in this group. Other studies identified a fair to moderate spatial correlation between metabolic covariance maps in the DMN, and a strong correlation between metabolic and FC networks in the visual and salience networks, and in motor areas [17, 36, 58]. These findings pointed out a common neural substrate for metabolic and functional networks both in healthy individuals and AD patients [17, 54, 59]. Indeed, total cortical Aβ deposition in signature AD cortical regions is associated with patterns of synchronized hypometabolism in those regions with a resultant loss of global metabolic connectivity in the brain [26].

The network degeneration hypothesis suggests that pathological changes responsible for neurodegenerative disorders, initiate in and propagate along with specific neuronal populations, a pattern that largely resembles the spatial patterns of intrinsic brain networks [60]. Indeed, vulnerability of cortical regions to Aβ pathology [61], their susceptibility to atrophy [62], and even tau spread patterns [63, 64], appear to follow the same outline of intrinsic anatomical-functional networks. The extent of these cross-modal network propagation was later investigated by several studies. One important finding was the disruption of global FC of the medial temporal lobe (MTL), which is particularly vulnerable to AD hypometabolism and depicts early Aβ accumulation and atrophy [39], was associated with a rebound increase in intrinsic metabolic activity in that region [65]. Likewise, the number of significant metabolic connections within the temporal lobe subregions increases in MCI compared to healthy controls [32]. Another finding was that regional Aβ deposition in the temporal cortex not only modulates regional functional activity within the MTL [66] but also correlates with hypometabolism in the prefrontal and precuneal regions, which are two remote but functionally connected regions to the MTL [67, 68]. Moreover, metabolic dysconnectivity in the ventral areas of the DMN, including MTL, is shown to be associated with worse memory scores [32]. Together these findings suggest that Aβ pathology underlies the metabolic dysconnectivity as well as functional: metabolic uncoupling of brain cortex in AD patients.

Carbonell et al. tested this hypothesis first through comparing the metabolic connectivity strength between amyloid positive and negative MCI patients, followed by modelling regional metabolic connectivity as a function of amyloid burden in MCI and AD patients [24, 26]. Adopting cortical Aβ as a dichotomous variable (positive versus negative), they demonstrated that highly metabolically correlated regions (including signature AD regions angular, inferior temporal, and supramarginal gyri). This was associated with a generalized reduction in metabolic connectivity in MCI patients with high amyloid burden, which was more notable in lateral parietal and inferior temporal cortices [24]. When treating total brain amyloid burden as a continuous variable they found a significant decrease in metabolic connectivity in signature AD regions in the inferior temporal, fusiform, precuneus, and angular gyri, along with an increase in total cortical amyloid burden in a sample of healthy controls, MCI and AD patients [26]. These results were corroborated by finding of significant negative correlation between total cortical Aβ burden and metabolic connectivity in the same regions in the MCI, but not the AD group [24]. Importantly, areas with less strong "betweenness centrality" features were more susceptible to metabolic dysconnectivity, suggesting a relative resistance of highly central hubs to metabolic dysconnectivity as a result of amyloid deposition. Nonetheless, Carbonell et al. did not address whether amyloid accumulation was spatially concordant with areas of loss of metabolic connectivity in any of these regions. A simultaneous FDG and Aβ PET imaging in a larger group of MCI patients yielded similar results, with a loss of metabolic correlation between the hippocampus and posterior cingulate gyrus along the clinical trajectory of AD [55]. They identified decreased betweenness centrality in the anterior cingulum, superior parietal, fusiform, inferior temporal and precuneal gyrus in MCI patients compared to controls, while clustering coefficient was increased and average path length had decreased in the metabolic correlation matrices [55]. Similarly, in MCI patients, increased clustering coefficient and functional segregation were observed in hub regions located within the DMN, along with a progressive reduction in betweenness centrality of the DMN, starting from MCI to AD [69]. Increased clustering coefficient observed in AD-signature regions in patients with MCI also agrees with the increased intrinsic metabolic activity of the hippocampus of MCI patients [70], which is believed to result from loss of global cortical FC of this region [70, 71]. In other words, while the DMN becomes progressively disconnected from the respective cortical regions in the frontal and posteromedial cortices [65], it develops a compensatory increase in activity of local hubs within the MTL, resulting in increased local segregation metrics of this region [72]. Further

supporting the role of Aβ pathology in metabolic dysconnectivity is the finding that AD-signature regions with more severe hypometabolism and atrophy in AD dementia, show increased Aβ deposition and an Aβ-related hypermetabolism in MCI [73]. As mentioned Aβ pathology is associated with hypometabolism in remote, but functionally connected cortical regions [67], and underlies the FDG-PET: FC decoupling in posterior DMN regions of AD patients [74].

Concluding remarks and future directions

Over the past decades, a large bulk of imaging studies with divergent imaging data (structural, functional, and metabolic) and methods of analysis have looked into the underpinnings of aging-related processes and its pathological branches, most prominently AD and dementia. Even so, the study of AD as disconnection disorder have recently received scientific attention. Using fMRI data, the majority of connectivity studies have investigated the defects in FC in individuals with AD, however, the study of AD as a metabolic disconnection disorder dates back only to a few years ago. For the time being, FDG-PET has been the sole modality for the study for metabolic connectivity, but several methodological approaches have been introduced for the study of metabolic connectivity, including seed-based correlation, ICA, PCA, and network analysis [6]. As described in detail in previous sections, each modality has its advantages and disadvantages and there is no superiority. Although metabolic connectivity is a very young scientific area, the overall findings from the existing studies imply a generalized metabolic disconnectivity in the brain rather local areas of disconnectivity. Even so, as depicted in Fig. 1, specific hubs and regions might be particularly affected by disease progress. The vulnerability of specific areas to disconnectivity is similar to the pattern of susceptibility to Aβ deposition, thus it has been suggested that Aβ deposition might be involved in metabolic disconnectivity. In fact, some studies have shown that patients with MCI have more localized deficits and as they convert to AD, more generalized pattern of disconnectivity emerges [69]. This is the beginning of the study of metabolic connectivity in AD and dementia, thus more studies with greater samples sizes are required to understand the underlying pattern of metabolic disconnectivity in AD. It is noteworthy that the study of AD and aging-related processes is beyond the scope of a single imaging modality as it compromises diverse and vast variables with numerous confounding factors, so future studies should simultaneously investigate the structural, functional, and metabolic connectivity in AD. Finally, although these findings might not be of significant value for clinical application at this stage, as network deficits consist the earliest changes in the course of AD, further research could convert these alterations in metabolic networks to a powerful biomarker for early diagnosis of dementia and early stages of AD.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest and received no funding to conduct this research.

Research involving human participants and/or animals This article does not contain any studies with human participants or animals performed by any of the authors..

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