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A Systematic Review of the Association between Amyloid-β and τ Pathology with Functional Connectivity Alterations in the Alzheimer Dementia Spectrum Utilizing PET Scan and rsfMRI

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Keywords
Alzheimer dementia · Amyloid-β · Positron emission tomography scan · Resting-state functional magnetic resonance imaging · τ protein

Abstract
The association between functional connectivity (FC) alterations with amyloid-β (Aβ) and τ protein depositions in Alzheimer dementia is a subject of debate in the current literature. Although many studies have suggested a declining FC accompanying increased Aβ and τ concentrations, some investigations have contradicted this hypothesis. Therefore, this systematic review was conducted to sum up the current literature in this regard. The PROSPERO guideline for systematic reviews was applied for development of a research protocol, and this study was initiated after getting the protocol approval. Studies were screened, and those investigating FC measured by resting-state functional MRI and Aβ and τ protein depositions using amyloid and τ positron emission tomography were included. We categorized the included studies into 3 groups methodologically, addressing the question using global connectivity analysis (examining all regions of interest across the brain based on a functional atlas), seed-based connectivity analysis, or within-networks connectivity analysis. The quality of the studies was assessed using the Newcastle-Ottawa Scale. Among 31 included studies, 14 found both positive and negative correlations depending on the brain region and stage of the investigated disease, while 7 showed an overall negative correlation, 8 indicated an overall positive correlation, and 2 found a nonsignificant association between protein deposition and FC. The investigated regions were illustrated using tables. The posterior default mode network, one of the first regions of amyloid accumulation, and the temporal lobe, the early τ deposition region, are the 2 most investigated regions where inconsistencies exist. In conclusion, our study indicates that transneuronal spreading of τ and the amyloid hypothesis can justify higher FC related to higher protein depositions when global connectivity analysis is applied. However, the discrepancies observed when investigating the brain locally could be due to the varying manifestations of the amyloid and τ overload compensatory mechanisms in the brain at different stages of the disease with hyper- and hypoconnectivity cycles that can occur repeatedly. Nevertheless, further studies investigating both amyloid and τ deposition simultaneously while considering the stage of Alzheimer dementia are required to assess the accuracy of this hypothesis.

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Introduction

Alzheimer dementia (AD) manifests in a spectrum consisting of a long-lasting preclinical stage, a phase of mild cognitive impairment (MCI), and, eventually, fully manifested dementia [1]. Related pathophysiological changes primarily occur decades before the manifestation of cognitive decline symptoms [2]. Thus, the current focus is on early diagnosis and therapeutic approaches at the MCI and even preclinical disease stages to prevent or delay dementia onset. Although the use of imaging biomarkers including structural magnetic resonance imaging (MRI), amyloid positron emission tomography (PET), and 18F-fluorodeoxyglucose (FDG)-PET is validated for diagnosis and prognosis at all stages of AD [3], functional connectivity (FC) measured by resting-state functional MRI (rsfMRI) promises a very early diagnosis in AD and other neurodegenerative diseases [4].

Extracellular deposits of amyloid-β (Aβ) peptides and intracellular neurofibrillary tangles of τ proteins are 2 important neuropathological hallmarks of AD [5, 6]. The correlation between these molecular hallmarks and alterations in FC remains a pivotal quest [7]. Regarding Aβ, the earliest accumulation starts within the default mode network (DMN) [8]. While the higher amyloid burden has been correlated with a lower FC in the posterior cingulate cortex and precuneus (i.e., major hub regions in the DMN) in some works [9–11], other studies have linked Aβ to increased connectivity in DMN regions [12]. In addition to DMN, an association between the global Aβ load and aberrant FC is seen in other intrinsic connectivity networks [13–15]. Moreover, when applying a voxelwise approach globally rather than within networks, the correlation between Aβ deposition and FC shows that a higher Aβ deposition can be related to both increased and decreased FC in various brain regions [13].

Regarding τ, some studies have found a positive association between FC and τ propagation, supporting the view of the trans-synaptic spread of τ across neuronal connections in AD [16, 17] either at the global connectivity level [18, 19] or at the seed-to-voxel level [20]. However, other researchers have shown that, at a local level of τ deposition, a higher τ burden in some regions such as the posterior DMN (pDMN) and the inferior temporal cortex is related to declining connectivity [21, 22].

Altogether, these discrepant results concerning the association between τ and Aβ deposition with alterations of FC and the difficulties of conducting original neuroimaging research urged us to systematically review the literature in this regard, aiming to interpret the related current literature comprehensively.

Materials and Methods

The present systematic review was prepared based on Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [23]. The study protocol was approved in PROSPERO with the registration code CRD42020154057 (https://www.crd.york.ac.uk/PROSPERO/).

Search Strategy

We searched the PubMed and Scopus Medical databases and used the Google Scholar search engine up to February 2021. The following search terms and combinations were used: ("functional connectivity" OR "intrinsic connectivity" OR "connectome" OR "resting state") AND (tau OR amyloid) AND (normal OR healthy OR Alzheimer OR "mild cognitive impairment" OR preclinical OR prodromal OR "subjective memory complaint"), without any language or publication time restrictions. Then, 2 authors independently screened all of the titles and abstracts. The full texts of those studies found to be eligible for inclusion based on their abstracts were further studied and assessed for inclusion. Further discussions among all of the authors resolved disagreements regarding the inclusion of the studies.

Inclusion and Exclusion Criteria

The applied inclusion criteria were as follows: original studies using rsfMRI to examine FC while measuring amyloid or τ deposition or both by PET. Opinions, book chapters, reviews, letters, conference abstracts, protocols, and animal studies were excluded.

Following the initial screening, in the full-text assessment phase, studies applying any statistical method other than correlation and regression analysis for assessment of the alterations of FC were excluded. Also, we only included studies in which the following categorization was considered: amyloid-negative normals, amyloid-positive cognitively normals (preclinical AD), subjective memory complaints (SMC), MCI or prodromal AD, and AD dementia.

Data Extraction

Two authors separately extracted the following data: bibliographic details of papers such as author name, publication year, study design, and demographic data of the participants, including the number of participants, age, gender, clinical inclusion, and exclusion criteria. Regarding rsfMRI and PET, we excluded some details such as: magnetic field strength, repetition time and echo time, connectivity analysis (e.g., seed based, whole brain, etc.), τ-PET or amyloid-PET tracers, and the cutoff of amyloid-PET tracer uptake for amyloid positivity. Finally, the following details of the association analysis were extracted: (1)the type of association analysis (e.g., correlation or regression), (2) the name of the region(s) or network(s) with FC involved in the association, and (3) whether the amyloid or τ burden that was involved in the association was global or local and, if it was local, the name of the region(s).

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Table 1. Quality assessment

Cross-sectional studies		Selection				Subscore	Comparability	Octcome		Subscore	Total
authors	year	representativeness of the sample	sample size	nonresponders	ascertainment of the exposure			assessment of the outcome	statistical test		
Chiesa et al. [33]	2019	*	*		**	4	*Age and MMSE score	**	*	3	8 (good)
Yokoi et al. [45]	2018	*			**	3	**Age, sex, and education	**		2	7 (fair)
Pasquini et al. [39]	2017	*	*		**	4	**Age, sex, and education	**	*	3	9 (good)
Elman et al. [13]	2016	*	*		*	3	**Age, scanner, motion, and voxelwise gray matter	**	*	3	8 (fair)
Koch et al. [14]	2015	*			**	3	*Age and gender	**	*	3	7 (fair)
Myers et al. [15]	2014	*			**	3	**Grey matter density, age, and gender	**	*	3	8 (fair)
Franzmeier et al. [19]	2019	*	*		**	4	**Age, gender, and education	**	*	3	9 (good)
Zhou et al. [46]	2017	*			**	3	NA	**	*	3	6 (poor)
Mueller et al. [29]	2017	*			**	3	NA	**	*	3	6 (poor)
Schultz et al. [7]	2017	*	*		**	4	**Age, sex, average movement, temporal signal-to-noise ratio, and scanner	**	*	3	9 (good)
Jones et al. [38]	2016	*	*		**	4	**Motion, age, gender, and APOE4	**	*	3	9 (good)
Song et al. [37]	2015	*	*		**	4	**Age, sex, and education	**	*	3	9 (good)
Adriaanse et al. [9]	2014	*	*		*	3	*Age and sex	**	*	3	7 (fair)
Drzezga et al. [10]	2011	*			**	3	*Age, level of education, and regional gray matter density	**	*	3	7 (fair)
Caldwell et al. [12]	2019	*	*		**	4	**Age, education, sex, and APOE4	**	*	3	9 (good)
Harrison et al. [21]	2019	*	*		**	4	**Age, sex, and hippocampal volume	**	*	3	9 (good)
Khan et al. [32]	2020	*	*		**	4	**Age, gender, years of education, and APOE ε4 genotype	**	*	3	9 (good)
Adams et al. [20]	2019	*	*		**	4	*Age and sex	**	*	3	8 (good)
Quevenco et al. [34]	2019	*	*		**	4	*Age and sex	**	*	3	8 (good)
Ossenkoppele et al. [17]	2019	*	*		**	4	**Age, sex, and atrophy	**	*	3	9 (good)
Cope et al. [43]	2018	*			**	3	Age	**	*	3	6 (poor)
Mormino et al. [35]	2011	*			*	2	**Age, gender, and education	**	*	3	7 (poor)
Hedden et al. [11]	2009	*			**	3	*Age and gray matter volume	**	*	3	7 (fair)
Hahn et al. [30]	2019	*	*		**	4	**Sex, age, clinical diagnosis (healthy, SCD), and APOE ε4 status (noncarriers vs. carriers of 1 or 2 alleles)	**	*	3	9 (good)
Lim et al. [36]	2014	*	*		**	4	**Age, gender, and education	**	*	3	9 (good)
Scherr et al. [40]	2018	*	*		**	4	**Age, sex, and years of education	**		2	8 (good)

Table 1 (continued)

Cross-sectional studies		Selection					Subscore	Comparability	Octome			Subscore	Total
authors	year	representativeness of the sample	sample size	nonresponders	ascertainment of the exposure				assessment of the outcome	statistical test			
Tahmi et al. [41]	2020	*	*		**		4	**Age, sex, education, and APOE4	**	*		3	9 (good)
Pereira et al. [42]	2021	*	*		**		4	*Age and sex	**	*		3	9 (good)
Sintini et al. [31]	2021	*	*		**		4	NA	**	*		3	7 (poor)
Longitudinal studies		**Selection**					**Subscore**	**Comparability**	**Outcome**			**Subscore**	**Total**
authors	year	representativeness of the exposed cohort	selection of the nonexposed cohort	ascertainment of exposure	the outcome of interest was not present at the start of the study				assessment of outcome	long enough follow-up	adequacy of follow-up of cohorts		
Franzmeier et al. [18]	2020	*	*	*	*		4	**Age, education, sex, ApoE4 status, diagnosis, and MMSE score	*	*		*	3	9 (good)
Mutlu et al. [28]	2017	*	*	*	*		4	*Age and education	*	*		*	3	8 (good)

A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories if the criteria is met fairly. A maximum of two stars can be given for Comparability.

Quality Assessment

The quality of all of the included studies was assessed using a modified version of the Newcastle-Ottawa Scale (NOS) for observational studies. This scale rates the quality of studies in 3 major fields, i.e., selection, comparability, and outcome. A quality score ranging from 0 (minimum) to 10 (maximum) stars was allocated to each cross-sectional study, and for longitudinal studies a maximum score of 9 was considered. The definition of SMC, MCI, and AD dementia was based on the following criteria: for SMC, having a self-reported persistent memory decline assessed using the Cognitive Change Index and a normal cognitive performance (a normal WMS-LM delay recall performance, a normal MMSE, i.e., between 24 and 30, and a CDR score of 0) [24]; for MCI, Petersen criteria (MMSE > 24, CDR = 0.5, and showing objective memory loss on the education-adjusted Wechsler Memory Scale-II but preserved activities of daily living) [25]; and for AD, National Institute on Aging research criteria for probable AD disease [26] (Table 1).

Results

Study Selection and Characteristics

A search of the PubMed database yielded 387 titles, while 609 records were identified through a search of Scopus, and 23,400 results were drawn from Google scholar. After extraction of those that did not fulfill the inclusion criteria and duplicates, 62 records were found to be eligible for full-text assessment. After application of the exclusion criteria, 31 studies were enrolled into this systematic review (Fig. 1; Table 2).

Quality of Studies

Study quality was rated as good, fair, or poor based on thresholds described in the Agency for Healthcare Research and Quality (AHRQ) standards [27]. Of the 31 included studies, 29 were cross-sectional and 2 had a longitudinal design. Regarding the sample size assessment of the cross-sectional studies, those with < 50 participants received no star (9 studies). None of the included studies displayed a response rate or described the characteristics of the responders and the nonresponders. We allocated 2 stars to studies that measured FC using a 3-T scanner and 1 star to studies that used a 1.5-T scanner (3 studies) to ascertain exposure. In the comparability section, age and sex were considered as the 2 most important confounding factors. We allocated only 1 star to studies that controlled their analysis for these 2 factors (8 studies). If a study used other factors, another star was allocated (17 studies). Four studies received no star in this part. In the outcome section, all of the included studies had an independent blind assessment, and only 2 studies did not present a *p* value for their correlation analysis. Overall, from 29 cross-sec-

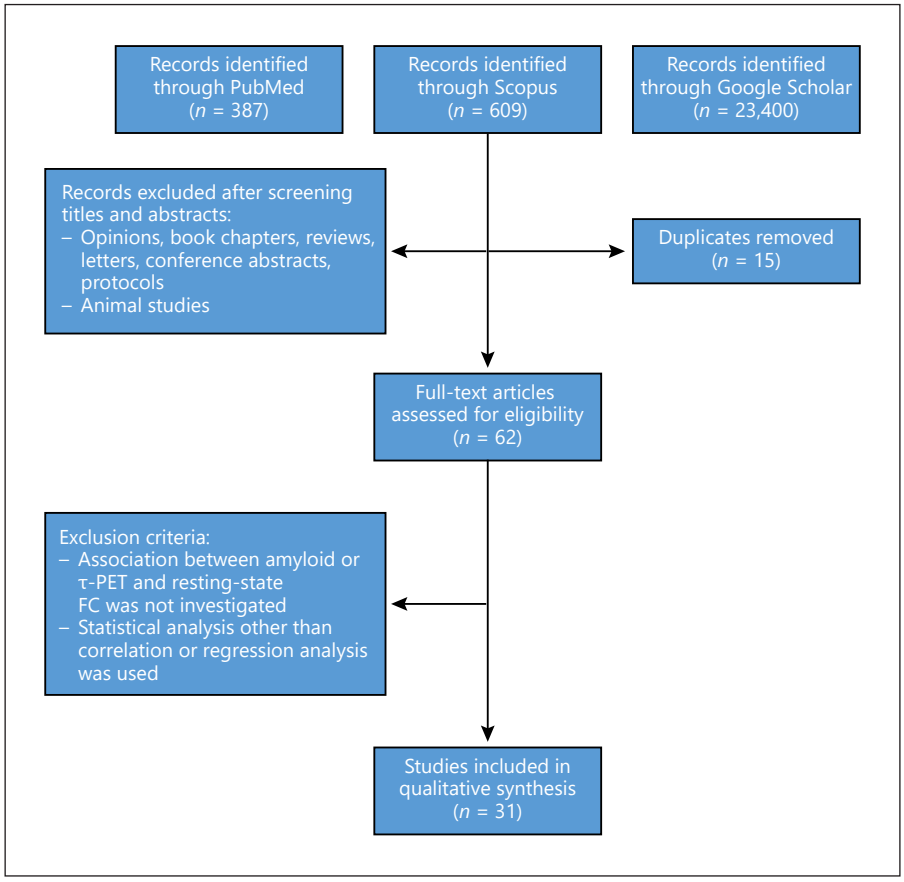

Fig. 1. Study selection flowchart.

Table 2. Summary of the results

	Studies reporting a positive association, *n*	Studies reporting a negative association, *n*	Studies reporting both positive and negative associations, *n*
Association between amyloid PET and FC	8	6	9
Association between τ-PET and FC	5	2	4

tional studies, 17 studies received good, 7 studies received fair, and 5 studies received poor ratings. Considering longitudinal studies, both of them were deemed to be of good quality.

Association between Amyloid PET and FC

Studies investigating the alterations of FC concerning amyloid deposits have addressed the question through global connectivity, seed-based connectivity, or within-network connectivity (Table 3).

While examining the global connectivity with all regions of interest (ROI) across the brain, 1 study indicated a positive overall association between connectivity in healthy elderly subjects and the baseline global Aβ burden in patients at the MCI and AD stages [28]. However, another study suggested both positive and negative associations based on graph analysis [29]. Two other studies reported a positive association [30, 31], while 1 had applied dynamic connectivity [30]. When static connectivity was used, a nonsignificant association was found [30].

Seed-based connectivity was investigated either through all voxels and ROI across the brain or within known networks. In 6 studies applying the first approach, 3 studies indicated a negative correlation between global

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Table 3. Association between amyloid PET and FC

FC analysis	Study	Year	Group	Amyloid deposition	Statistical analysis for association	FC regions or networks positively associated with PET data	FC regions or networks negatively associated with PET data	Nonsignificant association
Seed-based connectivity	Chiesa et al. [33]	2019	SMC	Global	Correlation		Voxelwise FC of PBF	
	Elman et al. [13]	2016	CN	Global/voxelwise	Regression	Between networks, within networks	Between networks, within networks	
	Koch et al. [14]	2015	Prodromal AD (MCI+)	Local	Voxelwise regression/Pearson correlation		pDMN, R ATN	
	Song et al. [37]	2015	CN	Global	Regression		Perirhinal cortex	
	Adriaanse et al. [9]	2014	(CN, MCI, AD)	Local	Voxelwise regression		PCC	
	Drzezga et al. [10]	2011	(CN–, CN+, MCI+)	FLR	Pearson correlation/ voxel-based regression		PCC/precuneus	
			MCI+	FLR	Correlation	PCC		
	Caldwell et al. [12]	2019	CN, SMC, eMCI	Global	Regression	DMN with the prefrontal region		
	Khan et al. [32]	2020	AD, CN	Global	Regression		Dorsal PCC/central precuneus	
	Adams et al. [20]	2019	FC in younger adults, amyloid PET in older adults	Global/local	Pearson partial correlations	Entorhinal cortex		
	Quevenco et al. [34]	2019	CN	Local	Voxelwise regression	Posterior cingulate and precuneus		
	Ossenkoppele et al. [17]	2019	PET covariance in AD patients (MCI, AD) and FC in young adults	Associations between the mean PET values within a seed region and the PET values for every cortical voxel across the brain	Spearman correlation	PCC, R MOG, R MTL, R MFG, L PCG, L STG		
	Mormino et al. [35]	2011	CN	Global	Regression	R dPFC, L amPFC, L middle temporal gyrus	L, R precuneus; bilateral vmPFC; L, R retrosplenial cortex; L, R PCC; R middle frontal cortex; R angular gyrus; R angular/ occipital cortex; L superior frontal gyrus	
	Lim et al. [36]	2014	CN+	Local	Regression	Middle frontal gyrus (CEN), inferior parietal gyrus (CEN)	Angular gyrus (DMN), PCC (DMN)	Salience network
FC within networks	Myers et al. [15]	2014	Prodromal AD (MCI+)	Voxelwise	Correlation	Voxelwise in the pDMN, anterior DMN, lATN, rATN, SN, and dATN		
				Local (neighborhoods around each voxel, in a 6-mm radius, in each network pDMN, anterior DMN, L ATN, R ATN, SN, dATN)	Correlation		Neighborhoods around each voxel (6-mm radius) in each network pDMN, anterior DMN, L ATN, R ATN, SN, dATN	
	Pasquini et al. [39]	2017	In each group of CN+, eMCI, lMCI, and AD	Voxelwise	Correlation	Voxelwise within the pDMN		
				Within a sphere (6 mm radius) in the pDMN	Correlation		Within a sphere (6-mm radius) in the pDMN	
	Hedden et al. [11]	2009	CN	Global	Correlation		DMN	
	Scherr et al. [40]	2018	Whole sample (CN–, CN+, eMCI, lMCI, AD)/eMCI/lMCI/AD	Local	Voxelwise correlation	pDMN		
			CN–/CN+)	Local	Voxelwise correlation		pDMN	

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Table 3 (continued)

FC analysis	Study	Year	Group	Amyloid deposition	Statistical analysis for association	FC regions or networks positively associated with PET data	FC regions or networks negatively associated with PET data	Nonsignificant association
	Tahmi et al. [41]	2020	CN	Global	Multivariable linear regression			DMN, FPCN, SN, DAN
	Pereira et al. [42]	2021	(CN, MCI, AD)	Global	Linear regression			Anterior DMN, pDMN
	Schultz et al. [7]	2017	Low-τ group	Global	Correlation	DMN/salience		High-τ group
	Jones et al. [38]	2016	AD spectrum (CN+, SMC, MCI, AD)	Global	Regression	Connection between the posterior and ventral DMN	pDMN connectivity	
Global connectivity between ROI across the brain	Mutlu et al. [28]	2017	FC in healthy elderly subjects and baseline amyloid PET in patients (MCI, AD)	Global	Correlation/regression	239 ROI (atlas of Power et al. [61])/R frontal gyrus as the epicenter of amyloid		
	Mueller and Weiner [29]	2017	(CN+, CN–)	Global Global	Spearman correlation	(AICHA atlas in Joliot et al. [62]) positive nodal strength and nodal strength dispersion in the L anterior superior temporal gyrus[1]/dynamic connectivity	(AICHA atlas in Joliot et al. [62]) negative nodal strength in the L orbital-frontal, anterior insula, parieto-occipital and precuneus regions and the R superior temporal region[1]	
	Sintini et al. [31]	2021	Atypical AD (LPA and PCA)	Global	Pearson *R* correlation	Degree of 210 cortical ROI chosen from 246 ROI of the Brainnetome atlas [60][1]		
	Hahn et al. [30]	2019	(SMC, CN)	Local	Regression	(atlas of Craddock et al. [63]) 840 regions, dynamic connectivity		(atlas of Craddock et al. [63]) static connectivity

PCC, posterior cingulate cortex; PBF, posterior basal forebrain; CN, cognitively normal; eMCI, early MCI; lMCI, late MCI; ATN, attention network; dATN, dorsal ATN; FLR, frontal, lateral parietal and lateral temporal and retrosplenial cortices; MOG, middle occipital gyrus; MFG, middle frontal gyrus; PCG, post-central gyrus; STG, superior temporal gyrus; L, left; R, right; dPFC, dorsal prefrontal cortex; amPFC, anterior medial prefrontal cortex; vmPFC, ventral medial prefrontal cortex; CEN, central executive network; SN, salience network; FPCN, fronto-parietal control network; DAN, dorsal attention network; PCA, posterior cortical atrophy; LPA, logopenic progressive aphasia.

[1] Graph analysis for FC, with nodal strength defined as the sum of weights of links connected to the node.

Aβ depositions and connectivity in AD patients and CN participants [32], all CN–, CN+, and MCI subjects [10], and SMC participants [33], among which 1 work also found a positive correlation when conducting the analysis merely in MCI patients [10]. Two other studies indicated a positive association between Aβ deposition and FC [17, 20]. The connectivity changes associated with local Aβ depositions were merely investigated in 1 study, which yielded a positive association [34].

Out of 7 studies applying the second approach, 3 studies suggested both higher and lower FC related to a higher global or local amyloid deposition [13, 35, 36]. Of the other 4 studies, 1 found increased FC between the left prefrontal cortex and the anterior DMN while the amyloid deposition increased globally [12]. The other 3 studies reported a decreased FC; 2 were related to the local amyloid burden [9, 14]; and 1 was related to the global amyloid burden [37].

FC within networks in association with Aβ was explored in 8 studies. While studying amyloid deposition globally, 1 work suggested a positive association, [7], 1 suggested a negative association [11], and another suggested both a positive and a negative association [38]. Two other studies revealed a positive association, using the voxelwise approach, for the correlation between FC and amyloid deposition. They also suggested a negative association when the correlation analysis was conducted locally on the scale of a 6-mm radius sphere [15, 39]. Using the voxelwise approach, another study showed both positive and negative associations [40]. Finally, 2 studies reported a nonsignificant correlation between amyloid PET and FC [41, 42].

Association between τ-PET and FC

In the association between FC and τ-PET, 3 approaches were utilized to investigate FC, i.e., examination of all ROI across the brain based on functional atlases, seed-based connectivity analysis, and exploration of FC within networks (Table 4).

While investigating global connectivity in association with τ, both studies suggested a positive association [18, 19]. Moreover, of the 2 other studies that used graph analysis for FC, one indicated both positive and negative correlations [43] and another reported a negative correlation [31].

Of the 4 studies applying seed-based connectivity, 2 indicated a positive association [20, 44] while 1 indicated a lower hippocampal FC in association with a higher τ burden in the inferior temporal cortex [21]. The last study mainly found a higher FC related to τ-PET covariance [17].

Exploring FC within networks in association with τ, one study observed a positive correlation in early AD patients and a negative association in CN– cases [45]. Another study suggested no association between global τ-PET and FC in the anterior DMN or the pDMN [42]. Investigation of local τ deposition yielded positive results in 2 studies [7, 46], and merely 1 prior work suggested a negative association when only CN+ cases were examined [7]. Finally, 1 recent work exploring τ-PET longitudinally revealed a higher FC-to-τ change in 7 brain networks [18].

Discussion

This study was conducted to systematically explore the current literature regarding the association between Aβ and τ deposition with FC alterations in the AD spectrum utilizing Aβ and τ-PET scan and rsfMRI. A significant body of literature has already been dedicated to identifying AD hallmarks through biomarkers and neuroimaging signature regions [47]; however, specifying structural and FC pattern alterations regarding Aβ and τ depositions remains controversial [22, 48, 49]. Recent findings attributing the neuropsychiatric symptoms of AD to connectivity alterations have signified that further studies are addressing this question [50].

Herein, we categorized the FC alteration analysis into the following 3 groups: global, seed-based, or within the network. Also, the following 3 categories of analysis were considered for τ-PET or amyloid PET scan: locally, globally, or in a voxelwise method.

Early works addressing this question regarding the correlation between amyloid and FC have suggested a hypoconnectivity accompanying amyloid deposition [10, 11, 51, 52]. However, this speculation was later challenged by studies indicating hyperconnectivity in both preclinical and clinical phases of the disease [13, 15, 35, 39]. The observed hyperconnectivity is speculated to be a system level compensatory mechanism to maintain function [7]. This hyperconnectivity possesses certain features, including region specificity, particularly regarding the pDMN [22, 44]. A particular pattern correlating with the disease stage was noted in some studies [38]. Eventually, the overwhelming pathology mechanism is indicted for altering this hyperconnectivity to hypoconnectivity as the disease progresses [53].

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Table 4. Association between τ-PET and FC

FC analysis	Study	Year	Group	τ deposition	Statistical analysis for association	FC regions or networks positively associated with PET data	FC regions or networks negatively associated with PET data	Nonsignificant association
Seed-based connectivity	Harrison et al. [21]	2019	CN	Local (entorhinal cortex/inferior temporal cortex/anterior temporal)	Pearson correlation/multiple regression		Hippocampus	
	Quevenco et al. [34]	2019	CN	Local regions	Voxelwise regression	Posterior cingulate and precuneus		
	Ossenkoppele et al. [17]	2019	PET covariance in AD patients (MCI, AD) and FC in young adults	Associations between the mean PET values within a seed region and the PET values for every cortical voxel across the brain	Spearman correlation	PCC, R MOG, R MTL, R MFG, L PCG, L STG	L STG	
	Adams et al. [20]	2019	FC in younger adults, amyloid PET in older adults	Global	Pearson partial correlations	Entorhinal cortex		
FC within networks	Zhou et al. [46]	2017	MCI	Local (R hippocampal)	Correlation	DMN		
	Schultz et al. [7]	2017	CN–	Local (inferior temporal cortex)	Correlation	DMN/SN		
			CN+	Local (inferior temporal cortex)	Correlation		DMN/SN	
	Yokoi et al. [45]	2018	CN–	Voxelwise in RSN masks	Pearson correlation		Within the network (each canonical RSN)	
			Early AD	Voxelwise in RSN masks	Pearson correlation	In some canonical RSN		
	Pereira et al. [42]	2021	(CN, MCI, AD)	Global	Linear regression			aDMN, pDMN
Global connectivity between ROI across the brain	Franzmeier et al. [18]	2020	ADNI (CN+, MCI+)/ BioFINDER (CN+, MCI+, AD)/ BioFINDER CN–	400 × 400 matrix of covariance in τ change/within DMN, DAN, limbic, FPCN, VAN, motor, visual	Spatial regression	400 ROI (Schaefer atlas) [59]/ within DMN, DAN, limbic, FPCN, VAN, motor, visual		
	Cope et al. [43]	2018	(AD, MCI)	Nodewise	Pearson and Spearman correlation	Most strongly connected nodes (weighted degree)/each node's unthresholded connectivity strength/ clustering coefficient[1]	Weighted participation coefficient[1]	
				Global	Pearson and Spearman correlation		Averaged weighted degree across the whole brain for each individual[1]	
	Sintini et al. [31]	2021	Atypical AD (LPA and PCA)	Global	Pearson *R* correlation		Degree and clustering coefficient of 210 cortical ROI chosen from 246 ROI of Brainnetome atlas [60][1]	
	Franzmeier et al. [19]	2019	CN–/AD spectrum (CN+, MCI, AD)	τ covariance 400 ROI (whole brain)	Spatial regression	400 ROI (whole brain) Schaefer atlas [59]		

(+), amyloid positive; (–), amyloid negative; aDMN, anterior DMN; PCC, posterior cingulate cortex; PBF, posterior basal forebrain; CN, cognitively normal; eMCI, early MCI; lMCI, late MCI; ATN, attention network; dATN, dorsal ATN; FLR, frontal, lateral parietal and lateral temporal and retrosplenial cortices; MOG, middle occipital gyrus; MFG, middle frontal gyrus; PCG, post-central gyrus; STG, superior temporal gyrus; L, left; R, right; dPFC, dorsal prefrontal cortex; amPFC, anterior medial prefrontal cortex; vmPFC, ventral medial prefrontal cortex; CEN, central executive network; SN, salience network; FPCN, fronto-parietal control network; DAN, dorsal attention network; PCA, posterior cortical atrophy; LPA, logopenic progressive aphasia; RSN, resting-state network; ADNI, Alzheimer Disease Neuroimaging Initiative; VAN, ventral attention network. [1] Graph analysis for FC.

The majority of works included in this study that evaluated FC alterations concerning τ deposition have found increased connectivity, which is consistent with the "trans-synaptic spread" model that proposing that, since τ proteins are transmitted through synaptic connections, its spreading pattern resembles the FC patterns across the brain [17, 19, 43]. This phenomenon is not influenced by the presence of amyloid or cognitive impairment [19, 20]. However, the lower FC related to a higher τ deposition has also been reported when the connectivity of the hippocampus, the critical component of the medial temporal lobe memory system, is considered. A higher τ burden in the anterior temporal regions is associated with functional disconnectivity between the hippocampus and other components of the medial temporal lobe (MTL) memory system, which predicts memory decline [21].

According to those works studying the amyloid, τ, and FC alterations altogether, when the age-related τ accumulation increases in MTL, the processing pressure will increase in brain networks. A compensatory shift may occur toward the pDMN, leading to a hyperconnectivity within it. In this stage, if the brain does not have a compensatory ability, the overloading phenomena are speculated to later cause the observed decreased connectivity in the pDMN and hyperconnectivity regarding other brain regions, particularly with the frontal lobe. Amyloid plaques are assumed to be subsequently created in response to the synapses' noisiness and mediate and facilitate the connections between τ deposition and the large-scale brain networks [20, 22]. Thus, the early amyloid accumulation phase is associated with a higher FC in the DMN and other hubs [7, 22], and it seems that this higher FC guides more and more spreading of τ, which later again decreases the FC [20]. If no compensatory mechanism atones this cycle, then neurodegeneration occurs [22]. The phase of hyperconnectivity continues until τ spreads to the neocortical regions [7]. Spreading of τ to the neocortical regions rarely happens in the absence of an amyloid burden, while in Aβ-positive individuals the τ pathology spreads to the neocortex [54]. Increasing τ in the inferior temporal cortex, as a neocortical region in which early τ propagation to the neocortex occurs, is associated with DMN hypoconnectivity in Aβ-positive healthy adults. In contrast, in Aβ-negative individuals, DMN hyperconnectivity related to τ has been observed [7].

As a total interpretation, amyloid pathology could be associated with hyperconnectivity, which is assumed as a signal for compensatory activity if τ has not yet propagated to the neocortex, but the spread of τ in neocortical regions leads to a loss of FC [54]. It may suggest that both a high amyloid deposition and a high τ deposition are unlikely to leave an individual clinically healthy [55]. The issue that should be considered concerning hyperconnectivity is whether compensation is a correct interpretation for increased FC [56]. An important study proposed another explanation, stating the hyperconnectivity may indicate a reduction in the dynamicity of FC in networks [7]. Moreover, the work by Elman et al. [13] demonstrated that an amyloid-related higher FC might reflect a decrease in anticorrelation between networks. Therefore, to have a more secure conclusion about the compensatory interpretation of hyperconnectivity, the association between increased FC and a better cognitive performance in individuals should be investigated [56].

Conclusion

We conclude that most controversies detected when investigating the connectivity alterations accompanying amyloid and τ depositions might primarily be due to methodological variances. That is to say, when studying the connectivity alterations globally (between ROI or voxels across the brain), a positive correlation is detected. This positive correlation is hypothesized to be caused by the transneuronal spreading pattern of both amyloid and τ proteins. However, while examining FC locally (in a network or even on a smaller scale), the positivity or negativity of the association depends on the stage of the disease. This is due to the fact that Aβ and τ overload urges compensatory mechanisms that manifest as potentially repeatedly occurring hyper- and hypoconnectivity cycles, which mainly occur in the pDMN and other hub regions.

Significance of the Study

Identification of distinct network features is of recent interest for early diagnosis and prognosis determination of neurological disorders. Among these are the connectivity alterations in different stages of AD [57]. Therefore, our study was conducted to recognize the specific connectivity alterations with τ and amyloid depositions, which might help to develop a network alteration pattern for early AD diagnosis and help to elucidate the network structure of the disease.

Future Directions

The recently developed τ PET tracers [58] have left many fundamental questions regarding the correlation between τ pathology and brain networks unanswered. More multimodal cross-sectional and longitudinal studies will be needed to illuminate the correlation and interaction between functional brain connectivity and AD pathogenic proteins. All 3 measures, i.e., amyloid and τ-PET and rs-fMRI, are to be investigated in all AD spectrum stages. Studying networks other than the DMN, connectivity between networks, and the dynamic feature of brain networks concerning both τ and amyloid deposition are pivotal quests to pursue [13, 30]. Eventually, the actuality of the compensatory role of hyperconnectivity is also to be assessed by examining whether higher FC is correlated with a more successful cognitive performance [56].

Statement of Ethics

As this study is a literature review and there was no direct contact with human or animal cases, no informed consent was obtainable. The methodology was approved by the PROSPERO community before the initiation of this study.

Conflict of Interest Statement

The authors have no conflict of interests to declare.

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Author Contributions

S.A.H. conceived and designed the evaluation and drafted this paper. M.M. participated in designing the evaluation, performed parts of the analysis, and drafted this paper. M.A.S. reevaluated the data and revised this paper. R.B.P. helped to interpret the data and revise this paper. All of the authors read and approved the final version of this work.

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