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Review

Breakdown of specific functional brain networks in clinical variants of Alzheimer's disease

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ABSTRACT

Alzheimer's disease (AD) is characterized by different clinical entities. Although AD phenotypes share a common molecular substrate (i.e., amyloid beta and tau accumulation), several clinicopathological differences exist. Brain functional networks might provide a macro-scale scaffolding to explain this heterogeneity. In this review, we summarize the evidence linking different large-scale functional network abnormalities to distinct AD phenotypes. Specifically, executive deficits in early-onset AD link with the dysfunction of networks that support sustained attention and executive functions. Posterior cortical atrophy relates to the breakdown of visual and dorsal attentional circuits, while the primary progressive aphasia variant of AD may be associated with the dysfunction of the left-lateralized language network. Additionally, network abnormalities might provide in vivo signatures for distinguishing proteinopathies that mimic AD, such as TAR DNA binding protein 43 related pathologies. These network differences vis-a-vis clinical syndromes are more evident in the earliest stage of AD. Finally, we discuss how these findings might pave the way for new tailored interventions targeting the most vulnerable brain circuit at the optimal time window to maximize clinical benefits.

1. Functional brain networks and behavior

In the last decades, the development of modern neuroimaging approaches has allowed researchers to shed light on the complex human brain functional architecture and its selective vulnerability to neurodegenerative diseases. Brain functional connections can be assessed through resting-state functional magnetic resonance imaging (rs-fMRI), which defines connectivity as the temporal dependence of neural activity pattern of anatomically separated brain regions (Biswal et al., 1995). This technique measures correlations over time in the blood oxygen level dependent (BOLD) signal across different brain areas during resting conditions. Regions showing statistically significant BOLD correlations are assumed to be functionally connected into large-scale neural networks (Damoiseaux et al., 2006).

Recent evidence suggests that these systems support, through a yet unknown set of processes (Laumann and Snyder, 2021; Pezzulo et al., 2021), our mental life, enabling us to interact with the surrounding environment, communicate with other people, and deal with daily issues (Laird et al., 2011; Petersen and Sporns, 2015; Yeo et al., 2014). For instance, human memory functions appear to critically depend on the intrinsic functional connectivity (FC) of two networks: (i) the default mode network (DMN), mainly involving the posterior cingulate cortex, inferior parietal lobe, ventromedial prefrontal cortex, and medial temporal cortex, and associated with spatial and autobiographical memory; and (ii) the limbic network (LMB), mapping to the anterior temporal lobe and orbitofrontal cortex, and supporting semantic memory (Catani et al., 2013; Ranganath and Ritchey, 2012; Ritchey et al., 2015). Different networks are involved in other cognitive domains, such as the frontoparietal (FPN), ventral-attention (VAN), and dorsal-attention (DAN) networks. These circuits sustain executive functions and

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attention abilities aimed at continuously monitoring and responding to the environment and shifting the focus of processing to relevant stimuli (Corbetta et al., 2008; Laird et al., 2011). Moreover, brain networks may exert effects beyond cognition, influencing social and emotional abilities. The salience (cingulo-opercular) network, through the integration of information within its core regions – the anterior insula and dorsal anterior cingulate cortex – plays a critical role in multiple functions, including task control, emotion, and interpersonal experience (Dosenbach et al., 2007; Menon, 2015).

The association between functional networks and specific task processes is based on two types of evidence: first, the spatial overlap between regions functionally connected at rest and regions co-activated during different tasks (Smith et al., 2009); second, FC impairment of different large-scale networks correlates with specific behavioral impairment in different neurological diseases. Possibly, some of the strongest associations occur in stroke where focal structural damage to cortical-subcortical regions causes specific FC networks abnormalities that correlate with behavioral impairment (He et al., 2007; Siegel et al., 2016). Another important functional property of brain networks is that they are distributed, and that their composing regions may be located more centrally or more peripherally within the whole brain network. In general, networks supporting cognitive functions are co-extensive with the association cortex and contain highly interconnected regions, either within or between networks. These central regions, defined as hubs, are densely interconnected forming a so-called "rich club" (Van den Heuvel and Sporns 2011). These connectors regulate connectivity through upstream and downstream mechanisms allowing a more flexible and integrated response to different types of stimuli (Mesulam, 2012). By contrast, regions that support sensory and motor functions are co-extensive with the unimodal cortex (e.g., somatomotor or visual), participate preferentially in local networks, and their connection with association networks occurs through peripheral hub regions (Yeo et al., 2015). These circuits show a higher level of synchronization within the same system and their activity is strongly dependent on sensory inputs (Cole et al., 2014).

2. Brain network abnormalities in Alzheimer's disease

A growing body of rs-fMRI studies suggests that failure of these networks is linked with the appearance of neuropsychiatric and neurological disorders, including several proteinopathies, such as Alzheimer's disease (AD) (Buckner et al., 2005; Pievani et al., 2014; Pini et al., 2020b; Schumacher et al., 2018; Seeley et al., 2009; Zhou et al., 2010). Alterations of network topology in AD patients can also be assessed by electroencephalography (EEG) (Franciotti et al., 2019; Cai et al., 2020), which suggests that functional alterations are consistent across different methods measuring different timescales of functional organizations and might be helpful for unraveling pathological mechanisms of the disease (Yu et al., 2020a; 2020b). According to the 'molecular nexopathy' model, pathogenic proteins spreading through large-scale networks produce macroscopic signatures of network dysfunction that might differentiate neurodegenerative diseases (Warren et al., 2013). The DMN plays a pivotal role in AD consistent with the role of this network in episodic memory, one of the early clinical symptoms in AD. Aggregation of amyloid beta (Aβ) peptides preferentially affects DMN regions (Palmqvist et al., 2017), while impaired DMN connectivity is associated with AD clinical severity and memory abilities (Brier et al., 2012; Buckner et al., 2005; Petrella et al., 2011). Moreover, in asymptomatic carriers of pathogenic mutations for AD, DMN disruption occurs before clinically evident symptoms, suggesting that functional disconnection might serve as marker of brain changes among patients earlier in the AD clinical course (Chhatwal et al., 2013). Additionally, other networks are involved in AD pathology, including the LMB (Pini et al., 2020a; Gour et al., 2014). As stated above, the DMN and LMB are two separate subunits of a memory circuit interacting to support memory-guided behavior (Ritchey et al., 2015). As pathology advances, other networks unrelated to episodic memory, such as the executive or the attention network, become affected (Agosta et al., 2012; Brier et al., 2012). These findings are consistent with the clinical progression of symptoms from memory to orientation, reasoning, language, and noncognitive domains, such as personal care, hobbies, and behavior.

However, AD pathology can present with a broad range of clinical manifestations (Snowden et al., 2007). Some individuals show an atypical profile at clinical onset, which may include a primary impairment of behavioral/executive, language, or visuospatial abilities (Snowden et al., 2007) with a relative sparing of memory (Frisoni et al., 2007; Kim et al., 2021; Smirnov et al., 2021). Patients with an atypical symptoms onset frequently show a younger age (<65 years old) than typical AD cases and are referred to as early-onset AD (EOAD). In posterior cortical atrophy (PCA), the initial complaints involve vision impairment without evidence of eye disorders (Crutch et al., 2017). By contrast, the language variant of AD, a form of primary progressive aphasia (PPA), involves isolated language impairment (Rogalski et al., 2016). Finally, several studies have reported on a dysexecutive/behavioral phenotype of AD (Bergeron et al., 2020; Mez et al., 2013; Ossenkoppele et al., 2015a). This variant, described first by Johnson et al. (1999), is characterized by behavioral dysfunctions associated with predominant executive impairment and relative sparing of memory (Taylor et al., 2008). Factors driving the panoply of clinical and cognitive manifestations associated with AD pathology are still unclear. Moreover, AD clinical symptoms/variants may overlap with the symptomatology of other proteinopathies. For instance, even though memory performance in Lewy body pathology (LBD) is better than in younger AD patients, it eventually becomes comparable to that of older AD patients. This poses serious problems in the differential diagnosis (Nagahama et al., 2020). Similarly, the behavioral/dysexecutive AD variant and behavioral variant frontotemporal dementia (bvFTD) patients present with largely overlapping symptoms (Musa et al., 2020).

Recent data support the hypothesis that different networks are disrupted by the same underlying molecular pathology, accounting for the heterogenous AD clinical presentation. Similarly, specific networks might be vulnerable to different diseases, explaining the (partial) clinical overlap between AD and different diseases (e.g., LBD and bvFTD). This review will cover the most recent findings, linking brain network abnormalities and atypical variants, with the intent to offer a brain network perspective in AD phenotypes (see Table 1 for an overview of the studies discussed). Quantification of large-scale brain networks involved early in the pathophysiology of AD phenotypes could help to bridge the gap between clinical and functional systems description, paving the way to new models explaining the multifaceted symptoms of AD and offering promising targets for the development of new clinical interventions or disease modifiers. To date, several pharmacological trials have been carried out, but results have been disappointing. This lack of progress might underline the need for better model systems aimed at relating pathophysiological processes to clinical symptoms. To this aim, we discuss how a network approach in AD variants might be promising to guide new personalized applications in the field of non-invasive brain stimulation, aimed at maximizing cognitive/clinical effects through brain network connectivity modulation.

2.1. Functional connectivity studies in early-onset Alzheimer's disease

Although typical AD accounts for more than 90% of AD cases, about 5% of patients develop the first symptoms before age 65 (EOAD) (Ferri et al., 2005). Atypical variants represent one third of EOAD patients (Koedam et al., 2010). Several studies reported greater clinical severity and a faster disease progression in EOAD than late-onset (LOAD) or typical AD, preferentially in neocortical-related functions (Barnes et al., 2018; Frisoni et al., 2007; Panegyres and Chen, 2013; Smirnov et al., 2021; Stanley and Walker, 2014; Van Der Vlies et al., 2009; Wattmo and Wallin, 2017). This clinical observation is congruent with post-mortem studies assessing neuropathological burden (Bulk et al., 2018; Marshall

Table 1
Brain functional connectivity studies in AD variants.

Reference	AD Sample	HC Sample	AD Age (y ± SD)	AD Education (y ± SD)	AD MMSE (mean ± SD)	Main Results	Analysis
Early-onset AD							
Adriaanse et al. (2014)	n = 20	n = 15	59 ± 2	5 ± 1	23 ± 3	↓ multiple networks	NOI
Gour et al. (2014)	n = 14	n = 14	60 ± 6	11 ± 4	19 ± 4	↓ DMN and FPN; ↑ LMB	Seed ROI
Lehmann et al. (2015)	n = 20	n = 60	61 ± 6	15 ± 4	22 ± 5	↓ FPN and LNG	Seed ROI
Pini et al. (2020a)	n = 10	n = 14	64 ± 5	11 ± 5	27 ± 2	↓ FPN and VIS	ICA
Posterior cortical atrophy							
Agosta et al. (2018)	n = 8 (sample 1) n = 13 (sample 2)	n = 24 n = 20	60 ± 5 62 ± 5	14 ± 2 10 ± 3	1.9 ± 0.9[a] 1.2 ± 0.4[a]	↓ VIS and DMN	ICA
Fredericks et al. (2019)	n = 26	n = 64	62 ± 8	16 ± 4	23 ± 5	↓ DAN; ↑ VAN and DMN	Seed ROI
Glick-Shames et al. (2020)	n = 10	n = 14	63 ± 8	17 ± 3	25 ± 4	↓ VIS and parietal-visual FC ↑ parietal-frontal FC	Seed ROI
Lehmann et al. (2015)	n = 16	n = 60	62 ± 6	16 ± 2	21 ± 5	↓ VIS, LNG and FPN; ↑ anterior DMN	Seed ROI
Migliaccio et al. (2016)	n = 10	n = 28	61 ± 4	Na	18 ± 5	altered occipital/parietal and frontal regions FC	NOI
Migliaccio et al. (2020)	n = 18	n = 29	63 ± 5	14 ± 3	20 ± 5	diffuse FC alterations centered on posterior regions	Graph
Sintini et al. (2021)	n = 31	n = 50	62 (59–68)	Na	16 (21–21)[b]	↓ occipital and limbic lobes	Graph
Veldsman et al. (2019)	n = 16	n = 19	64 ± 6	14 ± 2	55 ± 16[c]	↓ DAN and DMN	Seed ROI
Logopenic variant primary progressive aphasia							
Bonakdarpour et al. (2019)	n = 20	n = 33	66 ± 7	Na	Na	↓ LNG	Seed ROI
Lehmann et al. (2015)	n = 20	n = 60	62 ± 8	17 ± 3	19 ± 8	↓ LNG and FPN; ↑ anterior DMN	Seed ROI
Martersteck et al. (2020)	n = 26	n = 26	68 ± 7	16 ± 2	Na	↓ LNG and DMN	Seed ROI
Sintini et al. (2021)	n = 27	n = 50	67 (61–72)	Na	19 (16–22)[b]	↓ temporal pole	Graph
Whitwell et al. (2015)	n = 24	n = 24	66 ± 9	Na	25 ± 3	↓ LNG and FPN	ICA

↑ increased connectivity ↓ reduced connectivity; DMN: default mode network; FC: functional connectivity; FPN: frontoparietal network; ICA: independent component analysis; LMB: limbic network; LNG: language network; MMSE: mini mental state examination; Na: not available; NOI: network of interest; ROI: region of interest; VIS: visual network. a) reporting clinical dementia rating scale instead of MMSE; b) reporting MOCA instead of MMSE; c) reporting the Addenbrooke's Cognitive Examination III (100) instead of MMSE.

et al., 2007; Murray et al., 2011), supporting the idea that the disease in younger individuals deviates from the traditional Braak staging scheme (Braak and Braak, 1991). Congruently, LOAD and EOAD exhibit a different distribution of tau pathology in vivo, predominantly confined to the temporal region in the former group, and more distributed to neocortical regions in the latter (Schöll et al., 2017).

Interestingly, in EOAD, non-memory functional circuits are more affected, suggesting the involvement of networks outside the DMN/LMB dyad, which are critical for the episodic memory deficits observed in the typical AD phenotype. Lehmann et al. (2015) found that EOAD displayed lower FC in language and executive networks, while DMN connectivity was not different from healthy age-matched individuals, supporting the hypothesis of the specific vulnerability of different cortical systems. Similarly, Gour et al. (2014) found that patients with EOAD show abnormalities in the executive networks, whereas typical AD patients show memory network dysfunction. Recently, our group (Pini et al., 2020a) found that these two AD forms involve distinct networks even in the early stage. Specifically, in mild cognitive impairment (the prodromal phase of AD), early-onset was associated with disrupted connectivity of FPN and visual networks, while prodromal LOAD (typical) exhibited reduced connectivity of memory networks (DMN and LMB). Notably, LMB was linked with memory performance in LOAD but not in EOAD. By contrast, the FPN showed a close relationship with executive functions only in EOAD, suggesting that these networks are involved early on in these phenotypes (Pini et al., 2020a). This theoretical framework is supported by neuroimaging evidence of a relationship between metabolic, structural, and clinical/behavioral abnormalities within specific networks (Ballarini et al., 2016; Lehmann et al., 2013a; Ossenkoppele et al., 2015b). As pathology spreads throughout the brain, the pattern of functional abnormalities may converge onto the DMN (Ossenkoppele et al., 2015b). In fact, Adriaanse et al. (2014) reported a non-specific disruption of all the networks investigated (including the DMN) in EOAD with full-blown dementia rather than selective vulnerability.

Overall, these studies reported a consistent vulnerability of the FPN, despite the clinical heterogeneity of EOAD sample (i.e., in these studies, EOAD patients were not characterized by their clinical phenotype). The FPN includes the lateral prefrontal cortex and temporoparietal regions and it has been linked with executive functions (Smith et al., 2009; Laird et al., 2011; Vallesi et al., 2021). The FPN also plays a critical role in coordinating behavior in an accurate and flexible goal-driven manner (Marek and Dosenbach, 2018). A possible interpretation of FPN involvement in EOAD might be related to the behavioral/dysexecutive AD variant, characterized by predominant behavioral dysfunctions or executive impairment on cognitive assessment (Dubois et al., 2014). However, this phenotype remains poorly studied compared to language and visuospatial variants of AD. Indeed, no studies have investigated FC abnormalities in this variant, while only a few studies have investigated neurodegeneration patterns, which showed consistent hypometabolism and tau loads in frontal and parietal regions overlapping with the FPN (Bergeron et al., 2020; Ossenkoppele et al., 2015a; Phillips et al., 2018; Singleton et al., 2021; Townley et al., 2020). However, Therriault et al. (2021) reported tau aggregation predominantly in the medial prefrontal, anterior cingulate, and frontal insular cortices, in contrast to typical AD. These regions are key elements of the salience network, vulnerable in some neurological and psychiatric disorders that share behavioral dysfunctions (Quattrini et al., 2019; Zhou et al., 2010, Menon, 2015). The possible implication of this network might suggest a common neural pattern linked with behavioral alterations (Singleton et al., 2020). Further work is needed to determine whether behavioral and dysexecutive presentations of AD represent distinct phenotypes predicted by different network vulnerability.

2.2. Functional connectivity in posterior cortical atrophy

The clinical hallmark of PCA is a progressive impairment of higher

visual functions (cognitive processes responsible for visual perception, motor detection, and object recognition). The cardinal visual symptom, present in more than 80% of patients, is simultanagnosia (Tang-Wai et al., 2004), or the inability to visually recognize more than one object at a time (Bálint, 1909). Recently, clinical diagnostic criteria for PCA have been proposed, including presentation with progressive visual/-visuospatial impairment in the absence of ophthalmologic impairment, evidence of complex visual disorder, and relatively spared memory (Crutch et al., 2017). The pathological fingerprint is the presence of atrophy and/or hypometabolism in the parieto-occipital and temporo-occipital posterior cortices (Crutch et al., 2017). This rare clinical syndrome is often associated with AD pathology (Aβ and tau), determined post-mortem or through in vivo biomarkers (Crutch et al., 2017; Montembeault et al., 2018a; Tang-Wai et al., 2004). Aβ distribution is remarkably similar between PCA and typical AD, in contrast to occipital involvement on tau PET (Holden et al., 2020). Indeed, tau imaging showed increased tau binding in lateral occipital association cortices (Nedelska et al., 2019). This pattern can be useful to distinguish PCA due to AD from PCA due to LBD, while the overlapping pattern of Aβ and hypometabolism between these two diseases can lead to diagnostic ambiguity (Nedelska et al., 2019; Whitwell et al., 2017).

To date, several studies have investigated the FC fingerprint of this clinical phenotype. In line with the assumption of a visual disconnection, recent studies showed reduced connectivity within the visual network in PCA patients (Agosta et al., 2018; Glick-Shames et al., 2020; Lehmann et al., 2015; Sintini et al., 2021). Notably, non-visual networks are also affected in this atypical AD variant. Through a seed connectivity analysis, two independent studies reported reduced brain synchrony within the DAN (Fredericks et al., 2019; Veldsman et al., 2019). This network includes the frontal eye field and the posterior parietal cortex (i.e., intraparietal sulcus and superior parietal lobe), which are known to contribute to visuospatial attention (Corbetta et al., 2002; Meehan et al., 2017). Specifically, these prefrontal and posterior parietal regions are involved in generating and maintaining signals that descend in the visual system to select relevant stimuli and suppress irrelevant ones (Bressler et al., 2008; Corbetta et al., 2005; Lanssens et al., 2020; Ruff et al., 2009). Taken together, these studies suggest an early breakdown of the visual network and DAN in PCA, which could result in a dysfunction of integration processes regulating a bidirectional information transfer from the visual/parietal cortex to frontal brain regions. Accordingly, imaging studies in PCA patients showed abnormal connectivity between occipital/parietal and frontal regions (Glick-Shames et al., 2020; Migliaccio et al., 2016). These results were echoed by a graph analysis performed by Migliaccio et al. (2020), showing a diffuse pattern of functional network alterations at both global and local levels in PCA patients. This pattern was centered on posterior brain regions but also involved anterior regions, including the frontal lobes, which might account for the attentional/frontal deficits of this clinical phenotype. Interestingly, abnormal visual-attention metabolic connectivity has also been observed in LBD, a pathology with predominant alterations in visual perception (Zorzi et al., 2021). Disruption of these so-called "top--down" pathways may be the mechanism underlying simultanagnosia and visual hallucinations.

However, no correlations were reported between DAN abnormalities and visuospatial deficits in PCA patients. A possible explanation might be that the association between DAN and PCA core symptomatology may emerge early in PCA but then weaken as pathology advances. In full-blown PCA, FC alterations might involve other networks - in the same fashion proposed in typical AD and EOAD, weakening the coupling between core symptoms and FC. Indeed, abnormal connectivity within the DMN (a network associated with memory, which is relatively preserved in PCA) was reported in this population, although with mixed results (Agosta et al., 2018; Fredericks et al., 2019; Migliaccio et al., 2016; Veldsman et al., 2019).

2.3. Connectivity alterations in primary progressive aphasia

In contrast to typical AD patients who show language deficits later in the disease, patients with PPA present with language deficits as the initial symptoms (Kirshner, 2012). Deficits are mainly confined to language ability for the first few years, when other high-order functions are spared and patients continue to live a relatively normal life (Mesulam et al., 2012; Weintraub et al., 1990). PPA is a broad diagnostic category and has three typical clinical variants: nonfluent/agrammatic (agPPA), characterized by agrammatism and, often, speech apraxia; semantic (svPPA), characterized by anomia and difficulty with single-word comprehension; and logopenic (lvPPA), characterized by problems retrieving words, repeating sentences, and phonological errors (Gorno-Tempini et al., 2011). Each variant is characterized by a distinctive brain neurodegenerative pattern: agPPA patients predominately show decline in the left posterior fronto-insular region; the anterior temporal lobe is predominantly affected in svPPA patients; and lvPPA patients show decline in the left posterior perisylvian or parietal regions (Gorno-Tempini et al., 2011; Montembeault et al., 2018b). These imaging patterns have also been validated by an anatomical likelihood estimation meta-analysis (Bisenius et al., 2016). All three variants have histopathological evidence of tau, TAR DNA binding protein (TDP)-43, Aβ, or other proteinopathies, although these pathologies are differently distributed among these variants. In this review, we focus on the lvPPA variant because this is most frequently related to AD pathology (80–95% of cases) (Bergeron et al., 2018; Graff-Radford et al., 2021; Mesulam et al., 2014; Santos-Santos et al., 2018).

Not surprisingly, the language network is particularly vulnerable in this AD language variant. Whitwell et al. (2015) investigated FC in 24 lvPPA patients with evidence of brain Aβ accumulation. Compared to age-matched healthy controls, lvPPA patients showed reduced FC throughout the left posterior temporal and inferior parietal regions of the language network, extending to the right posterior temporal cortex. By contrast, the left language network was relatively spared in a sample of typical AD patients (Whitwell et al., 2015), suggesting that early involvement of this network might be a potential marker to differentiate lvPPA and typical AD in early stage. By contrast, reduced ventral DMN connectivity was found only in the latter group, in line with the assumption that DMN breakdown is associated with episodic memory impairments in typical AD (Whitwell et al., 2015). Similarly, two independent studies reported reduced language network connectivity in Aβ-positive individuals with lvPPA (Martersteck et al., 2020; Lehmann et al., 2015), while Sintini et al. (2021) reported widespread connectivity reduction in the temporal gyrus, a key region of the language network. These results were echoed by Bonakdarpour et al. (2019), reporting decreased FC between key hubs of the left-lateralized language network in a sample of 20 patients with a clinical diagnosis of lvPPA. By contrast, findings about the relationship between lvPPA and DMN are incongruent. While one study showed a widespread reduction of DMN connectivity in lvPPA (Martersteck et al., 2020), another reported null effects for the posterior DMN and increased anterior DMN connectivity (Lehmann et al., 2015). These findings suggest that – as reported for EOAD and PCA – DMN abnormalities in lvPPA might emerge as a function of time and disease severity. Additionally, other functional networks showed functional alterations. In their lvPPA cohort, Whitwell et al. (2015) reported reduced connectivity in the left FPN, which was associated with aphasia severity. Similar FPN abnormalities were reported by the Lehmann study (2015). These findings suggest that disruption of the FPN might be central to lvPPA process and progression. This is not surprising, because the language network shares a common spatial motif with the FPN (Braga et al., 2020).

Finally, language network connectivity abnormalities are not exclusive to lvPPA, as they have also been observed in agPPA and svPPA variants (Bonakdarpour et al., 2019; Montembeault et al., 2019). Specifically, all of these PPA subtypes showed reduced connectivity between two core language network hubs, the inferior frontal gyrus (IFG)

and the middle temporal gyrus. However, the relative paucity of FC studies in the language AD phenotype limits the conclusions that can be drawn. Further studies are necessary to elucidate brain functional mechanisms potentially linked with clinical symptoms in lvPPA patients.

3. Functional networks and neuropathological features

The hypothesis that AD variants are linked with different pathological trajectories was first put forward by a series of publications by Murray and colleagues (Murray et al., 2011, 2014; Janocko et al., 2012). Through a mathematical algorithm considering the regional distribution of neurofibrillary tangles (NFT) in a large postmortem sample, patients with a clinical diagnosis of AD were classified as hippocampal sparing (HpSp), limbic-predominant, or typical AD. Compared with limbic-predominant and typical AD, HpSp showed lower hippocampal NFT counts but higher NFT in the association cortices. Interestingly, these groups also displayed a different clinical profile, with HpSp patients showing the youngest age-at-onset. HpSp also had a shorter disease duration and a higher frequency of focal cortical clinical syndromes (Murray et al., 2011; Janocko et al., 2012). Thus, the HpSp profile might account for the FC breakdown of cortical networks reported in EOAD studies, in comparison to the hippocampal-DMN functional pathways that are affected in older (typical) individuals.

Notably, this study also found clinic-pathologic differences among patients on the LOAD spectrum. Patients with a limbic-predominant profile had an older age-at-onset and lower pathology in cortical regions (Murray et al., 2011). Recently, it has been suggested that limbic-predominant age-related TDP-43 encephalopathy (LATE) might account for 15–20% of all clinically diagnosed AD cases (Boyle et al., 2019). TDP-43 aggregation correlates with progressive amnestic cognitive decline, especially in patients over 80 years, while the prevalence of severe AD neuropathological changes decreases with age (Nelson et al., 2019). Early retrospective autopsy studies found that TDP-43-opathies mimic the AD clinical syndrome (Brenowitz et al., 2014; Pao et al., 2011), and although LATE can exist in tandem with other pathologies, it is a separate pathology and syndrome (Attems and Jellinger, 2006). TDP-43 aggregations in the brain progress from the amygdala to the hippocampus to the middle frontal gyrus, with greater hippocampal atrophy compared to typical AD (Nelson et al., 2019). Based on the assumption that the molecular pathology may initially arise from distinct brain regions and subsequently spread along large-scale pathways (Warren et al., 2012), it is likely that some patients with a very late-onset symptomatology mimicking or comorbid with AD will show FC alterations outside the DMN, involving the temporo-amygdala-orbitofrontal circuitry (or LMB), in line with the definition of LATE (Nelson et al., 2019). These assumptions remain speculative, since, to date, there have been no retrospective studies on functional brain alterations in this population. Moreover, diseases in the oldest old are complex, as multiple comorbid pathologies and interindividual differences are very common.

In the last few years, several studies investigated the pattern of brain tau accumulation in AD variants suggesting a specific localization mapping on several cognitive networks, while Aβ is distributed throughout the association cortex (Graff-Radford et al., 2021; La Joie et al., 2021; Ossenkoppele et al., 2016; Therriault et al., 2021; Whitwell et al., 2019). Recently, Vogel et al. (2021), using a mathematical algorithm combining traditional clustering with disease progression modeling, identified four distinct spatiotemporal trajectories of tau pathology. The higher proportion of patients exhibited a limbic-predominant phenotype with Braak-like progression. A second cluster of individuals showed a parietal-dominant phenotype with a relative sparing of the medial temporal lobe. This cluster showed early tau deposits in the precuneus and temporoparietal and frontal cortexes and was associated with dysexecutive symptoms and younger age at onset. The third and fourth phenotype resembled tau accumulation observed in PCA and lvPPA, with early occipital lobe binding and left-lateralized temporopatietal tau load, respectively (Vogel et al., 2021). The same mathematical model applied to structural MRI data of more than 1000 subjects revealed similar subtypes, labeled typical, cortical, and subcortical (Young et al., 2018). Results from these data-driven approaches are consistent with Bejanin's study highlighting a strong relationship between decreased cognitive performance in different domains with increased tau uptake in specific brain regions overlapping with neural networks. Specifically, (i) episodic memory performance was associated with tau load in DMN hubs (medial temporal lobe and angular gyrus); (ii) language was linked with tau in the left-lateralized language network; (iii) executive functions were related with tau accumulation in FPN nodes; and (iv) visuospatial deficits were coupled with tau in visual/DAN regions (Bejanin et al., 2017). Similarly, Cho et al. (2017) reported in AD patients a significant correlation between parieto-occipital tau binding and visuospatial dysfunction, while temporal cortex tau uptake was related to memory deficits.

Overall, these results are in line with studies suggesting a link between AD clinical phenotype and tau distribution (Sintini et al., 2019; Xia et al., 2017), recapitulating network-level findings in AD variants. Regional tau variability overlaps with functional networks linked with specific cognitive functions, suggesting heterogeneity in AD clinical profiles might be explained by differential effects on functional brain networks. A recent study in Aβ positive dementia patients found that FC together with tau baseline levels could predict future tau accumulation, further supporting the assumption that tau that spreads via functional pathways is linked with phenotypic presentations (Franzmeier et al., 2020). According to the cascading network failure hypothesis, functional networks are implicated in the pathophysiology of tau deposition, while Aβ is a mediator in this association (Jones et al., 2017). According to this model, tau-associated local network failure is followed by a global compensatory phenomenon associated with Aβ in brain hubs. After functional hubs saturate their compensatory resilience to local network failures, tau accumulation within those large-scale functional networks hastens (Jones et al., 2016, 2017). In a recent work, Sintini et al. (2021) reported a different association between functional connectivity and Aβ and tau proteins in atypical AD patients. Functional hubs were associated with Aβ, while region-to-region connectivity was linked with tau, consistent with the cascading network failure model (Sintini et al., 2021).

However, the mechanistic link between Aβ, tau, and FC accounting for regional and phenotypic discrepancies is currently unknown. FC might have a mediator role in the cascade of pathological events. Recently, it has been pointed out that the association between structure and function progressively diverges moving from unimodal (i.e., sensory) to transmodal (i.e., associative) cortices, suggesting a shifting from a bottom-up organization to a more top-down dense interconnectivity (Margulies et al., 2016). The organization of transmodal regions might allow a more flexible and integrated response to different types of stimuli (Mesulam, 2012). Alterations in these regions could propagate upstream and downstream through connectors (regions of integration between modules) or rich club hubs, with a cascade effect on cognitive abilities (Honey and Sporns, 2008). By contrast, sensory networks show a higher level of synchronization within the same circuit and their activity is strongly dependent on inputs (Cole et al., 2014). Moreover, Chan et al. (2014) reported different trajectories in the patterns of decreasing functional specialization between transmodal and unimodal systems. Thus, differential vulnerability within this hierarchical functional axis might be linked with clinical phenotypes in AD. Accumulation of tau pathology within unimodal circuits might lead to more focal cognitive deficits, such as early visual alterations observed in PCA, due to the lower interaction with neighboring regions. By contrast, tau deposits in functional hubs processing transmodal information (e.g., DMN and FPN hubs) might explain impairment in more complex functions, such as memory, behavior, and executive functions. This assumption is in line with previous stroke studies, reporting that network-specific

patterns of dysfunction predicted specific behavioral deficits (Siegel et al., 2016). Further studies should shed light onto the organization of functional gradients in AD patients. Moreover, different genetic risk factors might modulate molecular pathology and the downstream connectivity alterations in AD (Chiesa et al., 2017; Gaiteri et al., 2016; Sims et al., 2020). Examining the association between gene expression profile with molecular pathology and FC alterations might provide new insights.

4. Multifactorial association between clinical and network phenotypes

Taken together, these data suggest that different network pathways represent the functional underpinnings of brain dysfunction among AD clinical variants. In EOAD, studies reporting early dysfunction of executive networks might suggest a possible link between FPN and a behavioral/dysexecutive phenotype, characterized by attentional deficits. While in PCA, disrupted connectivity within the visual network and the DAN might account for early visual-spatial difficulties. Finally, language impairment in lvPPA is linked with connectivity alterations of hubs connected within the language network (see Fig. 1). Thus, atypical AD variants might follow different trajectories compared to typical AD, trajectories that arise from early topographical differentiation of pathological processes. Molecular pathology may spread along specific functionally connected neuronal pathways linked with specific cognitive abilities.

However, in the arena of the potential AD mediators, other factors might play a role in the association between networks and clinical phenotypes. Putative altered network connectivity likely interacts with genetic factors associated with AD (Fleisher et al., 2009; Wang et al., 2015; Zheng et al., 2018). For instance, the distribution of the apolipoprotein E ε4 allele (APOE4), the main genetic determinant of AD risk (Liu et al., 2013), differs among AD subtypes (Murray et al., 2011, 2014) and can affect network FC during aging (Chiesa et al., 2019). Other biological, cognitive, and environmental factors might also influence brain network FC, such as sleep quality, ethnicity, and cognitive reserve (Franzmeier et al., 2017; Misiura et al., 2020; Pini et al., 2020c; Yang et al., 2016). According to the cognitive reserve hypothesis, more education (or, more broadly, continued cognitive stimulation throughout life) may protect individuals from clinically expressing the disease for a longer period (Stern, 2009). A paradoxical effect of cognitive reserve is that higher reserve can attenuate clinical symptoms in prodromal AD, but it is related to accelerated cognitive decline after dementia onset (van Loenhoud et al., 2019). This effect can have a significant impact on cortical network FC in AD, as suggested by Franzmeier et al. (2017) in a sample of Aβ-positive patients with amnestic mild cognitive impairment. Future work should evaluate whether AD variants exhibit comparable associations between cognitive reserve and FC or if some variants are more prone to the cognitive reserve effect, such as EOAD, which shows a disease progression similar to patients with higher reserve (i.e., faster deterioration; Wattmo and Wallin, 2017) and for which higher education has been associated with cortical atrophy (Seo et al., 2011). Finally, growing evidence suggests that alterations in the gut microbiome might represent a potential factor for AD development (for a recent review see Chok et al., 2021). Preliminary findings showed a relationship between gut microbial diversity and network FC, especially with the DMN and executive/attentional networks (Cai et al., 2021; Kohn et al., 2020). Further studies will be needed to determine how such factors can interact with network breakdown in the different AD clinical phenotypes.

5. Toward a personalized network modulation approach in Alzheimer's disease

A systems-level understanding of the networks and their interconnections could provide new insights into the dependencies that exist between brain circuitry, clinical phenotypes, and molecular pathology in AD. This view can help to bridge the gap between macro-scale systems and micro-scale molecular mechanisms. Moreover, a precise definition of network abnormalities in the earliest stage of the atypical AD variants spectrum would pave the way for the development of new network biomarkers, useful as endpoints in large clinical trials in AD and as possible new targets for effective interventions. Specifically, functional network measures can serve as surrogate outcomes for both non-pharmacological and pharmacological interventions in the AD field, i.e., as a means of understanding how different interventions might impact brain dynamics by changing brain architecture (Klaassens et al., 2019; Koch et al., 2018; Lorenzi et al., 2011; Péran et al., 2021; Yu et al., 2018,

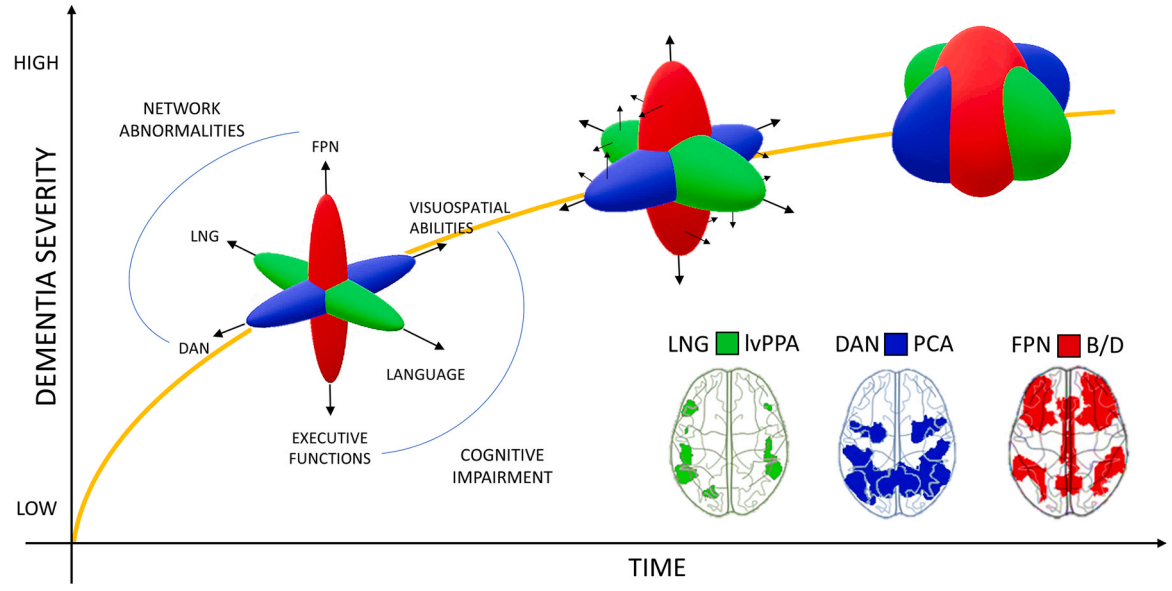

Fig. 1. Convergence of cognitive impairment and network abnormalities within Alzheimer's disease clinical phenotypes. Distinct network-clinical couplings characterize the earliest stages of atypical Alzheimer's disease (AD) variants. As the pathology proceeds, functional connectivity abnormalities and clinical deficits are widespread and converge to common networks/domains as a function of time and dementia severity. B/D: behavioral/dysexecutive; DAN: dorsal-attention network; FPN: frontoparietal network; LNG: language network; lvPPA: logopenic variant primary progressive aphasia; PCA: posterior cortical atrophy.

2021).

In the last years, non-invasive brain stimulation (NIBS) has been widely applied in the neurodegenerative field, showing promising potential to modulate the functional organization of large-scale brain networks affected by neurodegenerative processes (Pini et al., 2018). Recent seminal works showed the feasibility of targeting neural networks to improve specific cognitive deficits. In a cohort of heterogenous PPA patients (agPPA, svPPA, and lvPPA), Ficek et al. (2018) targeted the left IFG, a key hub of the language network, during a combined speech and NIBS interventions reporting beneficial effects in language scores linked with modulation of language network connectivity. These findings are echoed by a previous study in mild cognitive impairment patients, showing improvement in language performance after IFG stimulation (Meinzer et al., 2015). Similarly, targeting the DMN-precuneus showed improved episodic memory performance and increased DMN connectivity in a relatively small sample of AD patients (Koch et al., 2018).

Although these studies identified stimulation targets through stereotaxic (EEG 10–20 system) or anatomical references, functional imaging can be used to design personalized interventions by localizing specific targets for each patient. This personalized functional approach has been recently tested in healthy individuals (Ozdemir et al., 2020; Singh et al., 2019). Singh et al. (2019) investigated the feasibility of manipulating FC by stimulating personalized DMN targets in healthy volunteers. Moreover, personalized target selection has also been proposed for clinical application, such as in depression and AD (Bagattini et al., 2021; Cash et al., 2021). However, this methodology is still in its infancy and relies on a priori selection of specific functional networks as the target for stimulation, regardless of the clinical profile. Although the DMN might be a good candidate for typical AD (Koch et al., 2018), other networks may be considered for atypical AD, considering the specific functional signatures in the earlier stage. Indeed, as pathology advances, FC dysfunction might be widespread and converge across networks, leading to indistinguishable FC fingerprints (Fig. 1). For instance, early modulation of the FPN might be more suitable in prodromal EOAD patients or the dysexecutive variant compared to typical AD, who might benefit more from intervention targeting the DMN. By contrast, in full-blown dementia, target selection should consider that functional circuits showing the earliest breakdown might show the highest tau accumulation rate, thus stimulation of these networks might be less effective due to greater cortical plasticity impairment (Li et al., 2021). Moreover, connectivity within these networks might be uncoupled from clinical/cognitive symptoms in advanced stages. Thus, a phenotype/-network coupling approach could lead to new tailored interventions,

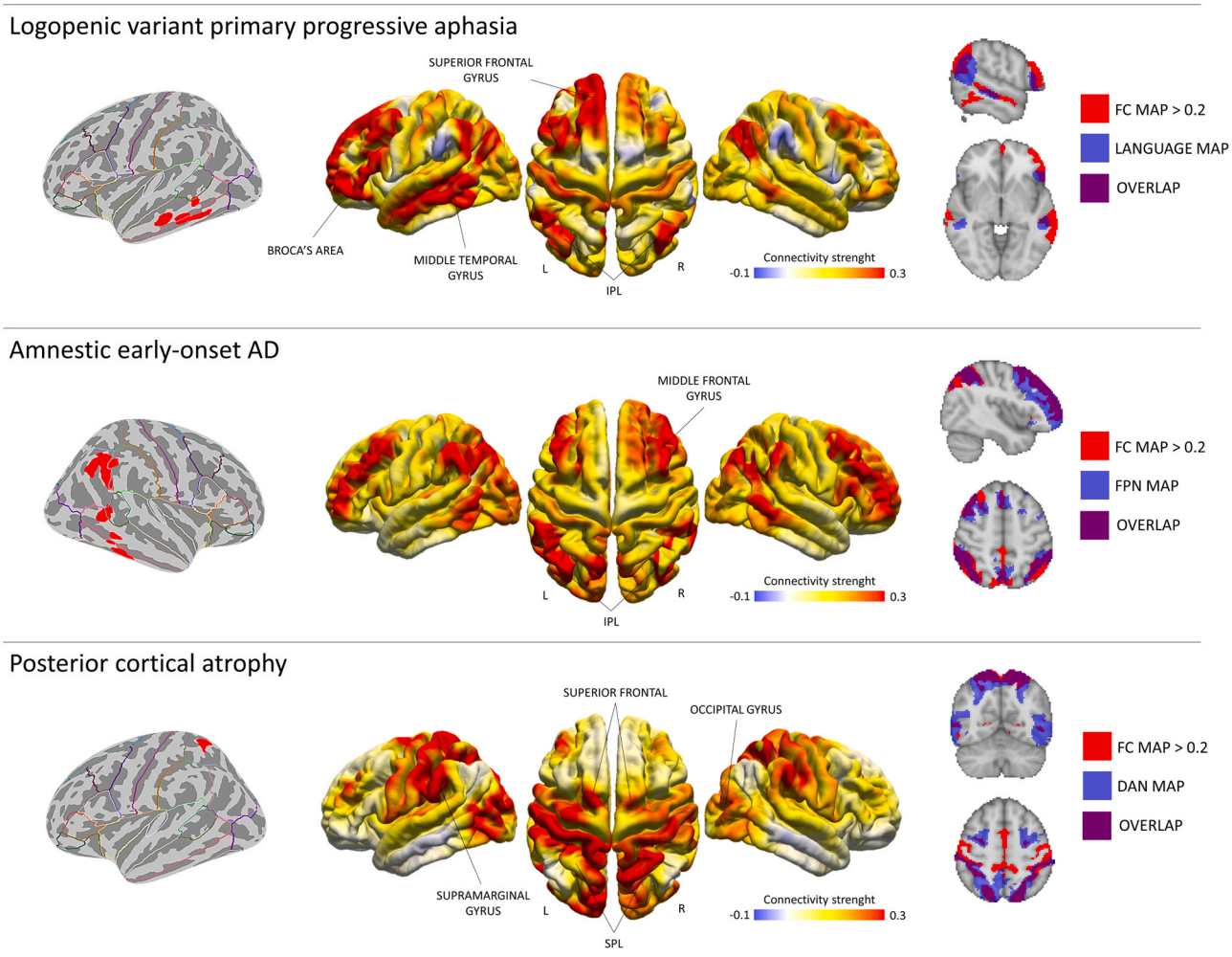

Fig. 2. Subject-specific atrophy network connectivity. Association between peak atrophy and indirect functional network measures at the subject level in different variants of Alzheimer's disease (AD). Top panel: logopenic primary progressive aphasia patient; middle panel: amnestic early-onset AD patient; bottom panel: posterior cortical atrophy patient. Left column: individual peak atrophy maps. Middle column: corresponding functional connectivity map. Left column: overlap between functional network map and network's template. Functional maps were computed from a 7 T dataset of healthy controls from the Human Connectome Project, preprocessed as in Salvalaggio et al. (2020). Right panels: Language template is from Shirer et al. (2012); frontoparietal network and dorsal-attention network maps are from Yeo et al. (2011). Abbreviations: DAN; dorsal-attention network; FC: functional connectivity; FPN: frontoparietal network; IPL: inferior parietal lobe; L: left; R: right; SPL: superior parietal lobe.

targeting the most optimal brain networks for different time-windows, maximizing clinical improvement.

Personalized network targeting might be further improved if network selection would be driven by both clinical phenotype and pathophysiological inter-subject variability. Recently, a new method known as "lesion network mapping" has been proposed. This approach assesses functional network abnormalities by embedding a patient's lesion into a functional normative connectome from large rs-fMRI dataset of healthy controls. Indirect dysconnectivity outcomes can inform on networks disconnected by the specific lesions (Fox, 2018). This technique has recently been extended to the AD field, using single-subject atrophy peak (in the place of lesion) as seed to localize the syndrome-specific networks. Tetreault et al. (2020) reported that single-subject atrophy maps in patients with a clinical diagnosis of AD were functionally connected to the same brain regions, localized within core regions of the DMN. However, this methodology might also be applied to localize network dissimilarities, rather than commonalities, between AD patients with distinct clinical phenotype.

As shown in Fig. 2, three AD patients with a diagnosis of lvPPA, PCA and amnestic AD with early-onset respectively, showed specific network-atrophy associations mapping to distinct large-scale brain networks associated with disease-specific cognitive impairment. In this qualitative analysis, peak atrophy was defined at the individual level as the cluster with the lowest grey matter density (z-scores) compared to a sample of 20 age-matched controls: (i) peak atrophy in a 63-year-old patient with a diagnosis of lvPPA and a positive Aβ profile, localized in the middle temporal gyrus; (ii) in a 62-year-old amnestic EOAD patient, peak atrophy localized in the parieto-temporal cortex; and (iii) a 65-year-old patient diagnosed with PCA and a positive brain Aβ profile showed greatest atrophy in the superior parietal cortex. The corresponding functional maps (thresholded at z-Fisher value > 0.2) showed low spatial overlap between patients, with dice coefficients ranging from 0.43 to 0.07 with an intermediate value of 0.27 between amnestic EOAD vs PPA, PPA vs PCA, and EOAD vs PCA, respectively. Clusters expressing stronger values of connectivity (thresholded at z-Fisher value > 0.4) mapped to completely different brain regions (dice coefficients $<$ 0.05 for all the comparisons).

Notably, individual indirect-personalized functional maps visually overlapped with the phenotype-specific large-scale networks, in line with the literature reported above. PPA maps showed stronger connectivity hubs within core regions of the language network and left FPN. By comparison, amnestic EOAD showed large frontal and parietal hubs of the right FPN, while PCA showed clusters in the visual and parietal cortex overlapping with the DAN and the visual network. Furthermore, these results are congruent with previous studies investigating the spatial convergence between functional networks and syndromic atrophy patterns computed at the group level (Lehmann et al., 2013b; Seeley et al., 2009), suggesting that this approach can be used at the individual level for personalized intervention. While a "one network fits all" approach may be flawed in AD due to its clinical heterogeneity, this promising methodology might offer an alternative strategy to identify new tailored targets for interventions informing on cortical hubs linked with brain regions expressing the earliest vulnerability in the individual pathophysiological trajectory. However, it is important to note that subject variability in brain connections might drive individual differences in human functions and brain disorders (Baldassarre et al., 2012; Greicius, 2008; Mueller et al., 2013), which is not captured by this indirect methodology. Thus, there is still considerable work that needs to be done identifying best target for network modulation, especially in the earliest stage of the different AD clinical variants, when these interventions might be more beneficial.

6. Conclusions

In this review, we have highlighted that different AD clinical phenotypes have separate network connectivity fingerprints, mapping to networks sustaining executive/attentional, visuo-attentional or language functions accordingly to the clinical phenotypes. However, other factors might drive this association and a one-to-one network/phenotype fashion might be too simplistic to capture the complex relationship between symptoms and network breakdown. Improved understanding of the relationship between clinical manifestation, brain circuit alterations, molecular mechanisms, and other factors are needed. Development of novel network paradigms might also be useful to understand overlapping clinical phenotypes between AD profiles and other proteinopathies (Filippi et al., 2017). Finally, delineation of network abnormalities in each clinical phenotype might complement previous research aimed at implementing new interventions for network restoration in AD (Pievani et al., 2016). Adding new pieces in the complex puzzle of FC breakdown in the AD phenotype would pave the way to new tailored interventions aimed at restoring connectivity breakdown linked with specific cognitive and clinical deficits.

Statement of ethics

All data were collected in accordance with the principles of the Helsinki Declaration. The study protocol was approved by the local ethics committee of the IRCCS Fatebenefratelli in Brescia. All participants signed written informed participation consent.

CRediT authorship contribution statement

Lorenzo Pini: Conceptualization, Visualization, Data curation, Software, Writing – original draft. **Alexandra Wennberg**: Writing – review & editing. **Alessandro Salvalaggio:** Writing – review & editing. **Antonino Vallesi**: Writing – review & editing. **Michela Pievani**: Writing – review & editing. **Maurizio Corbetta**: Writing – review & editing, Supervision.

Conflict of interest

The authors declare no conflict of interest.

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