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Default Mode Network Connectivity in Alzheimer's Disease

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SUMMARY

Objective: Alzheimer's Disease (AD) is a neurodegenerative condition characterized by functional and structural changes in the brain that are increasingly better visualized with the advances in new brain imaging techniques. Connectivity changes under the resting state condition especially in the internal connectivity network, named as the *default mode network* (DMN), are observed in AD. This paper aimed to investigate and discuss the findings on DMN connectivity.

Method: The studies carried out by functional magnetic resonance imaging (fMRI), using the two most widely applied techniques, the seed-based method and independent component analysis (ICA), have been investigated.

Results: Studies generally indicate a progressive impairment in DMN connectivity during the course of AD. It has been also stated that DMN subsystems show differential connectivity patterns in the preclinical and prodromal stages of AD. There is also evidence suggesting that impairment in DMN connectivity could be associated with different connectivity patterns in other networks. Furthermore, findings point towards a relationship between DMN and AD-related neuropathology and genetic risk factors.

Conclusion: It may be proposed that AD is a generalized disconnection syndrome that causes functional impairments in resting state networks, particularly in DMN. In addition to this, AD-related functional connectivity changes observed in preclinical cases and risk carriers might be a potential bio-marker for AD.

Keywords: Alzheimer's disease, magnetic resonance ımaging, functional neuroimaging

Resting State Functional Magnetic Resonance Imaging

The brain is a complex network consisting of areas that are functionally and structurally connected to each other. With the advances in the acquisition and analysis of neuroimaging data, it has become possible to investigate the functional connectivity of the human brain. Functional connectivity is defined as the temporal interdependence of neural activation patterns of brain regions that are anatomically distinct from each other (van den Heuvel and Hulshoff Pol 2010).

The level of co-activation between functional time series of different brain regions have been investigated in the recent years on a wide scale by the resting state functional Magnetic Resonance Imaging technique. Low frequency (~0.01-0.1 Hz) oscillations in blood oxygen level dependent (BOLD) signals between different brain regions were first discovered by Biswal et al. (1995). Following this discovery, a number of intrinsic connectivity networks (ICNs) have been identified (Beckmann et al. 2005, Fox et al. 2005, Damoiseaux et al. 2006) that are functionally connected to each other, showing parallel increased or decreased activity on similar spatial patterns (Smith et al. 2009), and frequently supporting higher cognitive functions (Biswal et al. 2010). Although there are different statistical and mathematical approaches to evaluate intrinsic connectivity (Lee et al. 2013), the most commonly used methods are the seed-based method and the independent component analysis (ICA).

In the seed-based approach, a "seed" – a region of interest (ROI) that has been selected a priori – is determined and

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the time series of the activation of this seed is obtained. Subsequently, the correlation between this time series and those of the a priori selected regions as well as all the other voxels in the brain is tested (Fox and Raichle 2007). The regions that show a strong positive correlation with the seed are depicted as functionally related regions, whereas those that show a negative correlation are accepted as belonging to different networks.

ICA, on the other hand, evaluates different brain areas simultaneously and separates spontaneous BOLD signals into networks that do not overlap with each other spatially but show temporal correspondence in their activation (Beckman et al. 2005). Unlike the ROI-driven seed-based approach, ICA is data-driven. Since ICA can be independent of a priori assumptions, it does not impose restrictions about the pattern of hemodynamic response function and therefore is considered to be a model-independent approach.

Resting State Networks

Both seed-based (Damoiseaux et al. 2006) and ICA-based (Beckmann et al. 2005) studies have identified similar intrinsic connectivity networks. Default mode network (DMN), the most widely studied ICN, involves brain regions that increase their activity during the absence of a task. It is therefore labeled as a "task-negative" network and is negatively correlated with "task-positive" networks (Fox et al. 2005). DMN includes the posterior cingulate cortex (PCC), the medial and inferior temporal lobe (MTL/ITL), and the inferior parietal lobule (IPL) (Greicius et al. 2003, Buckner et al. 2008). The tasks orienting the individual to internal mental processes such as autobiographical memory, self or future-related referential mental processing, theory of mind, and affective decision making, activate the regions included in DMN (Buckner et al. 2008, Spreng et al. 2009). Although the cognitive function of DMN is not fully understood, problems with shifting from task-negative state to a task-positive state that involves tasks requiring high-level cognitive processing (such as episodic memory, insight, and attention) is usually attributed to reduced DMN connectivity (Grady et al., 2010).

Research demonstrates that DMN is not homogenous and that it contributes by means of its subsystems to distinct functions (Uddin et al. 2009, Andrews-Hanna et al. 2010). Buckner et al. (2008) proposed that DMN comprises at least 2 subsystems. The MTL subsystem, that includes the PCC, the hippocampal formation and the parahippocampal cortex, is activated by memory functions and the successful retrieval of old information; and the mPFC subsystem, comprising the PCC, the ventral mPFC and the IPL, partakes in the self-related mental simulations. Andrews-Hanna et al. (2010), on the other hand, described a main system in the midline including the anterior mPFC, the PCC and 2 related subsystems consisting of a dorsal mPFC subsystem that gets activated during the processing of self-related and other-related mental states; and an MTL subsystem involved in simulating the future via mnemonic imaging processes. It was proposed that the main system facilitates the formation of mental models of personally salient experiences through its interaction with the MTL and the dorsal mPFC subsystems.

Although the specific function and anatomy of these functionally distinct subsystems are not fully known, the functional heterogeneity in the DMN and its different roles in the formation of memories is generally accepted. Studies have shown that DMN activity increases during the retrieval of past events and decreases during encoding new experiences in memory (Daselaar et al. 2009, Huijbers et al. 2013).

As a recent addition to this finding, it has been found that activation in the left mPFC predicts successful memory encoding processes, and that PCC activity increases during unsuccessful encoding processes (Maillet and Rajah 2014). In another study, Sestieri et al. (2011) determined an increase in the PCC/precuneus and angular gyrus activity together with a decrease in the mPFC activity during retrieval processes. A recent study also supported the previous findings, demonstrating that DMN subsystems support different memory processes in healthy elderly individuals (Huo et al. 2018).

Apart from DMN, a number of different RSNs have been also been described. Sensorimotor network (SMN), the first defined network, is related with motor execution and somatosensorial components (Biswal et al. 1995, Smith et al. 2009). Frontoparietal networks are associated with a variety of cognitive functions and language processing (Smith et al. 2009, Zuo et al. 2010). Whereas dorsal attention network (DAN) has been associated with attention modulation and cognitive control, ventral attention network (VAN) is proposed to contribute to the detection of salient (attention drawing) stimuli (Corbetta and Shulman 2002, Fox et al. 2006). In addition to these networks, salience network (SN), which includes bilateral ventral and dorsal anterior insula, anterior cingulate cortex (ACC), ventral striatum, thalamus, central nucleus of the amygdala, hypothalamus and the brain stem, gets activated during identification of emotionally important internal and external stimuli. The executive control network (ECN), on the other hand, directs the attention to these target stimuli (Seeley et al. 2007).

DMN Connectivity in Alzheimer's Disease

Alzheimer's Disease (AD), a neurodegenerative disorder that leads to structural and functional deterioration in the brain, is characterized by progressive cognitive decline, originating primarily from episodic memory problems. There are two main components of the neuropathology of the disease:

neurofibrillary tangles and amyloid plaques (Querfurth & LaFerla 2010). In typical AD, tau pathology underlying the neurofibrillary tangles first originates in MTL structures and this process is coherent with the clinical manifestation of the Alzheimer's dementia (Braak & Braak 1991). Although the progression of tau pathology corresponds with the clinical course of AD, the development of amyloid pathology begins years before the first clinical symptoms and affects primarily DMN structures (Buckner et al. 2005, Sperling et al. 2009). DMN is thought to be involved in episodic memory (Raichle et al. 2001). In addition, DMN has wide spread projections to MTL structures, which are affected by neurofibrillary tangles (Buckner et al. 2008). As a result, most of the functional neuroimaging studies in AD have been focusing on DMN. This article also aims to review functional connectivity in AD with a primary focus on DMN connectivity.

Initial studies focused on the hippocampus, a brain region that is first and foremost affected in AD and also highly correlated with the severity of the illness (Braak and Braak 1991). These studies have found a reduced connectivity between hippocampus and cortical and subcortical structures among patients with AD compared to healthy controls (Allen et al. 2007, Greicius et al. 2004). These findings have been replicated by more recent studies (Sohn et al. 2014, Tahmasian et al. 2015). In addition, similar connectivity patterns were observed among patients with mild cognitive impairment (MCI), a condition that is labeled as the prodromal stage of AD and has a high probability of progressing to Alzheimer's dementia (Das et al. 2015).

With increased interest in resting state connectivity changes, the focus shifted from hippocampus to large scale areas. A small number of studies have failed to find a change in DMN connectivity and argued that this finding might be due to high cognitive processing of the participants or obtaining the imaging data in a relatively earlier stage of the disease (for e.g., Gour et al. 2011, Lowther et al. 2014). In general, however, studies have shown a decreased connectivity pattern in AD (see Li et al. 2015, and Badhwar et al. 2017 for meta analyses).

In many studies using the ICA method, reduction in DMN connectivity in AD has been consistently demonstrated (Greicius et al. 2004, Zhou et al. 2010, Agosta et al. 2012, Binnewijzend et al. 2012, Balthazar et al. 2014a). Reduced connectivity has been reported between the central regions of DMN, including the posterior cingulate cortex (Wang et al. 2007, Zhang et al. 2010, Brier et al. 2012) and the precuneus (Wang et al. 2006, Sheline et al. 2010a), and the frontal, temporal, and parietal regions. Similar connectivity changes were also observed in MCI patients (Sorg et al. 2007, Qi et al. 2010, Tahmasian et al. 2015). These studies demonstrate that early impairment of DMN connectivity in AD involves the posterior cingulate cortex/precuneus (Greicius et al. 2004, Sorg et al. 2007, Qi et al. 2010, Zhou et al. 2010), which increases in parallel with the increased severity of AD, and spreads towards lateral parietal and medial temporal regions (Zhang et al. 2010). Results of the studies on DMN connectivity in AD are summarized in Table 1.

Petrella et al. (2011) have found that reduced DMN connectivity predicts conversion from MCI to Alzheimer's dementia. Furthermore, altered DMN connectivity has also been reported in preclinical stages of AD (see Sperling et al. 2014 for a review). As a result, resting state connectivity alterations have been proposed as a potential biomarker for AD (Hohenfeld et al. 2018). This, in turn, led to an increase in studies that focus on symptomatic as well as asymptomatic AD patients and individuals identified as belonging to risk groups for AD.

Changes in resting state connectivity patterns have been reported for individuals carrying genetic mutations related to early-onset AD as well as those who carry autosomal dominant AD-related mutations. In their study with a large sample, Thomas et al. (2014) have found that reduced DMN connectivity is more prevalent among early-onset AD patients compared to late-onset cases. Gour et al. (2014) on the other hand, found similar reduced DMN connectivity patterns among both early-onset and late-onset cases. This study found that, instead of DMN, it was attention and executive functions networks that differentiated the two groups. Disruptions in resting state connectivity for both DMN and other networks have also been consistently reported among those who are cognitively normal but carry genetic risk for late onset AD (those who carry at least one APOE ε4 allele) (Filippini et al. 2009, Sheline et al. 2010a, Machulda et al. 2011, Wang et al. 2015). In their study with ICA, Flippini et al. (2009) have found that young adults carrying APOE ε4 allele can show increased DMN connectivity. Sheline et al. (2010a), on the other hand, observed disruption in connectivity patterns between precuneus and other areas of DMN within such individuals. Matura et al. (2014) showed that increased PCC connectivity among asymptomatic APOE ε4 carriers is related to episodic memory performance. It is then possible to argue that increased connectivity patterns among risky individuals could be a compensatory mechanism for possible disruptions in cognitive performance. These findings overall support the idea that functional connectivity changes are present beginning from the earliest stages of the disease (Sperling et al., 2014).

Studies that focus on amyloid accumulation, one of the neuropathologic changes accompanying AD, have found that healthy older adults with increased cerebral amyloidosis, as observed by positron emission tomography (PET), show reduced DMN connectivity compared to those with low cerebral amyloidosis (Hedden et al. 2009, Sheline et al. 2010b). Similar findings were also obtained among MCI patients (Drzezga et al. 2011). Adriaanse et al. (2014), on the

Table 1. Studies Investigating DMN Connectivity in Alzheimer's Disease

Study	Sample	Method	DMN findings	Additional findings
Greicius et al. (2004)	13 AD – 14 old HC – 14 young HC	ICA	AD ↓ (PCC, HpC) (compared to old HC)	
Allen et al (2007)	8 AD – 8 HC	SB (HC)	AD ↓ frontal	
Wang et al. (2007)	17 AD – 17 HC	SB (PCC)	AD ↓ Pc, STG, left SFG	
Sorg et al. (2007)	24 MCI – 16 HC	ICA	MCI ↓ (PCC, right mPFC)	MCI ↓ executive control network
Gour et al. (2011)	13 AD (early AD + MCI) – 12 HC	ICA	No difference between groups	AD ↑ anterior temporal network Correlation between anterior temporal network and memory
Qi et al. (2010)	14 MCI – 14 HC	ICA	MCI ↓ (bilateral PCC, right IPL, right FG) MCI↑ (left SFG, mPFC, IPL, MTG)	
Zhang et al. (2010)	46 AD, 16 HC	SB (PCC)	AD ↓ HpC, Pc, mPFC, visual cortex AD ↑ FP	Correlation between disease severity and connectivity
Zhou et al. (2010)	12 AD – 12 HC – 12 bvFTD	SB - ICA	AD ↓ (mPFC, Pc, MTG)	AD ↑ SN Opposite connectivity pattern in bvFTD
Sheline et al. (2010)	35 AD – 68 HC (48 PIB(-) - 20 PIB(+))	SB (Pc)	AD ↓ HpC, ACC, PHc (compared to PIB(-)) AD ↑ visual network	Similar connectivity pattern between PIB (-) and PIB (+)
Petrella et al. (2011)	12 AD – 31 MCI – 25 HC	ICA	AD and MCI ↓ MCI converted to AD↓PCC/Pc and IFL (compared to non-converters)	
Brier et al (2012)	386 HC - 91 CDR 0.5 – 33 CDR1	SB (PCC)	CDR 0.5 and 1 ↓ (compared to CDR0)	In addition to DMN, other networks (SMN, ECN, SN, and DAN) were also investigated All networks showed decreased connectivity in CDR1 While SN connectivity was increased in CDR 0.5, other networks were decreased
Jin et al. (2012)	8 MCI – 8 HC	ICA	AD ↓ (PCC, MTG, MTL) AD ↑ (mPFC, left IPL)	
Binnewijzend et al. (2012)	39 AD – 23 MCI – 43 HC	ICA	AD ↓ (compared to HC) Stabile MCI ↑ (compared to AD)	AD ↓ visual network, basal ganglia and cerebellum networks Correlation between DMN and cognitive functions
Damoiseaux et al. (2012)	21 AD – 18 HC	ICA	AD ↓ posterior DMN AD ↑ anterior DMN	
Agosta et al. (2012)	12 AD – 12 MCI – 13 HC	ICA	AD ↓DMN	AD ↑ frontal networks
Li et al. (2013)	21 AD – 36 MCI – 23 SCI – 17 other dementias	SB (Pc)		Neuropathology was related with connectivity in AD, MCI, and SCI (especially in MCI)
Koch et al. (2015)	24 AD – 16 HC	ICA	AD ↓ DMN	AD ↓ attention network Connectivity was related with cognitive functions, negative correlation between PIB uptake in PCC and connectivity
Balthazar et al. (2014)	20 AD – 17 HC	ICA	AD ↓ DMN	AD ↑ anterior SN Correlation between neuropsychiatric symptoms and SN connectivity
Gour et al. (2014)	14 EOAD – 14 young controls 14 LOAD – 14 old controls	SB (PCC)	EOAD and LOAD ↓ DMN (compared to controls)	EOAD ↓ frontal network and ↑ ATN LOAD ↓ ATN and ↑ frontal network
Sohn et al. (2014)	28 AD – 38 MCI – 22 HC	SB (right and left HC)	For left HpC AD and MCI ↓ Pc and parietal lobe (compared to HC)	For Left HpC, MCI ↑ ACC Correlation between network disruption and disease severity
Myers et al. (2014)	24 MCI – 16 HC	ICA	MCI ↓ posterior and anterior DMN	MCI ↓ right attention network Beta-amyloid accumulation was related with DMN and fronto-parietal network

Table 1 continued

Study	Sample	Method	DMN findings	Additional findings
Lowther et al. (2014)	13 AD – 15 DLB - 40 HC	ICA	No difference between AD and HC	DLB ↓ DMN, SN, and ECN (compared to AD and HC) DLB ↑ Basal ganglion (compared to AD and HC)
Das et al. (2015)	30 MCI, 39 HC	SB (MTL)	MCI ↓ anterior and posterior MTL	Reduced cortical thickness in MTL regions among MCI
Tahmasian et al. (2015)	40 AD – 21 MCI – 26 HC	SB (HC)	AD ↓ Pc (compared to HC) MCI ↓ Pc (compared to HC)	Reduced PET detectable glucose metabolism in Pc
Chong et al. (2017)	47 AD – 47 AD +CV – 47 HC	SB (PCC)	AD ↓ (compared to HC)	AD ↓ DMN (compared to AD-CV)

AD: Alzheimer's disease, MCI: Mild cognitive impairment, HC: Healthy controls, ICA: Independent component analysis, SB: Seed based method,, DMN: Default mode network, HpC: Hippocampus, PCC: Posterior cingulate cortex, Pc: Precuneus, IFG: Inferior frontal gyrus ,mPFC: Medial prefrontal cortex, STG: Superior temporal gyrus, SFG: Superior frontal gyrus, MTG: Medial temporal gyrus, FG: Frontal gyrus, MTL: Medial temporal lobe, PHc: Parahippocampal cortex, ACC: Anterior cingulate cortex, CDR: Clinical dementia rating scale, ECN: Executive control network , SMN: Somatomotor network, SN: Salience network, DAN: Dorsal attention network, ATN: Anterior temporal network, bvFTD: behavior variant frontotemporal dementia, SCI: Subjective cognitive impairment, DLB: Dementia with Lewy Body, PIB: Pittsburgh component, PET: Positron emission tomography, EOAD: Early onset AD, LOAD: Late onset AD, CV: Cerebrovascular disease

other hand, failed to find a direct relationship between reduced DMN connectivity and amyloid load among patients with AD. The relatively small sample size of the study, together with the probability that amyloid accumulation might reach a plateau during the symptomatic stage, might have led to such results. PET studies have also suggested a relationship between amyloid level in the cerebrospinal fluid and reduced DMN connectivity (Li et al. 2013, Wang et al. 2013). It has been argued that since DMN regions are costly with regard to cerebral blood flow, aerobic glycolysis, and oxidative glucose metabolism, DMN might be more vulnerable to metabolic dysfunction/oxidative stress, and accumulation of toxic proteins such as amyloid beta (Badhwar et al. 2017).

The relationship between tauopathy, another major component of AD pathology, and resting state functional connectivity has also been investigated. Schultz et al. (2017) investigated individuals with amyloid accumulation and found that those with low tau levels show increased DMN connectivity whereas those with high tau levels show reduced DMN connectivity. They also obtained disrupted connectivity patterns within the salience network. The authors argued that increase in amyloid accumulation during the early asymptomatic phase might lead to an increase in connectivity, a pattern that might contribute to spreading of tau in the brain, and this would, in turn, result in reduced functional connectivity.

Observations indicating that DMN can partake with its subcomponents in different functions and that amyloid accumulation predominantly involves the posterior DMN regions including the PCC and the precuneus, have directed the current studies on AD to the subcomponents of DMN. Considering anterior and posterior regions of DMN, the reduction in connectivity is generally determined in the posterior region (Sorg et al. 2007, Agosta et al. 2012, Damoiseaux et al. 2012, Koch et al. 2015). In an ICA study with a wide population of 128 individuals, Jones et al. (2016) investigated DMN subsystems at the preclinical, prodromal, and clinical stages of AD, and claimed that reduced connectivity in the posterior DMN begins before amyloid accumulation which initiates the cascade of connectivity impairment that would continue throughout the course of AD. It is generally believed that there is a direct relationship between reduced functional connectivity, pathological changes, and the consequential cognitive decline. However, the question still remains on whether the reduced connectivity is an early indicator of amyloid toxicity or the result of amyloid pathology (Sheline et al. 2010b, Drzezga et al. 2011, Myers et al. 2014). Koch et al. (2015), on the other hand, proposed that posterior DMN connectivity, especially regarding the precuneus, has a regulatory effect in the process of disruption in cognitive functions as a result of amyloid beta pathology.

Some studies have also identified differential connectivity pattern of the anterior DMN. Damoiseaux et al. (2012), for instance, reported increased connectivity in anterior and ventral DMN, in addition to reduced posterior DMN connectivity, although in time the connectivity in all of these networks was reduced. Studies conducted in the recent years with MCI patients identified reduced posterior DMN connectivity together with increased anterior DMN connectivity (Qi et al. 2010, Jin et al. 2012). Furthermore, reduced connectivity in posterior DMN regions and increased connectivity in frontal and lateral DMN regions were determined by research on individuals carrying genetic risk for AD (Chiesa et al. 2017). These results may be reflecting the compensatory increases in connectivity as changes start at the early stages of AD and the decrease with the progress of AD.

The scope of recent studies is expanding towards the factors that are possibly associated with DMN in AD such as structural covariance and cognitive reserve. Some of these studies have concentrated on the relationship between intrinsic connectivity networks and the structural brain networks that are characterized by analyzing grey matter volume or differential cortical thickness levels in different brain regions in order to assess the distribution of neural changes underlying AD (Seeley et al. 2009, Spreng and Turner, 2013, Montembeault et al. 2016). Results of these studies point to the reduction in DMN structural covariance in AD. Montembault et al. (2016), argued that early impairment in the structural connectivity between heteromodal association areas and entorhinal cortex leads to isolation of hippocampal formation which could result in the progressive memory problems that are the clinical manifestation of AD. Weiler et al. (2018) argued that having a high cognitive reserve in AD enables better network patterns and better coping with the cognitive impairment. Another recent study reported a relationship between increased connectivity in left frontal cortex and preservation of cognitive functions during the progression of AD (Franzmeier et al. 2017). Chong et al. (2017), investigated the relationship between cerebrovascular disease, the incidence of which increases in AD, and DMN and showed reduced posterior DMN connectivity among patients without cerebrovascular disease. Similar and also future studies are important for understanding the complex relationship between neuropathology, connectivity, and cognitive decline in progressing AD.

Studies have also suggested connectivity disruptions within attention (Li et al. 2012, van Dam et al. 2013), executive control (Sorg et al. 2007, Weiler et al. 2014), and salience networks (Balthazar et al. 2014a, He et al. 2014) in AD, although the results are not as consistent as those that focus on DMN. Some studies have proposed a relationship between reduced DMN connectivity and increased ECN (Agosta et al. 2012) or SN (Zhou et al. 2010) connectivity. It has been suggested that progressive DMN disruption in AD might disrupt SN functioning and this would lead to differential effects on these two reciprocally working networks which have inhibitory effects on each (Zhou et al. 2010). Brier et al. (2012), in their large sample study, rated their participants levels of AD on the basis of their Clinical Dementia Rating (CDR) scores and investigated the connectivity patterns within DMN, SN, ECN, DAN, and SMN. They found that those with a CDR score of 1 (early-stage dementia group) demonstrated reduced connectivity in all networks, and those with a CDR score of 0.5 (MCI group) demonstrated reduced connectivity in all networks except for SN. They also observed increased SN connectivity among those with a CDR score of 0 and 0.5. These findings support the idea that specific networks are selectively affected within the progression of AD, and selective disruption patterns of ICNs might characterize the clinical symptoms that accompany the disease (Zhou et al. 2017).

Conclusion and Recommendations for Future Studies

In conclusion, studies investigating the resting state connectivity in AD have identified changes and patterns specific to different stages of the disease, primarily within DMN as well as other networks of the brain. Recent studies suggested altered connectivity patterns in posterior and anterior subsystems of DMN, and in the SN, ECN, and sensorimotor networks. Therefore, it is essential for future studies to expand their scope to investigate the specific interactions between the networks and evaluate their relationship with tau and amyloid pathology. Furthermore, findings indicating that altered connectivity patterns arise before the clinical symptoms of AD, and these connectivity patterns are evident among individuals who are at risk for AD, together with the observed correspondence between connectivity alterations and progression of the disease might suggest that functional connectivity might be a potential biomarker for AD.

Research findings indicate that altered connectivity patterns primarily in DMN and also other networks could discriminate healthy individuals from AD patients with a moderate to high level of success (Koch et al. 2012, Balthazar et al. 2014b). In addition, it has been found that connectivity patterns have also successfully differentiated amnestic AD patients from those with nonamnestic AD variants (Lehmann et al. 2015) or behavioral variant frontotemporal dementia (Zhou et al. 2010). However, use of different techniques during the acquisition and analysis of the data might cast doubt on the idea of using connectivity as a biomarker for diagnosis and differential diagnosis in the future. Therefore, investigation of the test-retest data of the softwares used in the analysis and using refined classification algorithms would be important for future studies and development of new methods (Hohenfeld et al. 2018). Finally, conducting longitudinal studies incorporating individuals with genetic and other risk factors, investigating altering connectivity patterns, and the accompanying compensatory mechanisms as well as the transitions between networks might pave the way for the effectiveness of using the resting state connectivity in the follow-up process of the disease.

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