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Review

Neurophysiology in mild cognitive impairment: focusing on the default-mode network

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ABSTRACT

Cognitive ability tends to decline with age and in some cases becomes severe cognitive impairment. The intermediate transition state is named "mild cognitive impairment" (MCI), identifying the onset of MCI is difficult. This difficulty is caused by the fact that current knowledge of MCI is limited. Amyloid beta (Aß) and tau are widely recognized as causative agents of Alzheimer's disease (AD). Abnormal pathophysiological changes lie below the threshold of detection for AD-related biomarkers, such as Aß42 and tau protein in cerebrospinal fluid. The Aß-tau interaction is initially generated in the brainstem and parahippocampal gyrus before the onset of MCI, and Aß and tau propagate into a default-mode-network (DMN) that is involved in endogenously mediated, self-referential mental activity. The DMN is frequently found to be abnormal due to the progression of AD. Aß-tau interactions affect not only functional connectivity, but also local synaptic activities, resulting in a lowered oscillation frequency by disturbing the balance of activity between excitatory and inhibitory networks (E/I balance). These changes reflect electroencephalogram (EEG) rhythms. The EEG alpha rhythm observed during the resting state tends to decrease, but theta rhythm increases. Before the emergence of clear symptoms of cognitive decline, a lowered frequency of EEG in the resting state becomes apparent. Thus, in the process of transitioning from normal to cognitive impairment, Aß and tau accumulate in the DMN, and Aß-tau interactions disturb the E/I balance. This lowers EEG frequency in the resting state, which may provide a sign of the onset of MCI.

Key words:
Mild cognitive impairment, Default-mode-network, Electroencephalogram, E/I balance, Aß-tau interaction

What is MCI?

Cognitive ability is particularly essential for performing daily activities throughout life. However, cognitive ability tends to decline with age, and in some cases the cognitive decline is accelerated compared with normal aging. In some of these cases, the accelerated cognitive decline transfers to severe cognitive impairment at the level of dementia[1-3]. Identification of this intermediate transitional state seems to be important for preventing the progression of cognitive impairment. This transition state is termed "mild cognitive impairment" (MCI).

Clinical criteria for MCI are based on symptoms, and are used in daily medical treatment. Outlines of the criteria have been proposed as follows. The basic criterion is the presence of a cognitive complaint. Sub-features include a cognitive ability that is not normal for age, but essential activities of daily living remain normal [4]. Although symptoms are variable, MCI is generally divided into two broad types: amnestic MCI; and non-amnestic MCI. The former is an MCI with memory loss, while the latter is an MCI involving "domains" of cognition other than memory[4]. However, making a diagnosis of MCI is currently difficult. This difficulty is because longitudinal population-based studies on cognitive aging and MCI are lacking, and the current state of knowledge regarding MCI is limited by inconsistent findings[4-6].

Recent advances in neuroimaging have enabled the detection of brain biomarkers in cognitively impaired patients.

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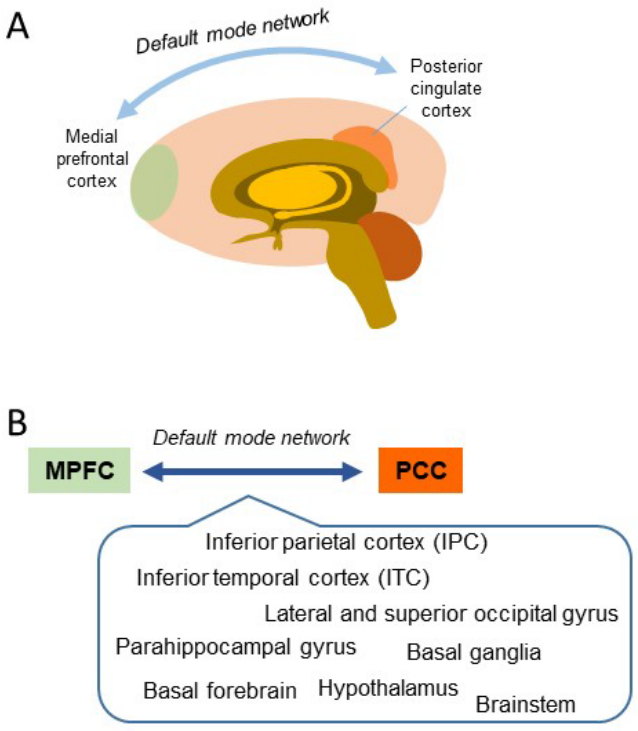

Fig. 1 DMN and subsystem areas of the DMN. **A)** Core functional hubs of the DMN. MPFC and PCC are functionally connected and form the DMN. **B)** Several areas functionally connected with the DMN form subsystem of the DMN.

Neuroimaging biomarkers of AD include measurement of beta-amyloid (Aß) deposition on Aß-Positron Emission Tomography (PET), tau deposition with tau-PET, and brain metabolism on fluorodeoxyglucose (FDG)-PET. Various investigations into MCI using biomarkers have been undertaken[7-9]. Jack et al. proposed a model of biomarkers in the AD pathological cascade[10]. Candidate biomarkers include Aß42 and tau protein in cerebrospinal fluid (CSF). Recently, abnormal pathophysiological changes have been demonstrated below the threshold of biomarker detection[11]. Tau pathology precedes Aß deposition, but the emergence of Aß deposition accelerates tauopathy. Due to this, biomarker levels rise above the threshold of detection. During the initial pathological cascade of AD, the important point is that these pathophysiological changes occur during the preclinical phase. For this reason, the onset of MCI is difficult to identify based on age-related biomarkers alone.

AD biomarkers and the default-mode-network (DMN)

Recently, several functional connections between nodes in the neocortex have been identified as large-scale networks[12-14]. The medial prefrontal cortex (MPFC) and posterior cingulate cortex (PCC) are functionally connected and form the default-mode-network (DMN), which is involved in endogenously mediated and self-referential mental activity[15-17]. The DMN is also referred to as the task-negative network, and exhibits higher metabolic activity at rest than during the performance of externally oriented cognitive tasks[18]. The MPFC and PCC are core functional hubs of the DMN (Fig. 1A). The MPFC is mainly involved in self-referential mental idealization, while the PCC is mainly involved in episodic memory retrieval[19,20]. The inferior parietal cortex, inferior temporal cortex, lateral and superior occipital gyri and parahippocampal gyrus including the hippocampus, are considered subsystem areas of the DMN[21,22]. In addition, the brainstem, hypothalamus, basal forebrain and basal ganglia are functionally connected with the DMN, representing a subcortical DMN map[23] (Fig. 1B).

The DMN is frequently found to be abnormal, due to not only AD but also MCI. Zhong et al. reported that effective connectivity between nodes in the DMN is decreased in AD patients. In particular, according to a study using independent component analysis (ICA) to identify DMN components and Granger causality analysis to explore effective connective patterns, it is found that the PCC is strongly connected with most of the DMN regions but tends to be attenuated in AD patients[22]. Greicius et al. reported that resting-state metabolic activity in the PCC and hippocampus is decreased during the progression of AD, and network activity between the two regions is disrupted[24]. Wang et al. also reported that resting state connectivity between right hippocampus and PCC is decreased in early AD[25]. Interestingly, the right hippocampus is associated with memory performance, and a moderate decrease in DMN functional connectivity between the PCC and right hippocampus is evident in mild AD[26]. These changes correspond to decreased glucose metabolism in the DMN, particularly in cases of amnestic MCI[27]. Further, Aß aggregation within the DMN leads to regional hypo-metabolism, and hypo-metabolism with overlapping Aß aggregation is associated with subsequent cognitive declines[8,28].

Studies using biomarker neuroimaging techniques have revealed the distributions of Aß and tau in the brain at different stages of cognitive impairment. Li et al. reported that in MCI patients, abnormal spatial distributions of tau PET correlate with abnormal spatial distributions of Aß PET, both located in the DMN and subcortical networks[29]. Multimodal imaging is an effective approach for distinguishing patients with MCI from normal controls. Even among cognitively normal older individuals, tau tangles are sometimes identified in brainstem

nuclei and the parahippocampal gyrus prior to the appearance of Aß[8]; this is termed primary age-related tauopathy. Jacobs et al. reported that higher amyloid pathology strengthens the association between hippocampal-cingulum bundle diffusivity and tau accumulation in the downstream PCC, and facilitates memory declines[9].

In the earliest period of AD, the following pathological changes appear in the DMN. In the first stage, hyper-phosphorylated tau appears within brainstem nuclei, the noradrenergic locus coeruleus (LC), the serotonergic dorsal raphe nucleus (DRN), and the cholinergic nucleus basalis (NB). These subcortical neurons project to DMN hub regions, where they release Aß at the projecting areas, resulting in neurofibrillary changes to the DMN via Aß-tau interactions[30]. In addition, the disruption of DMN functionality causes the hippocampal formation to become functionally disconnected from the DMN in the preclinical phase of AD[31]. These findings suggest that the emergence of Aß-tau interactions in the DMN may represent a critical event in the progression of cognitive decline[32] (Fig. 1A).

Slower EEG frequency and DMN

EEG recordings offer a great advantage compared to biomarker imaging methods, in that EEG directly reflects neural activities produced by cortical neuron networks at high temporal resolution. Among various EEG frequencies, the alpha band is the most relevant frequency in the DMN[33]. Previous EEG frequency studies have predicted that lowering resting-state EEG rhythms might reflect neurodegenerative processes along the preclinical and clinical stages of AD[34], and changes in EEG values between alpha and theta power may provide important predictors of MCI[35].

Yoshimura et al. reported that as cognition ability decreases, theta band activities increase, whereas alpha band activities decrease on frontal EEGs recorded from normal subjects and patients with MCI or mild AD under comfortable situations[36]. By comparing resting state EEG rhythms between normal aged controls and patients with stable MCI, progressed MCI, or AD, the amplitudes of widespread delta and theta sources were found to be increased, whereas the amplitudes of posterior alpha and/or beta sources decreased as cognitive impairment progressed, suggesting that declines in posterior slow-frequency alpha power represent a feature in the progression from MCI to dementia[34]. MCI subjects who progressed to AD showed decreased alpha power, higher theta power, and a shift in the source of alpha activity more anteriorly in the antero-posterior localization of alpha frequency[37,38].

During the resting state, alpha oscillations (8–12 Hz) are hyposynchronous in the occipital and posterior temporoparietal cortices, whereas delta-theta oscillations (2–8 Hz) are hypersynchronous in the frontal and anterior temporoparietal cortices of patients with AD compared to age-matched controls[39]. In this situation, alpha hyposynchrony colocalized strongly with tau deposition, whereas delta-theta hypersynchrony colocalized with tau and Aß deposition. In addition, Garćes et al. reported that the DMN is functionally impaired in MCI, and this disruption to connectivity is specifically in the alpha frequency band[33]. Actually, tau and Aß colocalize with the DMN and subcortical networks in patients with MCI[29].

Sorg et al. reported that functional connectivity between the medial temporal lobes and posterior cingulate lobe of the DMN is present in healthy controls, but absent in amnesic MCI patients, and functional brain disorders can be characterized by functional disconnectivity profiles of resting state networks[40]. Functional coupling of resting EEG rhythms becomes progressively more abnormal in amnesic MCI and AD patients as described below[34,41,42]. Studies using the cortical source analysis of EEG rhythms have revealed that frontal delta (2–4 Hz) sources are greater in amplitude in amnesic MCI, and parietal and occipital alpha (8–10.5 Hz) sources show lower amplitude in amnesic and non-amnesic MCI, compared to healthy elderly subjects[41]. Hsiao et al. reported that source-based EEG maps of resting-state activity in DMN regions show altered cortical spectral power in mild AD when compared to MCI. With the progression of AD, alpha and beta activities attenuate in the DMN, while delta and theta activities are enhanced[42]. Thus, the altered functional connectivity between the DMN and its related regions affects EEG rhythms in the resting state, dependent on the stage of cognitive impairment. Actually, the spectral magnitude of alpha EEG sources correlates with scores on the Mini-Mental State Examination (MMSE), suggesting that EEG evidence of decreased alpha power in MCI compared to normal subjects is related to behavioral cognition[34,35].

Neurophysiological mechanisms

In cases where Aß clearance is decreased in the brain, Aß monomers accumulate and Aß oligomers increase, affecting neural network activities. Aß was recently found to increase the excitability of pyramidal cells, resulting in perturbation of the excitation/inhibition balance (E/I balance) of the neural circuitry through dopamine D1 receptor-dependent disruption of GABAergic inhibitory neurons[43] and the

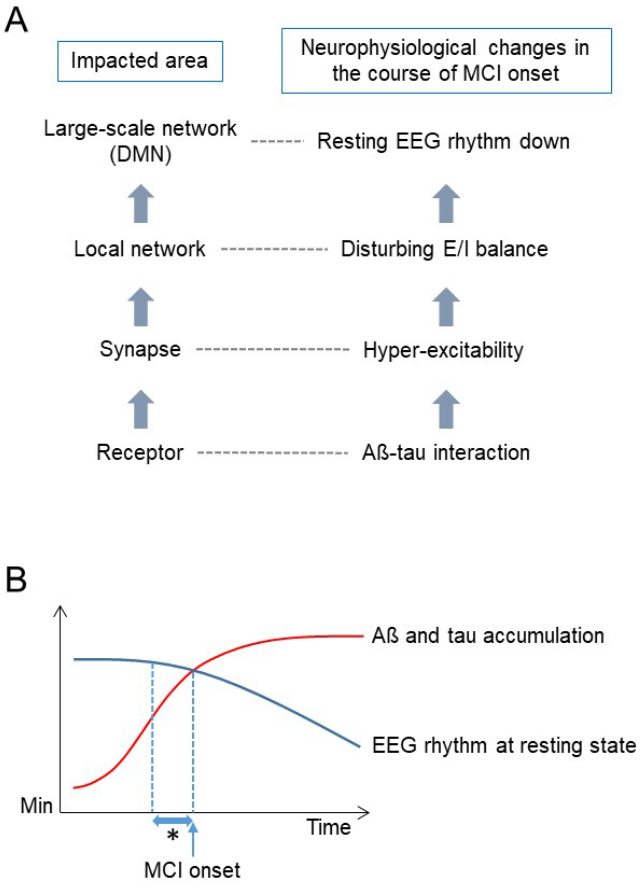

Fig. 2 Hypothetical mechanism of MCI induction and timing of MCI onset. **A)** Presumed neurophysiological changes that emerge during MCI induction, and respective areas impacted by changes are shown from the microscopic to macroscopic levels. **B)** Superimposition of the time courses of the magnitudes of Aß and tau accumulation and EEG rhythms in the resting state. An intersection point shows the presumed timing of MCI onset. Asterisk shows the underlying period before MCI onset. Note that the decrease in resting EEG rhythm from alpha to theta band starts in the underlying period before MCI onset.

suppression of glutamate reuptake[44]. A recent study using a neural mass model postulated Aß effects, and implementation of this model onto the Janse-Rir model containing clinical data of AD and MCI revealed that the number of hyperactive neurons is increased near Aß plaques, and EEG rhythms based on local neural activity shift from alpha to theta bands through the perturbation of E/I balance[45].

Changes in E/I balance are deeply involved in the dynamics of NMDA receptors. When Aß stimulates alpha7-nicotinic acetylcholine receptor (nAchR) at the postsynaptic dendritic spine, synaptic NMDA receptors move to the extra-synaptic region from the intra-synaptic spine, resulting in the production of extra-synaptic NMDA (eNMDA) receptors[46,47]. Since the GluN2B subunit is present in eNMDA receptors, voltage-dependent Mg^{2+} block at the NMDA receptor is reduced[48-50]. Aß also stimulates alpha7-nAchR at astrocytes near the glutamatergic synapse, and decreases the clearance of glutamate released from presynaptic terminals, resulting in a spillover of glutamate around glutamatergic synapses[51,52]. A characteristic of the eNMDA receptor is the low threshold of Ca^{2+} entry. Spillover glutamate thus stimulates eNMDA receptor, resulting in the generation of hyper-synaptic activity, and excessive entry of Ca^{2+} into the neuron. This neural hyperactivity causes damage to the DMN, resulting in the gradual progression of cognitive decline.

Inhibitory networks are particularly important for the E/I balance in normal network activities, as mentioned above. Ulrich et al. reported that Aß weakens synaptic inhibition via the endocytosis of $GABA_A$ receptors in cases of cognitive decline and AD[53]. Zhou et al. demonstrated another mechanism of hyperactivity for neural cells. Soluble Aß impairs GABA inhibition by mediating K^+-Cl^- cotransporter (KCC2) levels in early APP/PS1 mice, as an animal model of early-onset AD[54]. In APP/PS1 mice at 3–4 months old, soluble Aß42 levels were significantly increased, while KCC2 and $GABA_A$ receptor expressions were decreased. Soluble Aß42 produces brain-derived neurotrophic factor (BDNF) via tumor necrosis factor (TNF)-α production, then BDNF-induced TrkB inhibits $GABA_A$ synaptic responses by down-regulating the expression of K^+-Cl^- cotransporter KCC2, and impairs neuronal Cl^- extrusion, in which the equilibrium potential of Cl^- is positive relative to the resting membrane potential[55]. A decrease in inhibitory neurons thus results in increased excitability of the excitatory neurons. These synaptic changes induce a lower oscillation frequency, by way of changing the E/I balance (Fig. 2A).

Cholinergic system of the basal forebrain

Cortical activity in the theta and alpha ranges and functional coupling in the theta band are modulated by the cholinergic system[56]. Increased slow EEG power coupled with a decrease in alpha activity is linked to cognitive performance declines in MCI compared to normal subjects, as mentioned above. The basal forebrain is considered the major cholinergic output of the central nervous system[57], and contributes to DMN regulation[58]. The cholinergic basal forebrain system is selectively vulnerable to AD-related tauopathy and is actively targeted by Aß[59]. The relative decrease in the spectral magnitude of posterior low-frequency alpha sources in MCI may be related to an initial selective impairment of the cholinergic basal

forebrain system, which could induce a sustained increase in excitatory activity in the cholinergic brainstem pathway[34,60]. Under such circumstances, the increased excitability of the thalamocortical connections would desynchronize the resting alpha rhythms and enhance the cortical excitability. Al-Shaikh et al. reported that accumulation of neurofibrillary tangles in the nucleus basalis of Mynert (NBM), one of the major nuclei of the basal forebrain system, may underlie more widespread cholinergic deficits in early-onset AD[61]. Grothe et al. reported that atrophy of the posterior parts of the gray matter volume of the NBM is reduced in very mild AD, while the atrophy in AD is more extensive and includes the entire cholinergic basal forebrain system[62]. Thus, in considering decreases in DMN function, comprehensive reevaluation of the cholinergic basal forebrain system is warranted to elucidate the neurophysiological mechanisms underlying MCI.

Relationships between oral function and DMN

Hotta et al. reported that central commands from the cortical masticatory areas stimulate not only central pattern generator of mastication but also NBM neurons. Activation of NBM neurons leas to an increase in cortical regional cerebral blood flow (rCBF)[63]. Interestingly, the increase in rCBF is independent of activating CPG. In addition, Nair et al. demonstrated that oscillatory activity of the NBM has a directional influence on a hub of the DMN[64]. Takata et al. demonstrated that activation of NBM elevates intracellular Ca^{2+} of astrocytes, which provide a favorable condition for synaptic plasticity via the increased extracellular concentration of $_D$-Ser[65]. Thus, masticatory motor commands may induce increase in synaptic activity in the DMN via NBM activation. Therefore, it is suggested that motor commands from the cortical masticatory areas are especially important for maintenance of DMN function.

Conclusions and future directions

MCI represents a transitional state between normal and severe declines in cognitive ability. However, detection of the onset of MCI is difficult. The DMN, which is involved in endogenously mediated and self-referential mental activity, is frequently found to be abnormal not only in AD, but also in MCI. During the development or progression of cognitive impairment, Aß and tau accumulate in the DMN, and the interaction of these molecules disturbs DMN activities. However, Aß-tau interactions emerge long before the onset of MCI. In the first stage, Aß-tau interactions cause excitatory neurons to become hyper-excitable, leading to impairment of inhibitory transmission and disturbance of the E/I balance in local network activities. Various clinical studies have demonstrated that EEG alpha activities in the resting state are attenuated and delta and theta activities are instead enhanced as cognitive decline progresses. The transition of EEG rhythms is based on disturbance of the E/I balance, and initiates from the DMN at sites of co-localized Aß and tau. The disruption of functional connectivity in relation to the alpha frequency band underlies these alterations in EEG rhythms. Interestingly, a large-scale computational study using a neural mass model predicted that EEG rhythms would shift from alpha to theta bands when the cellular microenvironment is adjacent to Aß plaques in neuron networks. EEG analyses may thus hold potential as a predictor of MCI onset. Meanwhile, multimodal imaging of biomarkers such as CSF-Aß42, CSF-tau, Aß PET and tau PET appears useful for investigating the distributions of Aß and tau in the brain. The combination of biomarker imaging and EEG analysis is expected to contribute to the identification of the period leading up to the onset of MCI (Fig. 2B).

Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

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References

1) Morris JC, Storandt M, Miller JP, McKeel DW, Price JL, Rubin EH et al. Mild cognitive impairment represents early-stage Alzheimer Disease. Arch Neurol 2001; 58: 387-405.
2) Iwatsubo T, Iwata A, Suzuki K, Ihara R, Arai H, Ishii K et al. Japanese and north american Alzheimer's disease neuroimaging initiative studies: Harmonization for international trials. Alzheimer's & Dementia 2018; 14: 1077-87.
3) McCollum L, Karlwish JK. Cognitive impairment evaluation and management. Med Clin N Am 2020; 104: 807-25.
4) Petersen RC, Caracciolo B, Brayne C, Gauthier S, Jelic V, Fratiglioni L. Mild cognitive impairment: a concept in evaluation. J Intern Med 2014; 275: 214-28.
5) Petersen RC, Lopez O, Armstrong MJ, Getchius TSD, Ganguli M, Gloss D et al. Practice guideline update summary: mild cognitive impairment. Report of the guideline development, dissemination, and implementation subcommittee of the American Academy of Neurology. Neurology 2018; 90: 126-35.
6) Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, Fox NC et al. The diagnosis of mild cognitive impairment due to Alzheimer' disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diag-

nostic guidelines for Alzheimer's disease. Alzheimers Dement 2011; 7: 270-9.
7) Fortea J, Vilaplana E, Alcolea D, Carmona-Iragui M, Sánchez-Saudinos MB, Sala I et al. Cerebrospinal fluid b-amyloid and phosphor-tau biomarker interactions affecting brain structure in preclinical Alzheimer disease. Ann Neurol 2014; 76: 223-30.
8) Jagust W. Imaging the evolution and pathophysiology of Alzheimer's disease. Nat Rev Neurosci 2018; 19: 687-700.
9) Jacobs HIL, Hedden T, Schultz AP, Sepulcre J, Perea RD, Amariglio RE et al. Structual tract alterations predict downstream tau accumulation in amyloid positive older individuals. Nat Neurosci 2018; 21: 424-31.
10) Jack Jr CR, Knopman DS, Jagust WJ, Shaw LM, Aisen PS, Weiner MW et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. Lancet Neurol 2010; 9: 119.
11) Jack Jr CR, Knopman DS, Jagust WJ, Petersen RC, Weiner MW, Aisen PS et al. Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. Neurology 2013; 12: 207-16.
12) Bressler SL, Menon V. Large-scale brain networks in cognition: emerging methods and principles. Trends Cogn Sci 2010; 14: 277-90.
13) Petersen SE, Sporns O. Brain networks and cognitive architectures. Neuron 2015; 88: 207-19.
14) Qi S, Gao Q, Shen J, Teng T, Xie X, Sun T. Multiple frequency bands analysis of large scale intrinsic brain networks and its application in schizotypal personality disorder. Front Comp Neurosci 2018; 12: Article 64.
15) Raichle ME. The brain's default mode network. Ann Rev Neurosci 2015; 38: 433-47.
16) Davey CG, Pujol J, Harrison BJ. Mapping the self in the brain's default mode network. NeuroImage 2016; 132: 390-7.
17) Menon V. 20 years of the default mode network: a review and synthesis. Neuron 2023; 111: 1-19.
18) Uddin LQ, Kelly AMC, Biswal BB, Castellanos FX, Milham MP. Functional connectivity of default mode network components: Correlation, anticorrelation, and causality. Hum Brain map 2009; 30: 625-37.
19) Yang H, Wang C, Zhang Y, Xia L, Feng Z, Li D et al. Disrupted causal connectivity anchored in the posterior cingulate cortex in amnestic mild cognitive impairment. Front Neurol 2017; 8: Article 10.
20) Xue C, Yuan B, Yue Y, Xu J, Wang S, Wu M et al. Distinct disruptive patterns of default mode subnetwork connectivity across the spectrum of preclinical Alzheimer's disease. Front Aging Neurosci 11; Article 307.
21) Damoiseaux JS, Rombouts SARB, Barkhof F, Scheltens P, Stam CJ, Smith SM et al. Consistent resting-state networks across healthy subjects. Proc Nat Acad Sci USA 2006; 103: 13848-53.
22) Zhong Y, Huang L, Cai S, Zhang Y, von Deneen KM, Ren A et al, For the Alzheimer's Disease Neuroimaging Initiative. Altered effective connectivity patterns of the default mode network in Alzheimer's disease: An fMRI study. Neurosci Lett 2014; 578: 171-5.
23) Li J, Curley WH, Guerin B, Dougherty DD, Dalca AV, Fischl B et al. Mapping the subcortical connectivity of the human default mode network. NeuroImage 2021; 245: 118758.
24) Greicius MD, Srivastava G, Reiss AL, Menon V. Default-mode network activity distinguishes Alzheimer's disease from healthy aging: evidence from functional MRI. Proc Natl Acad Sci USA 2004; 101: 4637-42.
25) Wang L, Zang Y, He Y, Liang M, Zhang X, Tian L et al. Changes in hippocampal connectivity in the early stage of Alzheimer's disease: Evidence from resting state fMRI. Neuroimage 2006; 31: 496-504.
26) Grieder M, Wang DJJ, Dierks T, Wahlund LO, Jann K. Default mode network complexity and cognitive decline in mild Alzheimer's disease. Front Neurosci 2018; 23: Article 770.
27) Therriault J, Ng KP, Pascoal TA, Mathotaarachchi S, Kang MS, Struyfs H et al, For the Alzheimer's Disease Neuroimaging Initiative. Anosognosia predict default mode network hypometabolism and clinical progression to dementia. Neurology 2018; 90: e932-e939.
28) Pascoal TA, Mathotaarachchi S, Kang MS, Mohaddes S, Shin M, Park AY et al. Aß-induced vulnerability propagates via the brain's default mode network. Nat Commu 2019; 10: 2353.
29) Li Y, Yao Z, Yu Y, Zou Y, Fu Y, Hu B. Brain network alterations in individuals with and without mild cognitive impairment: parallel independent component analysis of AV1451 and AV45 positron emission tomography. BMC Psychiatry 2019; 19: 165.
30) Simic G, Babic M, Borovecki F, Hof PR. Early failure of the default-mode network and the pathogenesis of Alzheimer's disease. CNS Neurosci & Therap 2014; 20: 692-8.
31) Hedden T, Van Dijk KRA, Becker JA, Mehta A, Sperling RA, Jhonson KA et al. Disruption of functional connectivity in clinically normal older adults harboring amyloid burden. J Neurosci 2009; 29: 12686-94.
32) Busche MA, Hyman BT. Synergy between amyloid-ß and tau in Alzheimer's disease. Nat Neurosci 2020; 23: 1183-93.
33) Garćes P, Pineda-Pardo JA, Canuet L, Aurtenetxe S, López ME, Marcos A et al. The default mode network is functionally and structurally disrupted in amnestic mild cognitive impairment-a bimodal MEG-DTI study. NeuroImage: Clinical 2014; 6: 214-21.
34) Lizio R, Vecchio F, Frisoni GB, Ferri R, Rodriguez G, Babiloni C. Electroencephalographic rhythms in Alzheimer's disease. Int J Alz Dise 2011; 2011: Article ID 927573.
35) Jelic V, Johansson SE, Almkvist O, Shigeta M, Julin P, Nordberg A et al. Quantitative electroencephalography in mild cognitive impairment: longitudinal changes and possible prediction of Alzheimer's disease. Neurobiol Aging 2000; 21: 533-40.
36) Yoshimura H, Morimoto S, Okuro M, Segami N, Kato N. Evaluations of dementia by EEG frequency analysis and psychological examination. J Physiol Sci 2010; 60: 383-8.
37) Huang C, Wahlund LO, Dierks T, Julin P, Winblad B, Jelic V. Discrimination of Alzheimer's disease and mild cognitive impairment by equivalent EEG sources: a cross-sectional and longitudinal study. Clin Neurophysiol 2000; 111: 1961-7.
38) Jeric V, Johansson SE, Almkvist O, Shigeta M, Julin P, Norberg A et al. Quantitative electroencephalography in mild cognitive impairment: longitudinal changes and possible prediction of Alzheimer's disease. Neurobiol Aging 2000; 21: 533-40.
39) Ranasinghe KG, Cha J, Iaccarino L, Hinkley LB, Beagle AJ, Pham J et al. Neurophysiological signatures I Alzheimer's disease are distinctive associated with TAU, amyloid-ß accumula-

tion, and cognitive decline. Sci Transl Med 2020; 12: 534.
40) Sorg C, Riedl V, Mühlau M, Calhoun VD, Eichele T, Läer L et al. Selective changes of resting-state networks in individuals at risk for Alzheimer's disease. Proc Natl Acad Sci USA 2007; 104: 18760-5.
41) Babiloni C, Visser PJ, Frisoni G, De Deyn PP, Bresciani L, Jelic V et al. Cortical sources of resting EEG rhythms in cognitive impairment and subjective memory compliant. Neurobiol Aging 2010; 31: 1787-98.
42) Hsiao FJ, Wang YJ, Yan SH, Chen WT, Lin YY. Altered oscillation and synchronization of default-mode network activity in mild Alzheimer's disease compared to mild cognitive impairment: and electrophysiological study. PLOS ONE 2013; 8(7): e68792.
43) Ren SQ, Yao W, Yan JZ, Jin C, Yin JJ, Yuan J et al. Amyloid-ß causes excitation/inhibition imbalance through dopamine receptor 1-dependent disruption of fast-spiking GABAergic input in anterior cingulate cortex. Nat Com 2018; 8: 302.
44) Zott B, Simon MM, Hong W, Unger F, Chen-Engerer HJ, Frosch MP et al. A vicious cycle of ß amyloid- dependent neuronal hyperactivation. Science 2019; 365(6453): 559-65.
45) Stefanovski L, Triebkorn P, Spiegler A, Diaz-Cortes MA, Solodkin A, Jirsa V et al. Linking molecular pathways and large-scale computational modeling to assess candidate disease mechanisms and pharmacodynamics in Alzheimer's disease. Front Comp Neurosci 2019; 13: Article 54.
46) Gladding CM, Raymond LA. Mechanisms underlying NMDA receptor synaptic/extrasynaptic distribution and function. Molecu Cell Neurosci 2011; 48: 308-20.
47) Karpova A, Mikhaylova M, Bera S, Bär J, Reddy PP, Behnisch T et al. Encoding and transducing the synaptic or extrasynaptic origin of NMDA receptor signals to the nucleus. Cell 2013; 152: 1119-33.
48) Zamzow DR, Elias V, Shumaker M, Larson C, Magnusson KR. An increase in the association of GluN2B containing NMDA receptors with membrane scaffolding proteins was related to memory declines during aging. J Neurosci 2013; 33: 12300-5.
49) Avila J, Lliorens-Martín M, Pallas-Bazarra N, Bolós M, Perea JR, Rodriguez-Matellán A et al. Cognitive decline in neuronal aging and Alzheimer's disease: role of NMDA receptors and associated proteins. Front Neurosci 2017; 11: Article 623.
50) Fedele L, Newcombe J, Topf M, Gibb A, Harvey RJ, Smart TG. Disease-associated missense mutations in GluN2B subunit alter NMDA receptor ligand binding and ion channel properties. Nat Com 2018; 9: 957.
51) Revett TJ, Baker GB, Jhamandas JJ, Kar S. Glutamate system, amyloid ß peptides and tau protein: functional interrelationships and relevance to Alzheimer disease pathology. J Psychiatry Neurosci 2013; 38: 6-23.
52) Rudy CC, Hunsberger HC, Weitzner DS, Reed MN. The role of the tripartite glutamatergic synapse in the pathophysiology of Alzheimer's disease. Aging and Disease 2015; 6: 131-48.
53) Ulrich A. Amyloid-ß impairs synaptic inhibition via GABAA receptor endocytosis. J Neurosci 2015; 35(24): 9205-10.
54) Zhou Y, Cheng Y, Li Y, Ma J, Wu Z, Chen Y et al. Soluble ß-amyloid impaired the GABA inhibition by mediating KCC2 in early APP/PS1 mice. Biosci trends Adva Pub 2021; P1-P11.
55) Miles R. A homeostatic switch. Nature 1999; 397: 215-6.
56) Osipova D, Ahvenien J, Kaakkola S, Jääskeläinen IP, Huttunen J, Pekkonen E. Effects of scopolamine on MEG spectral power and coherence in elderly subjects. Clin Neurophysiol 2003; 114: 1902-7.
57) Goad M, Dan Y. Basal forebrain activation enhances cortical coding of natural scenes. Nat Neurosci 2009; 12: 1444-9.
58) Nair J, Klaassen AL, Arato J, Vyssotski AL, Harvey M, Rainer G. Basal forebrain contributes to default mode network regulation. Proc Natl Acad Sci USA 2018; 115: 1352-7.
59) Berry AS, Harrison TM. New perspectives on the basal forebrain cholinergic system in Alzheimer's disease. Neurosci & Biobehav Rev 2023; 150: 105192.
60) Villa AEP, Tetko IV, Dutoit P, Vantini G. Non-linear cortico-cortical interactions modulated by cholinergic afferences from the rat basal forebrain. BioSystems 2000; 58: 219-28.
61) Al-Shaikh FSH, Duara R, Crook JE, Lesser ER, Schaeverbeke J, Hinkle KM et al. Selective vulnerability of the nucleus basalis of Meynert among neuropathologic subtypes of Alzheimer's disease. JAMA Neurol 2020; 77: 225-33.
62) Grothe M, Heinsen H, Teipel S. Atrophy of the cholinergic basal forebrain over the adult age range and in early stages of Alzheimer's disease. Biol Pshychiatry 2012; 71: 805-13.
63) Hotta H, Suzuki H, Inoue T, Stewart M. Involvement of the basal nucleus of Meynert on regional cerebral cortical vasodilation associated with masticatory activity in rats. J Cerebral Blood Flow & metabolism 2020; 40 : 2416-28.
64) Nair J, Klaassen A-L, Arato J, Vyssotski A, Harvey M, Rainer G. Basal forebrain contributes to default mode network regulation. Proc Natle Acad Sci USA 2018; 115: 1352-7.
65) Takata N, Mishima T, Hisatsune C, Nagai T, Ebisui E, Mikoshiba K et al. Astrocyte calcium signaling transforms cholinergic modulation to cortical plasticity in vivo. J Neurosci 2011; 31: 18155-65.

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