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Studying the Alzheimer's disease continuum using EEG and fMRI in single-modality and multi-modality settings

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Abstract: Alzheimer's disease (AD) is a biological, clinical continuum that covers the preclinical, prodromal, and clinical phases of the disease. Early diagnosis and identification of the stages of Alzheimer's disease (AD) are crucial in clinical practice. Ideally, biomarkers should reflect the underlying process (pathological or otherwise), be reproducible and non-invasive, and allow repeated measurements over time. However, the currently known biomarkers for AD are not suitable for differentiating the stages and predicting the trajectory of disease progression. Some objective parameters extracted using electroencephalography (EEG) and functional magnetic resonance imaging (fMRI) are widely applied to diagnose the stages of the AD continuum. While electroencephalography (EEG) has a high temporal resolution, fMRI has a high spatial resolution. Combined EEG and fMRI (EEG–fMRI) can overcome single-modality drawbacks and obtain multi-dimensional information simultaneously, and it can help explore the hemodynamic changes associated with the neural oscillations that occur during information processing. This technique has been used in the cognitive field in recent years. This review focuses on the different techniques available for studying the AD continuum, including EEG and fMRI in single-modality and multi-modality settings, and the possible future directions of AD diagnosis using EEG–fMRI.

Keywords: Alzheimer's disease continuum; EEG–fMRI; multi-modality fusion; neuroimaging biomarkers

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1 Introduction

Over 55 million people worldwide live with dementia, and this figure is projected to reach 78 million by 2030. Alzheimer's disease (AD) is a predominant cause of dementia in people over the age of 65 years, and it accounts for 60–80 % of all cases of dementia (Serge Gauthier et al. 2021). On the basis of the fundamental research advances, AD does not have discrete and defined clinical stages. AD is a biological, clinical continuum that covers the preclinical, prodromal, and clinical phases of the disease (Aisen et al. 2017). Preclinical AD is conceptualized by an absence of cognitive unimpaired and the presence of evidence of cortical amyloid-β (Aβ) deposition, which is regarded as the most upstream process in the pathological cascade of AD (Jack et al. 2018, 2013). Subjective cognitive decline (SCD), a potential preclinical stage of AD, is defined as a self-experienced decline in cognitive function without evidence of objective cognitive impairment. This stage may increase the risk of progression to clinical AD (Dubois et al. 2016; Jessen et al. 2020, 2014; Rabin et al. 2017). About 50–80 % of elderly individuals (≥70 years) express several forms of a perceived decline in their cognitive functioning without any abnormal cognitive test results (Jessen et al. 2010; van Harten et al. 2018). A meta-analysis (Mitchell et al. 2014) showed that approximately 14 % of individuals with SCD decline into dementia and that in 27 % of individuals, SCD converts to mild cognitive impairment (MCI). MCI is considered a prodromal stage of dementia that is associated with objective cognitive impairment. However, it is characterized by the retention of essential day-to-day functioning independence and not meeting the criteria for clinically probable dementia (Petersen 2004; Winblad et al. 2004). About half of individuals with MCI will develop dementia within three years, and 6–15 % of patients with MCI convert to dementia per year (Breton et al. 2019). Therefore, SCD and MCI are

considered transitional stages between healthy aging and AD – related dementia. However, the low diagnostic rate and the absence of a cure substantially contribute to an increased socioeconomic burden and decreased quality of life, which necessitates an early diagnosis of preclinical stages of the AD continuum. Thus, finding the biomarkers, distinguishing the conversion from preclinical and prodromal stages to dementia, and diagnosing in a timely and accurate manner are vital to clinical practice.

The new diagnostic criteria indicate the importance of pathological changes, which coincides with the recently advanced theory that the pathological onset can precede the clinical manifestation of AD for many years (Dubois et al. 2016; Jack et al. 2018). Therefore, the asymptomatic stages of the AD continuum may be the potential and effective target periods for treatment. Currently, Aβ, p-tau, microRNAs, and inflammatory biomarkers are still common plasma biomarkers. Furthermore, some non-plasma biomarkers, such as ophthalmic, salivary, breath-related, and urinary biomarkers, could also reflect the early stages of AD (Chimthanawala et al. 2023). However, predicting reliable clinical trajectories of biomarker-positive asymptomatic individuals is currently unavailable (Dubois et al. 2021). Looking for reliable, non-invasively measured, reproducible peripheral biomarkers to address this gap is a great need, and this may necessitate a risk stratification of biomarkers.

From this point of view, electroencephalography (EEG) and functional magnetic resonance imaging (fMRI) have become important modalities for revealing changes in the brain function during the progression of AD from its preclinical stages. EEG has a high temporal resolution (on a millisecond timescale), but it is associated with a poor localization of signal sources. fMRI provides a submillimeter spatial resolution, but it does not provide adequate temporal sampling due to the slow hemodynamic response after the occurrence of changes in neural activity (Mele et al. 2019). For a more accurate diagnosis, combined EEG and fMRI (EEG–fMRI) has been extensively applied as an emerging technique to various diseased conditions, such as epilepsy (Omidvarnia et al. 2019; van Graan et al. 2015), sleep disorders (Li et al. 2022), and psychiatric diseases (Zotev and Bodurka 2020). This multimodal brain imaging technique provides an approach that takes advantage of the complementarity of information to overcome single-modality drawbacks and obtain multi-dimensional information simultaneously. Furthermore, it reveals the underlying mechanisms of the stages of the AD continuum and provides effective biomarkers.

Through a literature search, we found that there are fewer EEG–fMRI studies focused on cognitive diseases than those focused on epilepsy or sleep disorders. This raises the question of the presence of difficulties associated with studying the population with cognitive diseases. To this end, this article reviews the different techniques available for exploring the stages of the AD continuum, ranging from single modality-based techniques (EEG and fMRI) to dual modality-based techniques (including EEG and fMRI data collected asynchronously or simultaneously). This article also discusses the main research findings and the possible future directions.

2 Single modality

2.1 EEG

2.1.1 Resting state

EEG can offer an excellent temporal resolution. It can record the electric brain activity on a millisecond timescale using electrodes attached to the scalp. Conventional, quantitative, spectral analysis of a spontaneous electroencephalogram is the common and basic analytical approach. Furthermore, quantitative parameters on the spectrum of frequencies, amplitudes, and coherence can be achieved from EEG signals. The use of EEG rhythms as biomarkers for discriminating between healthy adults, individuals with MCI, and those with AD has been confirmed by some studies (Jackson and Snyder 2008; Lejko et al. 2020; McBride et al. 2014). EEG rhythms show age-related global slowing of brain activations (Celesia 1986), which might reflect alterations in neurotransmission and conduction velocity (Dustman et al. 1993). Decreases in the alpha and beta power and increases in the delta and theta power were reported by previous studies (Celesia 1986; Ishii et al. 2017; Vlahou et al. 2014). However, all these physiological EEG variations are pathologically more exacerbated in individuals with MCI and AD than in age-matched controls. The resting-state alpha rhythms of the global and posterior regions decrease gradually as people progress from healthy aging to MCI and then to AD (Lejko et al. 2020), and the decrease in alpha power and the increase in theta rhythm may play a role as possible markers for the onset of AD (Lejko et al. 2020; McBride et al. 2014; Prichep et al. 1994; Stam et al. 2005; van der Hiele et al. 2007). These results reflect a weakened state of arousal and cognitive processing. Other derangements include decreased complexity (Dauwels et al. 2010; McBride et al. 2014) and perturbed synchronization (Koenig et al. 2005; Stam et al. 2005). Moreover, the decrease in the resting-state EEG (rs-EEG) alpha rhythms may be more affected by the disease variants and cognitive deficits (Babiloni et al. 2015, 2021; Coben et al. 1985).

Another common analytical approach is microstates analysis, which models the brain electrical activity to be composed of a time sequence of non-overlapping microstates of variable duration (Lehmann et al. 1987; Lehmann and Skrandies 1980; Pascual-Marqui et al. 1995). In general, microstates are identified at the peaks of the global field power (GFP), and each microstate class is described by topography, mean duration, occurrence, and percentage analysis time occupied (Koenig et al. 2002). Furthermore, duration may be the key characteristic of a microstate, which aligns with the notion that precise timing is essential for the flow of information that is constantly processed by the brain to achieve perception, cognition, and ultimate consciousness (Van de Ville et al. 2010). However, studies on cognitive impairment showed inconsistent and, to some extent, conflicting results in the alteration of EEG microstates. Several studies found no significant difference in microstate parameters between patients with AD and healthy controls (HCs) (Grieder et al. 2016; Nishida et al. 2013; Schumacher et al. 2019). Because the results were not validated with clustering analysis, a shortening of EEG microstate duration in patients with cognitive impairment and AD was reported in a series of early studies, which used the approach of adaptive segmentation; when compared to young adults, there was no change in this parament with normal aging (Dierks et al. 1997; Stevens and Kircher 1998; Strik et al. 1997). Most recently, evidence showed that those basic metrics were significantly higher in patients with SCD, MCI, and AD than in HCs and that there was a positive correlation with cognitive impairment level (Lian et al. 2021; Musaeus et al. 2019, 2020; Smailovic et al. 2019; Tait et al. 2020). Unfortunately, regarding microstate syntax analysis, no consensus has been reached yet on whether or not the transition in AD is random. Nishida et al. first showed that the transition probabilities of patients with AD were indistinguishable from random transitions (Nishida et al. 2013).

In contrast, Schumacher et al. and Lian et al. demonstrated non-random transition probabilities in patients with MCI, those with AD, and healthy aging control, and there were no differences between them (Lian et al. 2021; Schumacher et al. 2019). Taking cholinergic medications, which can alter rs-EEG characteristics in patients with AD, may be a factor that leads to the opposite results (Babiloni et al. 2013b). Recently, some studies showed that EEG microstate topographies of microstate classes A, C, and D significantly deviate between controls and patients with SCD, MCI, and AD (Musaeus et al. 2019; Smailovic et al. 2019). These findings indicate that EEG microstates might be among the valid parameters of EEG analysis. Additionally, intracranial EEG (iEEG), which records electrographic activity across the subcortical areas through implanted electrodes, can provide more precise data on specific brain regions with a high temporal resolution. Although studies applied deep brain stimulation to patients with AD, such studies did not describe the alteration of iEEG findings (Lozano et al. 2016; Sankar et al. 2015). In brief, the diagnostic accuracy is limited due to the low spatial resolution.

2.1.2 Task state

Event-related potentials (ERPs) are ideal for assessing time-locked sensory, cognitive, or motor processing. The changes in different ERP components within the AD continuum have been reported. Early ERPs, including P50, N100, and P200, may be not ideal biomarkers in the AD continuum, due to they are mostly unaffected (Chang et al. 2014). However, there are still some studies found that significantly longer latencies and reduced amplitude for the N100 components among familial AD (Hirata et al. 2000; Olichney et al. 2006; Tarkka et al. 2002). With regard to the analysis of N200, P300, N400, and P600, varying degrees of amplitude and latency changes can be found in patients with preclinical AD, MCI, and AD. Among these ERP components, P300 is associated with cognition and memory, and it is the most extensively used ERP to study dementia and aging (Horvath et al. 2018). The topography on the scalp allows a distinction to be made between a more frontal early P3a component and a more parietally pronounced P3b component. The P3a component reflects automatic novelty detection, and P3b is associated with volitional deviant detection (Polich 2007). The latency of P300 increases in a linear fashion by approximately 1–2 ms per year in normally aging individuals (Fjell and Walhovd 2001), and patients with AD show a more prolonged P300 latency than HCs (Pedroso et al. 2012). Previous studies reported more prolonged P3a latency than P3b latency in patients with AD (Howe et al. 2014; Juckel et al. 2008). P300 changes can potentially differentiate between HCs, patients with MCI, and those with AD. Repeated sensory stimuli (e.g., visual and auditory stimuli) are the commonly used stimuli to evoke ERP components. However, many studies have demonstrated that the relative degree of sensitivity and specificity of auditory ERP to AD has yet to be high (Morgan and Murphy 2002).

Recently, increasing attention has been paid to the alteration of olfactory function through the AD continuum. Several lines of evidence have demonstrated the presence of neurofibrillary tangles in the olfactory bulb before the onset of typical symptoms (Kowalewski and Murphy 2012; Son et al. 2021). Additionally, odor identification dysfunction is an early marker that indicates AD pathology and predicts the development of dementia (Ubeda-Bañon et al. 2020; Wolfsgruber et al. 2020). Therefore, olfactory function tests

can detect the earliest sign of cognitive decline due to the anatomical proximity of the brain structures that control cognition and olfaction (Djordjevic et al. 2008; Jung et al. 2019; Mesholam et al. 1998). Several studies have focused on the role of olfactory ERP (OERP) test results as an early biomarker for AD. OERP test was employed to differentiate controls, patients with MCI, and those with AD (Invitto et al. 2018; Morgan and Murphy 2002).

2.2 fMRI

2.2.1 Resting state

fMRI, which uses the blood oxygenation level-dependent (BOLD) signal to reflect the changes in brain function, has been extensively used in patients with AD, and resting-state fMRI (rs-fMRI) is a task-free technique that can be easily applied to individuals with cognitive impairment to explore alterations in their intrinsic brain activity (e.g., regional homogeneity [ReHo] and amplitude of low-frequency fluctuation [ALFF]) and functional connectivity (FC). The FC of brain networks refers to inter-regional synchrony. Most studies were focused on the default mode network (DMN), frontoparietal/executive function network, dorsal attention network, ventral attention network, limbic network, somatomotor network, and visual network (McDonough et al. 2020). Hypoactivation, which is related to the function decreased in certain areas, is more commonly identified in patients with MCI/AD than in HCs. The implication of hyperactivation of some regions may be associated with compensatory responses to decreased function in other regions or other pathological changes (such as an early abnormal excitatory response to Aβ) (Gu and Zhang 2019).

Decreased ReHo in patients with MCI/AD was mainly found in the precuneus/posterior cingulate cortices, middle temporal gyrus, parahippocampal gyrus, and cingulate cortex (Liu et al. 2008, 2014). Additionally, a meta-analysis indicated that the severity of cognitive impairment in patients with amnestic MCI (aMCI) was associated with a decrease in ALFF in the cuneus/precuneus cortices (Pan et al. 2017). The impaired connectivity may exacerbate the effect of molecular pathology on cognitive function in patients with MCI and AD. Therefore, many studies examined brain network alterations in patients with cognitive impairment, which showed abnormal regional brain activation and large-scale brain networks. There has been consistent evidence of a lower FC in the frontoparietal network (FPN) and DMN of patients with AD than in that of HCs (Badhwar et al. 2017; Gu and Zhang 2019; Lau et al. 2016; Li et al. 2015; Wang et al. 2018). Furthermore, hypoactivated regions could also be found in the visual network of patients with AD (Talwar et al. 2021). On the contrary, MCI-related increased activation was found in specific brain regions, such as the inferior parietal lobule, superior parietal lobule, and right lingual gyrus (Gu and Zhang 2019; Pan et al. 2017). In brief, in patients with MCI/AD, brain activity mainly decreased, and few brain regions showed hyperactivity. The inconsistent conclusions might be explained by the use of small sample sizes and the inability of a single neuroimaging biomarker to accurately predict early AD risk and the conversion of MCI to AD, which indicate the urgent need for more effective imaging biomarkers.

Some studies identified the alteration of resting-state olfactory-related regions, which results from AD-related pathology that damages the primary and secondary olfactory areas and the neocortical association areas (Murphy 2002). Lu et al. used rs-fMRI data from the Alzheimer's disease neuroimaging initiative (ADNI). They found that the resting-state FC (rs-FC) between the olfactory network and the hippocampus was disrupted in patients with MCI (Lu et al. 2019). Similar to the conclusion reported by Chen et al., they found that the increased ALFF and ReHo and the decreased FC of olfactory-associated regions became increasingly severe in patients with SCD, MCI, and AD (Chen et al. 2022). These results highlight the ability of fMRI to identify abnormalities in the olfactory-related areas, which help differentiate between disease statuses.

2.2.2 Task state

The common fMRI task types include working memory, memory encoding, memory retrieval, executive function, language processing, emotional processing, attention, and visuospatial processing. A meta-analysis of 75 task-based fMRI studies revealed that hypoactivation in patients with MCI was mainly found in the frontoparietal, default, and visual networks, while in patients with AD, it was located in the visual, default, and ventral attention networks. MCI and AD-related hyperactivation fell in the frontoparietal, ventral attention, default, and somatomotor networks (Li et al. 2015).

In addition to the frequently used task types, some novel techniques such as odorant-induced brain activation are applied to patients with AD. Stiffener et al. (2021) found that patients with AD exhibit worse odor-detection-related brain activity in the primary olfactory cortex and secondary olfactory regions than HCs. Furthermore, their results indicated that entorhinal cortex (EC) activity best differentiates individuals with AD from healthy adults. A more comprehensive recruitment of the EC during odor detection tasks may represent a compensatory response to disease progression. Although the use of resting-state or task-based

fMRI as a neuroimaging biomarker showed promising results, in order to acquire more consistent results, improving the implementation is necessary. The findings discussed so far suggest that the diagnostic ability of a single modality could be improved by using these techniques in conjunction with each other.

3 EEG and fMRI data collected asynchronously

3.1 Resting state

A single neuroimaging technique is not sufficient to fully reveal the underlying pathological alterations of AD. Notably, combining two heterogeneous data sources allows for significantly improved diagnostic and differential diagnosis accuracies (Colloby et al. 2016; Ferri et al. 2021; Patel et al. 2008; Polikar et al. 2010) and low variability (Jesus et al. 2021), and these features indicate the advantages of monitoring AD progression. Therefore, scientists tried integrating two modalities and evaluating the relationship between EEG abnormalities and brain structure (anatomical MRI) changes in every AD stage. At the early stage of AD pathology, atrophy can be found in the Papez circuit (this involves the hippocampus, fornix, mammillary bodies, anterior thalamic nuclei, and posterior cingulate region), which is critical for episodic memory (Aggleton et al. 2016). Furthermore, the hippocampus is one of the first and most affected brain regions in patients on the AD continuum, and the neuronal loss in the hippocampi that is associated with theta activity was initially confirmed by autopsy in patients with AD (Rae-Grant et al. 1987). Moreover, several studies found that progressive hippocampal atrophy corresponded with decreased cortical alpha power (parietal, occipital, and temporal regions) and increased bilateral frontal theta rhythm in the continuum along MCI and AD conditions (Babiloni et al. 2009; Grunwald et al. 2001, 2007; Moretti et al. 2007). The amygdala-hippocampal complex plays a role in memory formation, and its atrophy is correlated with an increase in theta/gamma and alpha3/alpha2 ratios and cognitive decline (Moretti et al. 2009). The neuronal loss arises also in the thalamus and basal ganglia in patients with AD. Moreover, it has been shown that the increased alpha3/alpha2 ratios are related to the minor atrophy of bilateral caudate nuclei and accumbent nuclei in the basal ganglia and that of the pulvinar nuclei in the thalamus (Moretti et al. 2012). Babiloni et al. showed that for cortical and occipital gray matter, the atrophy is correlated with the increased delta power and the decreased alpha1 power (Babiloni et al. 2013a, 2015). However, Hampel et al. showed that posterior interhemispheric coherences (alpha2 and beta1 band) were significantly positively correlated with total and posterior callosal sizes in patients with AD, which are mainly affected by the integrity of the long commissural fibers connecting the hemispheres through the callosum (Hampel et al. 2002). Mattia et al. reported contrary results of the absence of a correlation between EEG rhythms and brain atrophy. They showed that a lower level of hypoperfusion correlates with the higher theta and the lower alpha frequency bands distributed over the anterior/central and central regions within the brains of patients with AD (Mattia et al. 2003).

Combining rs-EEG and fMRI is a promising approach for exploring neurodegenerative disease. The study by Cakir showed that the decrease in the synaptic strength between the neurons in the striatum has a dominant effect on the slowing of alpha rhythm and that this decrease also causes a reduction in the fractional ALFF (fALFF) of the slow-4 band in the striatum (Cakir 2020). fMRI-driven EEG analysis, a common analytical method in EEG–fMRI integration, highlights the role of the alpha2 band density as a potential neurodegeneration biomarker by correlating it with disease progression (Cecchetti et al. 2021). And there are several models have been presented for studying the relationship between EEG and BOLD signals. For instance, Sotero et al. proposed a model that had the potential to predict EEG and BOLD responses in AD patients (Sotero and Trujillo-Barreto 2008). EEG and MRI data fusion improved the understanding of the correlation between brain electrical activity and brain structural changes in the AD continuum.

3.2 Task state

On the basis of the results obtained in the resting state, the relationship between EEG and MRI under task state was applied in some studies on the AD continuum. Yener et al. reported that frontal delta event-related oscillations (EROs) following visual oddball targets represent a functional positive correlation with cortical frontal neurodegeneration, which may indicate a conversion from a healthy state to MCI (Yener et al. 2016). Increased task-related activation of motor imagery (as indexed by ERP amplitude) in patients with aMCI significantly mediated the association between increased gray matter and cognition (Chen et al. 2020). However, because the data are collected separately, although the subjects complete the same task, differences are expected due to the state of the subjects and the surrounding environment.

4 Simultaneous EEG–fMRI acquisition

4.1 Resting state

Simultaneous EEG–fMRI acquisition allows us to overcome the intrinsic limitations of both techniques and to obtain high temporal-spatial resolution information. However, because of the strict equipment requirements, data acquisition process, and data analysis associated with this technique, only some studies have investigated the AD continuum by acquiring EEG and fMRI simultaneously. The characteristics of the selected articles are listed in Table 1.

The current studies mainly focus on the correlation between the BOLD signal and EEG metrics (majoring rhythm and microstate). Brueggen et al. reported the first study that compared the AD population to healthy elderly individuals using EEG and fMRI simultaneously. They showed that positive associations of the alpha rhythm with BOLD activity decreased significantly in the thalamus, inferior temporal lobe, and frontal cortex in the AD population (Brueggen et al. 2017). Furthermore, more positive associations were found within the upper alpha band (10–12 Hz) in HCs than in patients with AD, which indicates the necessity to differentiate the alpha band into sub-bands and the possibility of identifying older individuals at the risk of AD progression by using EEG upper/low alpha power ratio (Moretti 2015). Similarly, in a study by Michels et al., unlike HCs, patients with MCI lacked thalamocortical alpha-BOLD signal-coupling, which supports the view that this disturbed positive correlation might be a sign of altered neurophysiological processing (Michels et al. 2021). DMN, salience network, FPN, and thalamus also displayed differences in EEG–fMRI signals. In addition, beta-amyloid confirmed the association with the abnormal functional connectivity of the DMN in the AD continuum (Mormino et al. 2011; Quevenco et al. 2020; Sheline et al. 2010; Sperling et al. 2009) and affects EEG metrics (Michels et al. 2017). On the basis of these conclusions, Michels et al. reported the first study that investigated

Table 1: Characteristics of simultaneous EEG–fMRI studies about AD continuum.

Reference	Type of Study	Number of participants	Age in years (mean ± SD)	Sex (M/F)	Education in years (mean ± SD)	MMSE score (mean ± SD)	State	Primary purpose
Brueggen et al. 2017	Case-control study	AD = 14	75.3 ± 5.7 (range: 64–82)	10/4	14.4 ± 2.7 (range: 8–17)	24.6 ± 3.1	Resting	To investigate the association of alpha-band power and BOLD signal in the DMN, thalamus, and occipital cortex
		HC = 14	73.4 ± 3.1 (range: 68–79)	10/4	13.6 ± 2.8 (range: 11–20)	28.7 ± 0.8		
Teipel et al. 2021	Case-control study	Same sample as Brueggen et al. 2017					Resting	To investigate whether the time courses of EEG microstate topologies correlate with the time courses of spatially corresponding fMRI networks and if these correlations differ between patients with AD and controls
Michels et al. 2021	Case-control study	MCI = 14	75.6 ± 8.9	9/5	14.2 ± 3.8	28.5 ± 1.6	Resting	1. To compare fMRI and EEG–fMRI signal differences between healthy elderly individuals and patients with MCI using 64-channel EEG recordings
		HC = 21	71.8 ± 4.2	14/7	14.6 ± 2.9	29.6 ± 0.7		2. To dissociate fMRI and EEG–fMRI signal-coupling differences between individuals with significant amyloid-beta deposition (MCI and HC combined) from HCs with low amyloid deposition
Shu et al. 2021	Case-control study	aMCI = 26	62.35 ± 6.34	10/16	9.58 ± 1.60	27.38 ± 1.53	Task	To explore whether the temporal dynamics of brain episodic retrieval activity were disturbed in patients with aMCI
		HC = 29	60.48 ± 6.22	11/18	10.95 ± 1.78	28.9 ± 1.01		

MMSE, minimum mental state examination; HC, healthy control; MCI, mild cognitive impairment; aMCI, amnestic mild cognitive impairment; AD, Alzheimer's disease.

the impact of high cerebral amyloid deposition on simultaneous EEG–fMRI signals. As expected, aberrant EEG–fMRI signal coupling can be found in the visual network, FPN, para-hippocampus, cerebellum, and brain stem. Alterations from subcortical regions were detected, which indicates that EEG–fMRI is sensitive to disease-related functional alterations in individuals with abnormally high amyloid levels.

As mentioned above, although EEG microstate analysis is a common method, to date, only one study analyzed the association between the time courses of EEG microstate topologies and the time courses of spatially corresponding fMRI networks using simultaneous EEG–fMRI recordings in patients with AD (Teipel et al. 2021). Teipel et al. found that an anteriorization of the microstate topology in AD is accompanied by corresponding spatial expression changes in rs-fMRI networks, which represent those microstates as building blocks of brain FC. With regard to the strengths analysis of correlations, a less negative correlation between the anterior microstate 1 and posterior rs-fMRI networks was found in patients with AD than in cognitively healthy aging controls. The predominant degeneration of long-reaching intracortical projections in AD may lead to this result. Of course, this conclusion needs to be verified in future studies.

4.2 Task state

Although various analytical methods that integrate separately collected EEG and fMRI signals exist, the differences in acquisition times and environments may influence patients' mental states and lead to inaccuracies in data, especially in the task state. Simultaneous task EEG–fMRI allows the establishment of the cerebral regions that are assigned to the specific task and the precise linkage of electric signals with the BOLD signals. Until now, only one study compared the spatiotemporal characterization of episodic retrieval patterns between healthy elderly subjects and patients with aMCI via simultaneous task EEG–fMRI technique (Shu et al. 2021). In that study, the sequence of the verbal retrieval task is the rest phase, study phase (40 different nouns), distracter task, and retrieval phase (40 studied + 40 unstudied nouns). Finally, fMRI-constrained ERP analysis revealed that the temporal dynamics were impaired in the left inferior parietal lobule and the left lateral prefrontal cortex in patients with aMCI. Using ERP-informed fMRI analysis, diminished precuneus activity was found in subjects with aMCI, which indicated that familiarity-related processing was impaired.

This small volume of literature suggests that the simultaneous EEG–fMRI enables us to explore the changes in the fMRI correlate of the EEG/ERP components and provides an approach to establish a link between the electrophysiological properties and hemodynamic activities.

4.3 Strengths and limitations of the currently available studies on EEG–fMRI in the context of AD

Facilitating the early diagnosis and screening in high-risk groups for AD is an advantage of EEG–fMRI (Brueggen et al. 2017; Michels et al. 2021; Shu et al. 2021; Teipel et al. 2021) (Figure 1). Furthermore, simultaneous EEG–fMRI is notably more advantageous than single-modality testing or the integration of two separate sets of data. For instance, EEG–fMRI guarantees that a participant is examined with two different modalities in the same environment, position, and mindset, with the same fluctuations in their attention levels and comfort, while eliminating habituation effects and shortening the total experimental time. These advantages of synchronous recording are more pronounced when the recordings occur in patients with cognitive instability under different environments (Debener et al. 2006).

The brain regulates its oxygen supply via a process called neurovascular coupling (NVC), whereby active neurons signal to dilate local blood vessels, and this leads to an increase in blood flow and the supply of oxygen and glucose to these active brain areas, which is called functional hyperemia (Shaw et al. 2021; Zhu et al. 2022). The pathology of AD follows a typical spreading pattern through the brain. However, the first affected area in the AD spectrum is still unclear. Neurovascular uncoupling may occur before the occurrence of pathological changes, which makes it possible to apply EEG–fMRI for detecting early imaging biomarkers of AD. On the basis of what the data represents, some researchers tried to combine EEG and fMRI data to evaluate the NVC in the human brain (Jafarian et al. 2020; Van Eyndhoven et al. 2021). It is promising to identify the lesion site of AD on the basis of NVC changes in the early stage and then treat it with targeted therapies, such as transcranial magnetic stimulation (TMS), transcranial electrical stimulation, and transcranial direct current stimulation (Chu et al. 2021; Menardi et al. 2022). When multiple locations are involved, it helps to select the optimal therapeutic target.

However, it is necessary to consider the limitation of simultaneous recording. Safety should come first. Although MRI-compatible EEG devices have matured, improper use of these devices may lead to potential risks. For example, heating conducting leads during MR radio frequency transmission may result in discomfort to patients or even burns, especially in children and vigilance-reduced subjects

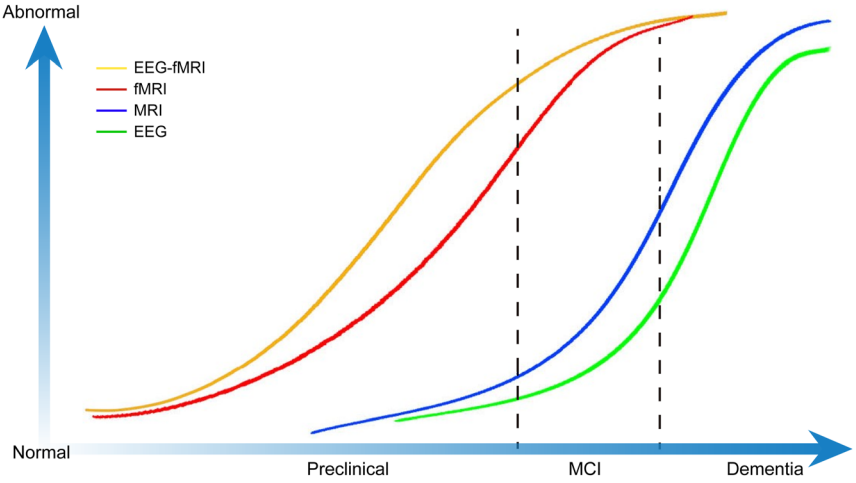

Figure 1: Alzheimer's disease continuum with corresponding pathological changes.

(Kugel et al. 2003; Mele et al. 2019). Regarding technological issues, the presence of the helmet produces a variation in the magnetic field homogeneity, which involves changes in image quality. Consequently, broad-band artifacts generated from the magnetic field may cover the EEG signal (Steyrl and Müller-Putz 2019), which may result in gradient artifacts, pulse-related artifacts, and motion-related artifacts. Furthermore, the data quality directly affects the interpretation of the results.

The scarcity of AD-related EEG–fMRI studies and the small sample sizes used influenced the interpretation of the results, even though some of the studies were of high sample quality. Few studies applied simultaneous task-state EEG–fMRI to patients with AD. The possible reason is the poor compliance of subjects. The duration and comfort of the EEG–fMRI test may significantly affect the subjects' tolerance. Therefore, a reasonable paradigm design by researchers and a good understanding of experimental procedures by subjects will substantially promote the progress and success rate of the experiment, especially the task-state experiments. Although there are various experimental paradigms for ERP or task-fMRI, until now, only one simultaneous task-state EEG–fMRI study applied to AD patients, which used the episodic retrieval paradigm, a word-list memory retrieval task (Shu et al. 2021). This shows the difficulty of paradigm design for task-state EEG–fMRI.

5 Future potential of EEG–fMRI in exploring the AD continuum

5.1 Combining TMS with EEG–fMRI

Non-invasive TMS is a neuromodulation technique. Accumulating evidence from clinical and animal studies has shown that TMS is a promising technique for treating and diagnosing mild and moderate AD (Chou et al. 2020; Lin et al. 2021; Rajji 2019). EEG–fMRI mainly bridges the relationship between brain operations and behavioral processes. Furthermore, the real-time neural effects induced by TMS still need to be clarified with concurrent imaging studies. Therefore, researchers began to test the feasibility of using EEG–fMRI for this purpose.

Peters et al. first confirmed the feasibility of the three-way combination of TMS–EEG–fMRI (Peters et al. 2013), which improves the accuracy of individualizing the involved cortical area to a specific cognitive task (Esposito et al. 2020). Cortical coordinates for TMS–EEG are derived from the co-registration of fMRI for detecting task-based activation, as well as structural imaging of each individual. Guiding TMS with EEG–fMRI can provide spatiotemporal resolution information on where, when, and how to apply the stimulation, which enhances the precision of TMS.

In addition, TMS has excellent potential as a novel biomarker for diagnosing the stages of the AD continuum. TMS pulses can be used as system probes, which manipulate brain activity as an independent variable to transiently induce "virtual lesions" to stimulate neural populations, enhance or decrease cortical excitability, and even induce local oscillations (Peters et al. 2013). Concurrent EEG permits the capture of fast neuronal fluctuations evoked by TMS. Numerous studies assessed the alteration of neuroexcitability, neurotransmission, and neuroplasticity by TMS–EEG in the AD spectrum, while some of the results are still controversial (Mimura et al. 2021). As a compensatory tool, fMRI monitors the TMS-evoked propagation patterns with high spatial resolution. Recently, Peters et al. showed that a stronger pre-TMS alpha power could reduce TMS-evoked hemodynamic activation throughout the bilateral corticocortical motor system through concurrent

human TMS–EEG–fMRI, which indicated the TMS–EEG–fMRI integrative approach makes it possible for precise and direct monitoring of causal dependencies between oscillatory states and signal propagation throughout cortico-subcortical networks (Peters et al. 2020).

5.2 MRI–PET–EEG

The feasibility of measuring accompanying MRI–PET–EEG data in a single session has already been reported in normal participants and different disease conditions. Rajkumar and Shah first reported simultaneously acquired trimodal data (MR–PET–EEG) in 11 healthy volunteers and revealed significantly higher metabolic activity in the DMN of the brain in comparison to structures outside the DMN (Rajkumar et al. 2021; Shah et al. 2017). Golkowski et al. collected 20 patients and determined the potential contribution of simultaneous FDG-PET/fMRI/EEG assessment for the diagnosis and prediction of prognosis in patients with disorders of consciousness (Golkowski et al. 2017).

For the AD continuum, several biomarkers, such as perfusion, glucose metabolism, Aβ, and tau protein deposition, have been included in the revised diagnostic criteria for the AD continuum as essential biomarkers for improving diagnostic accuracy (Dubois et al. 2021). Positron emission tomography (PET), as a non-invasive imaging technology, offers this valuable information to a great extent with the location of pathology. Currently, ^{18}F-fluorodeoxyglucose (^{18}F-FDG)-PET, amyloid-PET, and tau-PET imaging studies are applied to the early diagnosis and longitudinal monitoring of AD. However, the limitations of these techniques cannot be ignored, such as diagnostic inaccuracy and weak correlation between Aβ deposition and disease severity (van Oostveen and de Lange 2021). It is necessary to obtain multi-dimensional information about AD. Thus, combining PET with EEG–fMRI has recently gained attention. The main advantage is that pathological and metabolic changes can be recorded simultaneously with structural, functional, and electrophysiological information under the same psychological and physiological conditions. A study confirmed that multimodal EEG, MRI, and PET data fusion can improve diagnostic accuracy by up to 10–20 % (Polikar et al. 2010). Hampel et al. showed that neocortical neuronal loss has potential as a vivo biomarker for AD by utilizing multimodal evidence from PET, MRI, and EEG (Hampel et al. 2002). Recently, Van et al. focused on the link between cortical excitability using TMS-evoked EEG potential over the frontal cortex, $^{[18F]}$THK5351 PET signal in the brainstem monoaminergic gray matter, and MRI, and found that brainstem tau neurofibrillary tangles and neuroinflammation correlated with the increased excitability in the earliest stages of AD neuropathology (Van Egroo et al. 2021). However, both studies did not involve simultaneous recording of multimodal data.

5.3 Electrical impedance tomography

Multi-modality fusion has the potential to provide insights into brain function in patients with AD. However, we must acknowledge that the EEG data recorded inside the MR environment is subject to significant noise sources. Thus, the scalp electrical signals collected from simultaneous EEG–fMRI still need to be improved, even after artifact elimination. Additionally, electrical impedance tomography (EIT) is probably a way to reduce partial artifacts in the future.

The magnetic field may have effects on the intracranial currents of subjects. As we know, EIT is a non-invasive and non-radiational imaging technique that mathematically reconstructs images of a region of interest based on the electrical conductivity of biological tissue (Mansouri et al. 2021). Fabrizi et al. proposed a method, using which EIT and EEG could be acquired simultaneously after filtering EIT artifacts from the EEG signal (Fabrizi et al. 2006). Thus, it may be feasible to introduce the concept of electrical impedance into the artifact reduction method of EEG–fMRI. The magnetic field can be regarded as the input current, and then the voltage signals are acquired via scalp electrodes. More clear data can be obtained by calculating and eliminating these voltage signals from EEG data. It would be a promising method to apply to simultaneous EEG–fMRI.

6 Conclusions

Combined EEG and fMRI (EEG–fMRI) can overcome single-modality drawbacks and obtain multi-dimensional information simultaneously, and it can help explore the hemodynamic changes associated with the neural oscillations that occur during information processing. Furthermore, simultaneous EEG–fMRI acquisition has shown significant advantages in the early detection of possible markers of AD. Early identification of brain function impairment, screening of individuals at a high risk of AD, and even locating the neurodegenerative sites will be the main clinical application of EEG–fMRI in older adults and patients with cognitive impairment. However, characterizing molecular processes for resting-state analysis or a specific task is not achievable through EEG–fMRI, even if these tools have a high temporal-spatial resolution. The question of the best integrated and

standardized analysis of EEG-fMRI for the patients of AD still needs to be explored and represents a real challenge posed by the development of the technology. Therefore, in the future, trimodal approaches which provide a comprehensive analysis of the brain network, brain microstate, and the dynamic process of information processing have the potential to help improve our understanding of the disease transformation process.

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