

# Role of Magnetoencephalography in the Early Stages of Alzheimer Disease



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## KEYWORDS

- Magnetoencephalography • Mild cognitive impairment • Preclinical stages • Prodromal stages
- Functional connectivity • Power • Alzheimer disease

## KEY POINTS

- Alzheimer disease (AD) can be understood now as a continuum where mild cognitive impairment (MCI), is one of the key stages.
- The most frequently used AD biomarkers are devoted to the detection of A $\beta$  deposition and tau pathology by means of cerebrospinal fluid analysis or PET imaging (ie, PET-amyloid or PET-tau).
- The role of electroencephalography and magnetoencephalography in the diagnosis and investigation of the AD-continuum is growing and better defined.

## INTRODUCTION TO ALZHEIMER DISEASE

Alzheimer disease (AD) is the most common cause of dementing illness around the world and comprises 60% of all dementia cases.<sup>1</sup> The risk of developing AD increases with age. This is a crucial issue considering the tendency to older populations in the western countries, and consequently AD became one of the main health challenges of our societies. From a neurobiological perspective, AD is characterized by the accumulation of amyloid-beta (A $\beta$ ) protein, the hyperphosphorylation of tau protein and neuroinflammation. These pathologic processes are believed to lead to a synaptic dysfunction/neurodegeneration and finally to neural death and severe cognitive deterioration. A closely related concept, now involved in the so-called AD-continuum, is mild cognitive impairment (MCI). MCI was a term initially used to describe the transitional state between a

healthy cognitive status and dementia. Patients with a diagnosis of MCI were considered at a higher risk of developing AD, with a much higher conversion rate to dementia when compared with healthy controls.<sup>2</sup> With the progression of research, it appeared more and more clear that MCI was a too unspecific concept, with subjects showing different courses, including the reversion to a cognitively “normal” condition. Recent diagnosis criteria stressed the importance of a correct detection of the actual underlying pathology that is producing the cognitive manifestations, leading to concepts such as “MCI due to AD” or “prodromal AD.”<sup>3,4</sup> The detection of these prodromal or predementia cases is essential, and the electrophysiological techniques demonstrated a notable performance (see later in this article).

Currently, the most frequently used AD biomarkers are devoted to the detection of A $\beta$  deposition and tau pathology by means of

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cerebrospinal fluid (CSF) analysis or PET imaging (ie, PET-amyloid or PET-tau). PET with fluorodeoxyglucose is considered a marker of synaptic dysfunction, whereas MR imaging volumetry is the most common measure of atrophy (for a full perspective on these issues see Refs.<sup>5–7</sup>). Other techniques might allow an additional assessment of some of these basic pathologic changes. As previously noted, synaptic dysfunction is one of the earliest manifestations of AD pathology. In this regard, electroencephalography (EEG) and magnetoencephalography (MEG) are capable of detecting the synchronized oscillatory activity of thousands of neurons that relies on the integrity of neural connections. Moreover, both techniques measure neural activity directly and with millisecond temporal resolution.<sup>8</sup> Despite these clear advantages, the role of EEG and MEG in the diagnosis and investigation of the AD-continuum is not well defined. As Stam<sup>9</sup> pointed out in his excellent review on the role of EEG in dementias, some investigators claimed that such a role may be limited to exclude rare neurologic conditions. On the contrary, Winblad and colleagues<sup>10</sup> suggested that a relevant focus of AD/MCI research should be the development of guidelines for neurophysiological evaluation techniques, as they are cheaper and totally noninvasive compared with CSF or PET-derived biomarkers, whereas their sensitivity is very similar.<sup>9</sup> In the next pages we present some of the evidence that may support the affirmation of Winblad and colleagues.<sup>10</sup>

### ELECTROPHYSIOLOGICAL CORRELATES IN THE ALZHEIMER DISEASE SPECTRUM

The “abnormalities” of EEGs of patients with AD were first described by Hans Berger.<sup>11,12</sup> After a century of EEG investigations, the pattern of resting-state brain electrical activity in AD has been characterized in terms of a gradual and relatively diffuse “slowing.” Overall, the literature on spectral measures revealed a progressive increase of the absolute and relative power in delta and theta bands and a power decrease in alpha and beta within patients with AD, usually focused in the temporoparietal and occipital regions.<sup>13–16</sup> Perhaps one of the most straightforward procedures to perceive this pattern of slowing is the calculation of the alpha peak frequency. A slowing of the alpha peak (typical range 8–13 Hz) has been observed in normal aging.<sup>17</sup> The alpha peaks in patients with AD exhibit a more pronounced “shift to the left,” sometimes interpreted as support for the hypothesis of an accelerated aging process. In fact, abnormally low alpha peak frequencies are usually described in patients with AD.<sup>18</sup> In

addition, the sources of alpha activity may move to a more frontal localization, the so-called “frontalization” of alpha, and such shift to anterior regions seems to correlate with the severity of the disease.<sup>19</sup> Of note, subjects with MCI tend to show an intermediate situation between patients with AD and healthy controls in the previously described measures.

This evidence may be solidly based on 2 physiologic determinants that could explain the slowing of brain electrical activity in AD. The first candidate is a cholinergic deficit. Some classic studies<sup>20,21</sup> reported a significant correlation between loss of cholinergic neurons, reduced acetylcholinesterase levels, and delta power in patients with AD. This correlation was experimentally supported in animal and human models by the administration of scopolamine (a cholinergic antagonist) infusions that generated an increased delta and theta power.<sup>22</sup> However, some other investigations revealed that a more widespread neurodegenerative process involving cholinergic, monoaminergic, glutamatergic, and even other neurotransmitter systems are necessary to produce the frequency slowing.<sup>23</sup> A complementary hypothesis relies on the notion that AD can be considered a disconnection syndrome.<sup>24</sup> It is well-known that corticothalamic deafferentation and white-matter lesions produce a typical pattern of polymorphic delta activity described by Gloor and coworkers.<sup>25</sup> Holschneider and Leuchter<sup>26</sup> claimed that such a disconnection syndrome could play a role not only in the increased delta activity but also in the decreased beta activity observed in AD.

Following this reasoning thread, it is not surprising that the brain activity slowing in AD correlates with other manifestations of the disease, such as cortical and hippocampal atrophy (signs of neurodegeneration) or cognitive performance.<sup>27,28</sup> From a genetic perspective, Lehtovirta and colleagues<sup>29,30</sup> described an extra slowing of the EEG spectrum in patients with AD carrying the APOE4 allele, in comparison with noncarriers, that was explained by the influence of APOE on cholinergic neuron functioning.

### MAGNETOENCEPHALOGRAPHY CORRELATES OF ALZHEIMER DISEASE

Similar to EEG, MEG is a noninvasive technique that offers a direct measure of neural activity. MEG is a young technique as compared with EEG, and its application to the AD-continuum has been relatively recent. In fact, the first papers devoted to the investigation of AD by means of MEG appeared in the late 1990s.<sup>31,32</sup> In the forthcoming pages it will be shown that most of the

previously described EEG evidence of electrophysiological changes in AD have been replicated by MEG studies. Notwithstanding, it is important to bear in mind that MEG has some technical features due to physical properties of the magnetic fields, such as the more accurate source reconstruction and the sensitivity to a broader frequency spectrum, that offer an important advantage as compared with EEG. In this section, the studies of spectral variations observed in AD and its prodromal stages (both in sensor and source space), as well as functional networks research are reviewed. Of particular interest are the follow-up studies investigating MEG markers of progression to AD.

### ***Resting-State Magnetoencephalography Spectral Analysis***

As previously noted, MEG studies virtually mirrored the results obtained by EEG. Berendse and coworkers<sup>33</sup> demonstrated in early investigations that brain activity slowing was also reproduced in MEG recordings. When an exhaustive frequency analysis was accomplished, the relative power in 2 intervals (2–4 Hz and 16–28 Hz) allowed a correct classification of healthy controls and AD cases.<sup>34,35</sup> In addition, mean frequency analysis also supported a progressive slowing, not only in patients with AD but also in MCIs, with the latter group exhibiting an intermediate position between ADs and controls<sup>34,35</sup> (Table 1). This study confirmed the progressive “shift to the left” of the dominant alpha activity with the progress of the disease. Interestingly, when the MCI subtype was considered, the amnesic multidomain cases showed increased delta and theta power as compared with the single-domain cases, thus indicating that brain activity slowing in multidomain MCI resembled the typical pattern observed in AD.<sup>36</sup>

All the preceding MEG studies were performed in the sensor space. However, as was previously stressed, MEG offers a clear advantage in terms of source localization as compared with EEG. In this vein, Fernández and coworkers<sup>37</sup> performed the first MEG source localization of delta and theta activity in AD, demonstrating a significant increase within temporoparietal regions that correlated with cognitive status. Mirroring EEG, that temporoparietal low-frequency activity correlated with hippocampal atrophy, but more importantly, a combination of MEG and volumetric data allowed the correct classification of 87.1% of patients with AD vs controls.<sup>38</sup> Osipova and coworkers<sup>39,40</sup> confirmed that alpha sources in posterior brain regions were substituted by lower frequencies in

ADs but the evidence was not reproduced in MCI cases. Engels and coworkers<sup>41</sup> showed that the pattern of slowing observed in AD was present not only at the cortical level but also in the hippocampus, as evidenced by means of the utilization of virtual electrodes.

Recently, this line of research has been extended to earlier stages, such as subjective cognitive decline (SCD). It is well-known that SCD increases the risk for developing dementia; however, this population cannot be considered as having any memory problem because patients perform within the average on standard neuropsychological tests. It was of great interest to see whether that “average” behavioral performance was accompanied by some type of differential feature at the neurophysiological level. López-Sanz and colleagues<sup>42</sup> showed how patients with SCD exhibited a decreased alpha power over bilateral prefrontal areas, bilateral middle and superior temporal lobe, and also bilaterally over calcarine fissure and cuneus in the occipital lobe. In a subsequent study, López-Sanz and colleagues<sup>43</sup> scanned with MEG 252 older adults (70 healthy controls, 91 SCD, and 91 MCI). Alpha relative power in the source space was used to train a LASSO classifier and applied to distinguish between healthy controls, and SCD and MCI patients. The reduction of the alpha band power was able to classify subjects with SCD with an area under the curve (AUC) of 0.81. When unseen data were classified, the AUC went to 0.75, which is still a high rate for blind approaches.

### ***Functional Network Disruption in the Disease Process***

Amyloid deposition may have a toxic effect on inhibitory terminals,<sup>45</sup> impairing the normal balance between excitation and inhibition of neuronal activity, increasing neuronal excitability and damaging neural network function.<sup>46–48</sup> Tau deposition disrupts axonal microtubule organization<sup>49</sup> and its deposits correlate with cognitive impairment<sup>50</sup> and network dysfunction.<sup>51</sup> This progressive loss of synaptic efficiency disrupts interregional and intraregional communication, leading to the proposal that AD is a disconnection syndrome.<sup>52,53</sup> Pathologic changes associated with AD, such as amyloid deposition, start decades before the first clinical symptoms appear, and most clinically relevant functional loss is thus far irrecoverable once the disease process has gone unchecked. Therefore, this depletion of the inhibitory activity could lead to increased brain activity not associated with better cognitive function.<sup>54</sup>

**Table 1**  
MEG studies in preclinical AD and MCI

Author	Comparison	Sample Size	Methodology	Result
Bajo et al, <sup>59</sup> 2010	MCI vs CN	22 MCI, 19 CN	Sensors, Task, MEG, FC	Increased long-distance interhemispheric FC and decreased anteroposterior FC.
Buldú et al, <sup>56</sup> 2011	MCI vs CN	19 MCI, 19 CN	Sensors, Task, MEG, Graphs	Increased network strength and outreach.
Cuesta et al, <sup>69</sup> 2015	MCI vs CN f(ApoE)	20 MCI $\epsilon$ 4–, 16 MCI $\epsilon$ 4+, 8 CN $\epsilon$ 4+, 19 CN $\epsilon$ 4–	Sources, Resting, MEG, FC	Decreased alpha and beta hippocampal and IPL FC in MCI. Decreased delta FC in ApoE34. Dual increased/decreased FC pattern affecting frontal/temporal regions.
Cuesta et al, <sup>70</sup> 2015	MCI vs CN f(ApoE)	20 MCI $\epsilon$ 4–, 16 MCI $\epsilon$ 4+, 6 CN $\epsilon$ 4+, 19 CN $\epsilon$ 4–	Sources, Resting, MEG, Power	Increased theta power in CN ApoE34, and extra slowing in MCI ApoE34.
Fernández et al, <sup>35</sup> 2006	AD vs MCI vs CN	22 AD, 22 MCI, 21 CN	Sources, Resting, MEG, Median frequency	Slowing of the mean frequency with the progression of the disease. MCI intermediate position between AD and CN.
López et al, <sup>36</sup> 2014	MCI subtypes vs CN	33 a-sd-MCI, 36 a-md-MCI, 36 CN	Sources, Resting, MEG, Power	Low-frequency increase in both MCI groups. The a-md-MCI group showed an extra slowing that correlated with cognitive status.
López-Sanz et al, <sup>42</sup> 2016	MCI vs SCD vs CN	51 MCI, 41 SCD, 39 CN	Sources, Resting, MEG, Power	Decreased alpha power. MCI showed slowing in their alpha peak.
López-Sanz et al, <sup>43</sup> 2017	MCI vs SCD vs CN	51 MCI, 41 SCD, 39 CN	Sources, Resting, MEG, FC	Increased alpha anterior FC and decreased posterior alpha FC.
López-Sanz et al, <sup>44</sup> 2017	MCI vs SCD vs CN	69 MCI, 55 SCD, 63 CN	Sources, Resting, MEG, Graphs	SCD showed an intermediate degree of network disruption in multiple parameters.
Maestú et al, <sup>54</sup> 2008	MCI vs CN	15 MCI, 20 CN	Sources, Task, MEG, Activation	Bilateral higher activity in the ventral pathway.
Maestú et al, <sup>57</sup> 2015	MCI vs CN	102 MCI, 82 CN	Sensors, Resting, MEG, FC	Enhanced fronto-parietal and interhemispheric broadband FC.
Nakamura et al, <sup>65</sup> 2017	CNp vs CN	13 CNp, 32 CN	Sources, Resting, MEG, FC	Decreased local FC in Pcu. Increased FC between Pcu and both IPL.

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**Table 1**  
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Author	Comparison	Sample Size	Methodology	Result
Nakamura et al, <sup>66</sup> 2018	MCI vs CNp vs CN	28 MCI, 11 MCI/NoAD, 13 CNp, 17 CN	Sources, Resting, MEG, Power	Increased frontal alpha power in MCI and CNp. Increased frontal delta power in MCI vs CNp. Global increased theta power in MCI.
Osipova et al, <sup>40</sup> 2006	AD vs MCI vs CN	11 AD, 9 MCI, 10 CN	Sources, Resting, MEG, Power	Alpha slowing and anteriorization in AD, no differences in MCI group.

*Abbreviations:* AD, Alzheimer's disease; a-md-MCI, amnesic multidomain MCI; a-sd-MCI, amnesic single-domain MCI; CN, control; CNp, controls amyloid positive; FC, functional connectivity; IPL, inferior parietal lobule; MCI, mild cognitive impairment; MEG, magnetoencephalography; Pcu, precuneus; SCD, subjective cognitive decline; ε4, APOE4 carrier.

This synaptic dysfunction and disruption of local and long-distance connectivity can be studied with MEG. MEG provides a direct measure of neuronal field potentials that can be used to assess the organization of brain functional architecture in AD.<sup>55</sup>

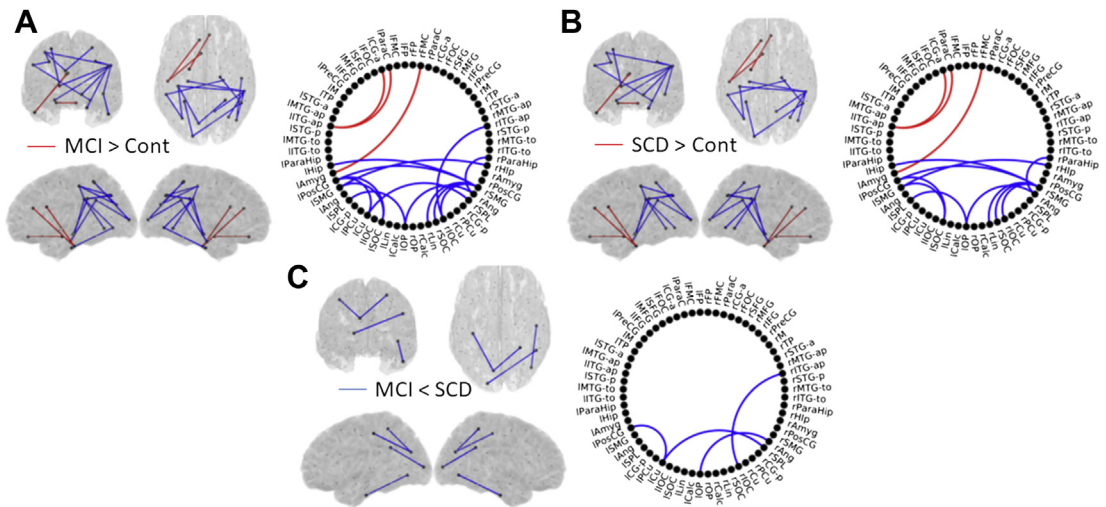
### Functional Network Disruption at Different Stages of the Disease

Although the dementia stage of AD may be associated with functional disconnection,<sup>55</sup> earlier stages also may be associated with communication disruption.<sup>56</sup> Indeed, MEG studies of patients with MCI found alterations in network organization across the cortex preceding clinical dementia.<sup>57,58</sup> In the past 20 years, the research in this field has been very active in evaluating the utility of resting-state MEG functional connectivity (MEGfc) as a biomarker of synaptic dysfunction in the early stages of AD. Resting-state functional connectivity analysis has shown a dual pattern of increasing and decreasing functional connectivity over prefrontal and posterior regions, respectively<sup>43,54,59</sup> (Fig. 1). To explore in more detail whether hypersynchronization could be a hallmark of network disruption, some MEG groups across the world joined in an international consortium (5 countries and 3 different continents). This study evaluated MEG functional networks as a biomarker at the individual level in a blind design and provided an accurate classification between MCI and controls of more than 80%.<sup>57</sup> Again, increased synchronization between anterior and posterior regions provided the best classification rate. However, MEGfc should be compared with current biomarkers, such as CSF or PET measures of tau and amyloid-beta.

### Magnetoencephalography as a Biomarker for Conversion from Mild Cognitive Impairment to Dementia

A crucial factor for considering MEG as a biomarker for AD is its capability to predict conversion across the different stages of the disease (preclinical-prodromal-dementia). There are very few longitudinal studies, and all focused on the conversion from MCI to dementia. For example, Fernández and colleagues<sup>60</sup> (Table 2) demonstrated that the estimated relative risk of conversion to AD was increased by 350% in those MCI cases with high delta activity in left posterior parietal region. In subsequent investigations using more sensitive localization algorithms, an augmented delta activity in posterior parietal and precuneus cortices was involved in the transition from MCI to mild, and from mild to more severe dementia.<sup>61</sup> A recent follow-up study established that the combination of left hippocampal volume, occipital cortex theta power, and clock drawing copy subtest scores predicted conversion to AD with 100% sensitivity and 94.7% specificity.<sup>62</sup> This evidence supported the idea that source analysis of MEG spectral changes might be a serious candidate to reflect disease progression within the AD-continuum. Profiles of conversion from healthy subjects to MCI also were described in the context of a memory task in which medial temporal lobe number of sources was reduced in converters versus nonconverters during a memory task.

From a functional connectivity perspective, 3 longitudinal studies (2 years of follow-up) with a similar sample demonstrated that those patients with MCI who developed dementia showed higher alpha band synchronization than those who remained stable.<sup>58,63</sup> The higher the synchronization between the anterior cingulate cortex and the posterior



**Fig. 1.** Depicted are the functional connectivity differences among healthy controls, SCD, and patients with MCI. Coronal, sagittal, and axial views of MR imaging with hypersynchronized (red) and hypersynchronized (blue) links. Also represented are circle plots showing schematic views of the significant links. (A) The increased connectivity of the MCI group in comparison with controls in red and decreased in blue. (B) Increased connectivity in favor of SCD compared with controls and in blue, decreased connectivity. (C) Decreased connectivity of the subjects with MCI compared with SCD. (Adapted from López-Sanz D, Bruña R, Garcés P, et al. Functional Connectivity Disruption in Subjective Cognitive Decline and Mild Cognitive Impairment: A Common Pattern of Alterations. *Front Aging Neurosci.* 2017;9:109; with permission.)

cortical regions, the higher the likelihood for developing dementia.<sup>58,63</sup> Furthermore, patients who showed high levels of p-tau in the CSF and later developed dementia showed again an increased synchronization between the medial temporal lobe and the anterior cingulate cortex in the beta frequency band.<sup>64</sup>

### Magnetoencephalography and Alzheimer Disease Biomarkers

To confirm the role of MEG as a diagnostic tool in the actual clinical scenario, it is crucial to compare its results with the current biomarkers of the disease. For instance, healthy elders without hypometabolism or brain atrophy, but with a positive amyloid burden, showed a hypersynchronization in posterior networks of the brain in comparison with amyloid-negative subjects. These profiles were directly associated with local amyloid deposition.<sup>65,66</sup> Canuet and coworkers<sup>64</sup> reported significant correlations between the levels of the p-tau protein and the functional connectivity values between medial temporal lobe and anterior cingulate cortex in subjects with prodromal AD. This finding agrees with the tau neuropathology network model as described by Braak and Braak,<sup>67</sup> and with recent ideas of “transneuronal neurodegeneration.”<sup>68</sup> The potential network alterations driven by transneuronal degeneration shape a unique framework to assess, with MEG

and tau-PET, the cascade of neuropathological changes underlying AD progression. Unfortunately, this comparison has not yet been done.

A very recent paper<sup>66</sup> offered a new perspective on the role of MEG spectral analysis in the AD-continuum (Fig. 2). Patients with MCI and control subjects were evaluated and classified according to the level of amyloid burden in A $\beta$ -positive and A $\beta$ -negative cases. Results indicated 2 clear effects. The first one was associated with A $\beta$  positivity and consisted of a frontalization of alpha activity that, importantly, was not correlated with cognitive status. The second one consisted of a significant increase of occipital and frontal delta that was associated with the transition from control to MCI status in the A $\beta$ -positive cases, and consequently was considered a specific marker within the AD-continuum. This delta increase correlated with cognitive status and with 2 classic synaptic dysfunction/neurodegeneration markers, such as entorhinal atrophy and hypometabolism in posterior cingulate/precuneus. Perhaps the most intriguing finding of the study was evidence that the typically generalized theta power increase that has been considered a key electrophysiological marker of AD was not specific for the disease, as it appeared in A $\beta$ -negative cases. Theta increase was rather a nonspecific marker of cognitive deterioration that correlated with hippocampal atrophy.

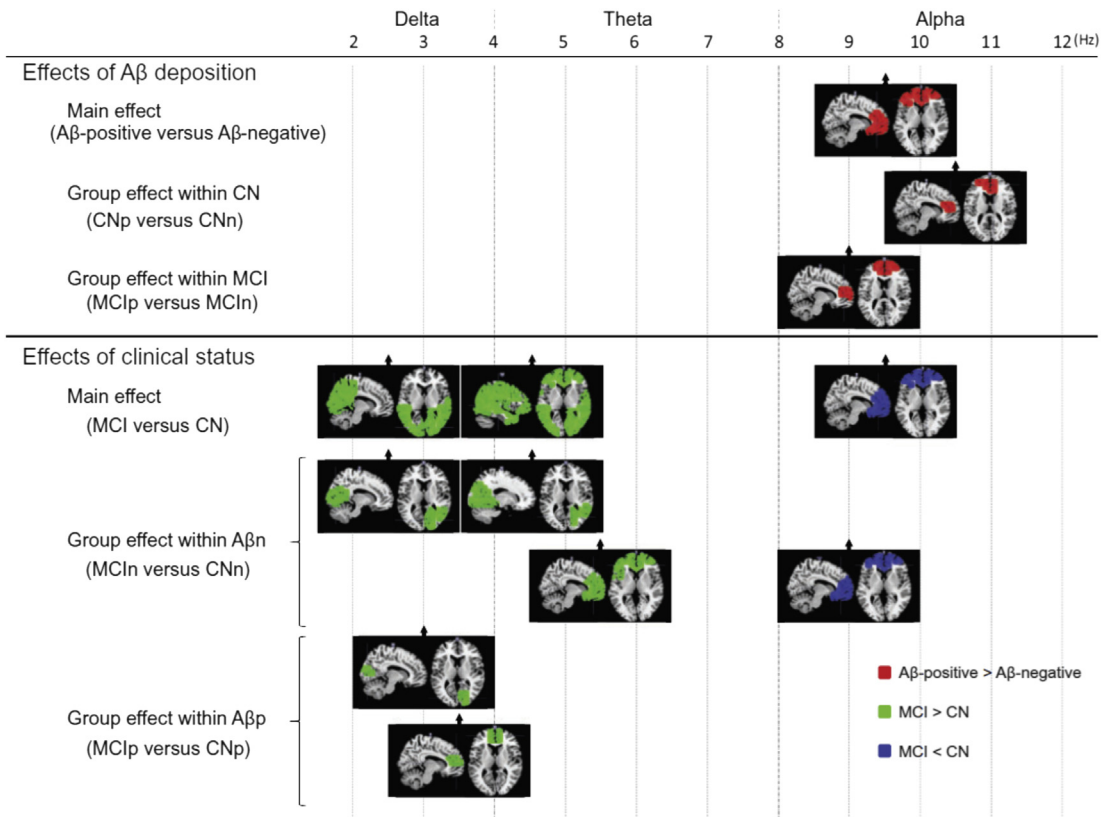
**Table 2**  
MEG studies on the progression along AD-continuum

Author	Comparison	Sample Size	Methodology	Result
Bajo et al, <sup>63</sup> 2012	pMCI vs sMCI	5 pMCI, 14 sMCI	Sensors, Task, MEG, FC	Increased parieto-occipital and frontal FC.
Canuet et al, <sup>64</sup> 2015	pMCI vs sMCI	3 pMCI, 9 sMCI	Sources, Resting, MEG, functional connectivity	Increased beta band between hippocampus and anterior cingulate cortex, in correlation with increased tau-CSF.
Fernández et al, <sup>60</sup> 2006	pMCI vs sMCI	17 MCI, 17 controls	Sources, Resting, MEG, DeltaPower	Increased parietal low-frequency increases by 350% the relative risk of progressing to AD.
Fernández et al, <sup>61</sup> 2013	AD vs MCI vs CN	35 AD, 23 MCI, 24 CN	Sources, Resting, MEG, DeltaPower	Increased delta power in posterior parietal and precuneus indexed the transition from MCI to mild AD. Significant correlation between delta power and cognitive status.
López et al, <sup>58</sup> 2014	pMCI vs sMCI	19 pMCI, 30 sMCI	Sources, Resting, MEG, FC	Increased alpha FC between right anterior cingulate and temporo-occipital regions.
López et al, <sup>62</sup> 2016	pMCI vs sMCI	12 pMCI, 21 sMCI	Sources, Resting, MEG, DeltaPower	A combination of hippocampal volume, occipital theta power and cognitive scores classifies pMCI and sMCI with 100% sensitivity and 94.7% specificity.

*Abbreviations:* AD, Alzheimer's disease; CN, control; CSF, cerebrospinal fluid; FC, functional connectivity; MCI, mild cognitive impairment; MEG, magnetoencephalography; pMCI, progressive MCI; sMCI, stable MCI.

Finally, genetic factors, such as APOE-carriage, also play a modulatory role on functional networks, and healthy elders carrying the APOE- $\epsilon$ 4 allele showed an increased synchronization<sup>69</sup> and a theta power augmentation in anterior regions of the brain.<sup>70</sup> A common factor discovered in the connectivity research was an increased synchronization between brain regions, reflecting a lack of balance between inhibition/excitation and leading to spurious synchrony. One question

about these findings could be the reproducibility of the functional network results. Garcés and colleagues<sup>71</sup> published a study in which subjects underwent 3 MEG scans in the same day (morning time) of 3 separate weeks and the intraclass correlation was very high for phase synchrony metrics. This allows the use of the functional network approach as a monitor for future studies involving pharmacologic or nonpharmacological interventions.



**Fig. 2.** MEG power markers representing the effects of amyloid- $\beta$  deposits and clinical status. Each arrow indicates the peak frequency where the maximum effect was detected. The red color indicates that the amyloid- $\beta$ -positive groups showed greater power than the amyloid- $\beta$ -negative groups. The green colors indicate larger power in the MCI groups than a healthy control group, and the blue color indicates the opposite. CN, control; n, negative; p, positive.

## SUMMARY

All of the literature reviewed in this article demonstrated that MEG is an excellent candidate biomarker for the AD-continuum. The ability of MEG to describe the patterns of synaptic disruption in the transitions from the preclinical to prodromal and dementia stages, allows its potential utilization as a diagnosis as well as a prognosis tool. The fact that a multicenter blind study provided high classification rates, using a nonhypothesis-guided approach of analysis (machine learning), demonstrated its potential for helping in the diagnosis process at the individual level.

Although all previous information supports the role of MEG as a biomarker, 3 main issues still hinder its use in the clinical scenario: (1) the presence of MEG devices in clinical facilities worldwide is still not as common as MR imaging or EEG, suggesting that MEG knowledge needs to be replicated with EEG; and (2) the correlation of MEG with current biomarkers has not been extensively

evaluated yet. The investigation of how protein deposition alters the electromagnetic patterns may help to further understand the neuropathology of AD and other amyloidopathies, tauopathies, or synucleinopathies, such as Parkinson disease dementia and fronto-temporal dementia. (3) A class I prospective study in a multicenter setting is still missing. MEG manufacturers should convene to join forces and support such a study to definitively establish this new clinical application for MEG.

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