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Functional connectivity changes in mild cognitive impairment: A meta-analysis of M/EEG studies

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HIGHLIGHTS

- Functional connectivity changes in Alzheimer's disease are already detectable at the prodromal phase, Mild Cognitive Impairment.
- An early non-invasive detection of electrophysiological biomarkers is a priority.
- Alpha temporo-parietal desynchronization could be a potential early neurophysiological biomarker.

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ABSTRACT

Objective: Early synchrony alterations have been observed through electrophysiological techniques in Mild Cognitive Impairment (MCI), which is considered the intermediate phase between healthy aging (HC) and Alzheimer's disease (AD). However, the documented direction (hyper/hypo-synchronization), regions and frequency bands affected are inconsistent. This meta-analysis intended to elucidate existing evidence linked to potential neurophysiological biomarkers of AD.
Methods: We conducted a random-effects meta-analysis that entailed the unbiased inclusion of Non-statistically Significant Unreported Effect Sizes ("MetaNSUE") of electroencephalogram (EEG) and magnetoencephalogram (MEG) studies investigating functional connectivity changes at rest along the healthy-pathological aging continuum, searched through PubMed, Scopus, Web of Science and PsycINFO databases until June 2023.
Results: Of the 3852 articles extracted, we analyzed 12 papers, and we found an alpha synchrony decrease in MCI compared to HC, specifically between temporal-parietal (d = -0.26) and frontal-parietal areas (d = -0.25).
Conclusions: Alterations of alpha synchrony are present even at MCI stage.
Significance: Synchrony measures may be promising for the detection of the first hallmarks of connectivity alterations, even at the prodromal stages of the AD, before clinical symptoms occur.

1. Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by memory loss and cognitive dysfunction. It is the most prevalent cause of cognitive impairment in aging, representing 60% to 80% of cases worldwide (Tahami Monfared et al., 2022) with an incidence that increases with age: 3% among people aged 65–74, 17% of people from 75 to 84 years old and 32% of people of age 85 or older have Alzheimer's dementia ("2020 Alzheimer's Disease Facts and Figures", 2020). Alzheimer's disease has therefore become a global public health concern with a huge impact on health systems and societal costs.

Neuropathological changes due to AD include extra-cellular accumulation of the amyloid-β (Aβ) and neurofibrillary tangles of hyperphosphorylated tau protein (p-Tau) causing neuronal death that consequently leads to brain atrophy and synaptic dysfunction (Braak and Braak, 1991; Jack et al., 2018). The earliest stages of this process start in the entorhinal cortex and the hippocampus and spread in a cascade through neocortical regions (Hardy and

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Higgins, 1992; Jack et al., 2016) as the disease progresses. However, growing evidence supports the hypothesis that the neuropathology of AD is not global (Delbeuck et al., 2003), and could at first target specific and functionally connected areas that are considered to be crucial nodes of larger brain networks (Manuello et al., 2018).

The neurodegenerative process of AD is characterized by a silent phase that may last years or decades during which the neuropathophysiological process has started and is ongoing, but the clinical hallmarks are still subtle. Then, the neurodegenerative progression may result in a preclinical phase, called Mild Cognitive Impairment (MCI) (Petersen et al., 1999), which gradually and irreversibly leads to a loss of autonomy that characterizes the dementia phase (Sperling et al., 2011). MCI is defined as an intermediate phase between normal aging and the clinical diagnosis of probability for AD onset (Albert et al., 2011; Petersen, 2004). It is characterized by an objective cognitive impairment in memory (amnestic MCI, "aMCI") or in other cognitive domains (non-amnestic MCI, "naMCI") as documented by neuropsychological assessment (Winblad et al., 2004). Moreover, MCI subjects show essential preservation of basic cognitive functions and daily life activities (Petersen et al., 2018).

Within the framework that views the brain as a set of complex and dynamical neural networks (Bullmore and Sporns, 2009; McKenna et al., 1994) brain functions are supposed to rely on the integrity of interconnections between brain regions, both in terms of structural circuits and functional dynamics (Friston, 2011). Disruptions of network communication could lead to the neurocognitive changes observed during physiological aging, as well as to neurological disorders (Babiloni et al., 2013; Courtney and Hinault, 2021; Vecchio et al., 2013; Voytek and Knight, 2015). A network perspective accounting for such functional interactions has the potential to provide new and meaningful information about the state-dependent patterns of alteration of functional connectivity that characterize the intermediate phase of the neuropathology (Pievani et al., 2011). Therefore, identifying early-stage *in vivo* functional biomarkers that allow tracking changes affecting large-scale brain networks can help develop new strategies to optimize the management of the dementia syndrome via new therapies (Prvulovic et al., 2011).

Connectivity footprints of AD neurodegeneration and MCI have already been detected through several neuroimaging methods, such as positron emission tomography with fluorodeoxyglucose (FDG-PET), diffusion tensor imaging (DTI) (Honea et al., 2009), magnetic resonance spectroscopy (MRS) (Gao and Barker, 2014), and Arterial Spin Labeling (ASL-MRI) (for a review, see Wolk and Detre, 2012). Functional magnetic resonance imaging (fMRI) is a technique frequently used for the exploration of brain changes in AD (Dennis and Thompson, 2014) as well as in the MCI phase (Farràs-Permanyer et al., 2015). Although less invasive than the above-mentioned functional neuroimaging methods, fMRI is highly expensive (Crosson et al., 2010). Furthermore, it is well known that the blood-oxygen-level-dependent (BOLD) signal measured by fMRI is limited by the hemodynamic response time, so that the BOLD response builds up in approximately 5 to 6 seconds following the onset of the neural stimulus. This response time, which is much slower than the underlying neural processes, makes the temporal information heavily disturbed (Glover, 2011).

In contrast, neurophysiological measures, such as electroencephalography (EEG) and magnetoencephalography (MEG), are non-invasive methods that record electromagnetic signals produced by the ionic currents that are generated by neural activity (microscale) (Buzsáki and Draguhn, 2004). In addition, EEG is cost-effective and versatile compared to the other neuroimaging tools. Neurophysiological techniques enable the investigation of brain rhythms generated by the oscillatory activity of large groups of cortical neurons (mesoscale) (Babiloni et al., 2020) with a high temporal resolution (few milliseconds). Brain areas can communicate via five main frequency bands: delta (0.5–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), beta (12–30 Hz) and gamma (35–100 Hz). Electrophysiological signals reflect the functional synchronization (or desynchronization) orchestrated by the oscillation of large groups of cortical neurons of several neural systems (macro-scale) supporting alertness, motivation, and several cognitive processes. The interactions between inputs and outputs of neural systems can be represented by a spectrum of values along the axes deterministic-stochastic, complexity-simplicity, linear-nonlinear, stationary-nonstationary, and phase-non phase locking dimensions that may be differently affected by AD processes (Babiloni et al., 2020).

There are several methods to evaluate functional connectivity between brain areas based on signal synchronization and coupling (Table 1). Coherence quantifies the linear relationship between two signals from brain regions in the frequency domain. Its squared value represents the amount of variance in one of the signals that can be explained by the other signal, or vice-versa (Nunez et al., 1997). It is represented by a correlation coefficient ranging from 0 (i.e., no coherence) to 1 (meaning "total coherence") that estimates the consistency of relative amplitude and phase between a given pair of signals in each frequency band (Srinivasan et al., 2007). Another method based on linear relationships is the Amplitude Envelope Correlation (AEC), which measures the correlation between envelopes of the amplitude of two signals (Bruns et al., 2000). These measures yield fundamental information about network formation and functional integration across brain regions, although distortions can stem from incorrect modeling of volume conductivity of head tissues and from imprecise electrode location. Also, since these measures are estimators of linear relationships, they might not reflect the nonlinear nature of brain network dynamics.

To address the above issues, other methods such as the imaginary part of coherency (iCOH)(Nolte et al., 2004), the Phase Locking Value (PLV)(Lachaux et al., 1999) Phase Amplitude Coupling (PAC) (Tort et al., 2010), or Phase Lag Index (PLI) (Stam et al., 2007) have been developed. While iCOH is extracted by simply evaluating the imaginary part of the complex-valued coherency, PLV captures the variability of phase differences between two signals over time. Similarly, PLI measures the asymmetry of the phase difference distribution ($\Delta\phi$) between two signals and reflects the consistency with which one signal is phase leading or phase lagging with respect to another signal. PAC is instead based on the principle that the amplitude of high-frequency oscillations is modulated by the phase of low-frequency rhythms. If no phase coupling exists, then this distribution is expected to be flat. These methods allow for the extraction of information on the phase difference (i.e., the time delay) between two signals and are therefore complementary to coherence because they capture coupling independently from amplitude correlations (For an extensive review, see Bastos and Schoffelen, 2016). Finally, methods derived from information theory have been implemented to give an estimate of the dynamical interdependence between two or more simultaneously recorded time series. Among these, Synchronization Likelihood (SL) quantifies the probability that two signals are in the same "dynamical state" (Stam and Van Dijk, 2002).

Overall, all these measures are capable of detecting neuropathophysiological processes affecting brain networks before the onset of clinical symptoms and structural alterations (Sadaghiani et al., 2022), thus representing a useful asset for clinical applications and leading to new theoretical considerations (Babiloni et al., 2020). Several studies using machine learning classification methods have indeed proven high rates of accuracy in distinguishing MCI from healthy control (HC) subjects through the computation

Table 1
Indexes that evaluate functional connectivity based on signal synchronization and coupling.

Connectivity Index	Description
Coherence (Coh)	A measure of the covariance of the frequency components of two signals. In EEG studies, COH typically corresponds to the covariance of spectral activity between two electrode locations (Nunez et al., 1997).
Imaginary Part of Coherency (iCOH)	It is the imaginary part of the Fourier-transformed coherency. Coherency between two EEG signals is a measure of the linear relationship of the two at a specific frequency while Coherence is its absolute value. Coherency essentially measures how the phases in channel *i* and *j* are coupled to each other assuming that signals are stationary. (Nolte et al., 2004)
Phase Locking Value (PLV)	A measure of the variability of phase differences between two regions. PLV is close to 1 (i.e., high synchrony between regions) while, with large variability in the phase difference, PLV is close to zero (Lachaux et al., 1999).
Phase Lag Index (PLI)	A measure of the asymmetry of the phase difference distribution between two EEG signals. PLI reflects the consistency with which one signal is phase-leading or phase-lagging with respect to another signal (Stam et al., 2007).
Synchronization Likelihood (SL)	A measure of the statistical likelihood that two signals are in the same "dynamical state". States are defined as time-delay embedding vectors of the signals (Stam and van Dijk, 2002).
Phase Amplitude Coupling (PAC)	A measure of coupling that relies on the assumption that the phase of a low-frequency oscillation is coupled to the amplitude of a higher-frequency oscillation within a single brain region, or across cortical regions (e.g., low-frequency phase in region A driving high-frequency amplitude in region B) (Tort et al., 2010).
Amplitude Envelope Correlation (AEC)	A measure of correlation between envelopes of the amplitude of two signals (typically, two channels) for each frequency of interest. AEC corresponds to Pearson's r between the log-transformed power envelopes. (Bruns et al., 2000).

of synchrony measures at resting state, a condition that is particularly sensitive for detecting the earliest changes of the AD progression (Babiloni et al., 2013; Rossini et al., 2008; Yang et al., 2019). For instance, Dauwels and colleagues (2010) used a combination of linear and nonlinear measures of the interdependence of resting-state EEG (rsEEG) signal and found a classification accuracy of 80% and 85% in the discrimination of HC and MCI individuals. Moreover, Musaeus and colleagues (2019) obtained a diagnostic accuracy of 95% in distinguishing between HC, MCI, and AD patients: using coherence, the iCOH and weighted PLI, they observed a significant decrease in alpha coherence in AD patients.

However, findings of functional connectivity changes in MCI have been inconsistent (Wen et al., 2015): both a global hypersynchronization (Jiang and Zheng, 2006; Pons et al., 2010) in delta and theta (Handayani et al., 2018; López et al., 2014) and hyposynchronization (Youssef et al., 2021) specifically in delta (Koenig et al., 2005; Požar et al., 2020; Tóth et al., 2014), alpha and beta (López et al., 2014) bands have been observed in MCI compared to HC. Many studies observed a slow-down of EEG activity in MCI and a recent meta-analysis reported a significant reduction in alpha activity (Lejko et al., 2020) at rest as a valid biomarker for AD (Cecchetti et al., 2021). However, information about local activity could be insufficient to explain the temporal dynamic evolution of a neurodegenerative disease as a proper "disconnection syndrome" (Bajo et al., 2010; Neufang et al., 2011; Pasquini et al., 2019). As the boundaries between physiological aging and MCI are blurred, a deeper understanding of this intermediate stage is crucial when searching for neurofunctional biomarkers in clinical settings. To this purpose, a systematic review of the available evidence concerning alterations of brain connectivity linked to MCI is required.

The present meta-analysis sought to identify the most frequent and early signs of connectivity changes linked to MCI by quantitatively elucidating previous findings on synchrony alterations in MCI patients compared to HC at resting state. To do so, we computed the standardized mean difference (smd) of the effect sizes reported by the studies retrieved through systematic research of the literature conducted until June 2023. Moreover, we used a novel method, namely a random-effects analysis that allows the unbiased inclusion of Non-statistically Significant Unreported Effect sizes ("MetaNSUE", Albajes-Eizagirre et al., 2019; Radua et al., 2015). To our knowledge, this is the first study using this innovative methodological approach in a meta-analysis of synchrony changes occurring in pathological aging. Identifying an electrophysiological biomarker of AD would help the early and easily accessed diagnosis of the disease, thus providing optimal management of the disease progression.

As already observed in AD patients (Adler et al., 2003; Jeong, 2004) and in line with previous findings (Babiloni et al., 2006; Handayani et al., 2018) supporting the "disconnection hypothesis" (Delbeuck et al., 2003), we expected an overall synchrony decrease in MCI patients compared to healthy older adults between frontal and parietal, and frontal and temporal regions (Vecchio et al., 2013). Specifically, we expected a specific loss of synchrony between temporo-parietal regions and frontal areas in MCI patients, both in theta (reflecting memory impairment) and alpha bands (Handayani et al., 2018). This pattern of decline in MCI was deemed to reflect the loss of cholinergic connectivity pathways connecting fibers from temporal and parietal regions with the frontal areas of the brain and the cholinergic projections from the basal forebrain with the cortex and hippocampus (Mesulam, 2004).

2. Methods

2.1. Literature search

The literature search was conducted from December 10 until February 28, 2022, and updated to June 9, 2023, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements for systematic reviews and meta-analyses (Page et al., 2021). PubMed, Scopus, Web of Science and PsycINFO databases were independently searched by AP, GB and CF, using the following keyword strings: 1) ("EEG" OR "MEG" OR "electroencephal*" OR "magnetoencephal*") AND ("connectivity" OR "synchronization") AND ("Alzheimer" OR "MCI" OR "mild cognitive impairment" OR "aging") NOT "child*" (Table S1a) and, from June 22, 2023 2) All Fields (eeg OR meg OR electroencephal* OR magnetoencephal*) AND (connectivity OR synchronization OR coherence OR phase locking value OR phase lag index OR synchronization likelihood OR phase amplitude coupling OR amplitude envelope correlation) AND (Alzheimer OR mci OR "mild cognitive impairment" OR aging) NOT ("child*) (Table S1b).

Filters for (a) article type (only original articles and reviews), (b) language (only articles in English) and (c) population (only humans) have also been applied to the query. No limitations to the year of publication were applied. Once the papers were screened for abstract, GB and CF cross-checked for the eligibility criteria to proceed with the selection process.

2.2. Quality assessment (QA)

To assess the risk of bias of each study to be included in the analysis, the Modified Newcastle-Ottawa Quality Assessment Scale based on Reilly et al. (2018) was used. See the Supplementary Material.

2.3. Study eligibility

Eligible papers were selected according to the following inclusion criteria: (1) the age of the sample included had to be over 65 years old for older adults and at least 18 for the younger counterpart; (2) studies had to show an effect size (z, t, or p values) of the change in synchronization between two brain areas for each group of comparison: older adults (OA) *vs* young adults (YA); HC *vs* MCI; MCI *vs* AD.

Papers were discarded according to the following exclusion criteria: (1) studies with small sample sizes ($n \leq 6$); (2) reporting global functional connectivity values only (i.e., averaging of all channels for each frequency band, such as Global Synchronization Index or Global Coupling Index); (3) studies involving psychiatric and or neurologic diseases (e.g., Parkinson's disease, vascular disease, Huntington's disease, epilepsy, multiple sclerosis, psychiatric illness, diabetes mellitus) were excluded; (4) articles including carriers of genetic variants deemed to increase the risk to develop Alzheimer's Disease Dementia; (5) studies that were methodologically inappropriate (e.g., study design, within group, studies with incomplete data, studies that did not consider the contrast of our interest and/or that were no open access) and that include other variables (e.g., sleep, cognitive tasks).

2.4. Data extraction

To avoid imbalance in the sample sizes for the various contrasts, we decided to analyze the HC > MCI contrast only (12 studies per condition; k(YA > HC) = 4 and k(MCI > AD) = 4). The following data were extracted from each study: (1) Basic bibliographic information (i.e. first author's name, year of publication, journal); (2) EEG parameters such as montage, number of electrodes (spanned from 16 to 128), placement of the analyzed electrodes (Table 2) and frequency band considered; (3) Functional connectivity metrics implemented; (4) sample demographic data (i.e. samples size, age); (5) paradigm and type of the task or (6) resting state modality (eyes open (EO) or eyes closed (EC)); (7) the effect size of the between groups contrast quantifying any change in functional connectivity.

2.5. Statistical analyses

To explore synchrony alterations between healthy and MCI, a meta-analysis of the standardized mean difference (SMD) for each pair of areas of interest (among Frontal, Temporal, Parietal and Occipital) was computed for each of the four frequency bands selected, namely Alpha(α), Beta (β), Theta (θ) and Delta (δ). The standardized mean difference is used as a summary statistic in meta-analysis when the studies all assess the same outcome but measure it in a variety of ways (McKenzie et al., 2019). We then represented the effect estimates and confidence intervals for both individual studies and meta-analyses by means of forest plots, showing synchrony changes between Fronto-Temporal (FT), Fronto-Parietal (FP), Fronto-Occipital (FO) and Temporal-Parietal (TP) regions and for each frequency band.

For each frequency band and pair of brain areas, differences in the corresponding functional connectivity between groups were collected and converted to t-values on https://www.sdmproject.com/utilities/?show=Statistics.

Some of the selected studies did not report any values for significant effects (“non-statistically significant unreported effects” [NSUEs]). To include these studies with NSUEs in this meta-analysis, we used the “MetaNSUE” package (Albajes-Eizagirre et al., 2019; Radua et al., 2015) implemented in R (https://cran.r-project.org/). This novel method estimates the bounds where NSUEs fall and transforms them to unbiased effect sizes. The first step consists in using the following formula Eq. (1) implemented in the function “smd_from_t” to convert two-sample t-values into standard mean difference:

$$y_i = J(df_1) \cdot \sqrt{\frac{1}{n_{i,1}} + \frac{1}{n_{i,2}}} \cdot t_i \quad (1)$$

where J is the exact form of the Hedge's correction factor, df_1 are the degrees of freedom and $n_{i,1}$ and $n_{i,2}$ are respectively the size of the first and the second sample. Then, an estimation of the parameters for subsequent imputations, namely the upper and lower limits within which the effect size should fall, is conducted by maximizing the likelihood (MLE) of the unreported effect sizes through the multiplication of the likelihood that each unreported effect size lies within its two effect size bounds. Noteworthy, these parameters account for the within-study variance (Q) (i.e., a standardized measure sensitive to the ratio of the observed variation to the within-study error). In addition to serving as a significance test for the homogeneity of the effect sizes, this metric is used to compute the excess of variation *(Q - df)* (namely, the part that will be attributed to differences in the true effects from study to study), the between-studies variance (τ^2, Borenstein et al., 2009), and the ratio of true heterogeneity to the total variation in the observed effect (I^2). This value ranges from 0 to 100, it is independent of the effect size and of the number of studies (Borenstein et al., 2009), and it is calculated according to Eq. (2).

$$I^2 = \left(\frac{Q - df}{Q}\right) \cdot 100 \quad (2)$$

In short, I^2 is the percentage of total variation across studies that is due to heterogeneity rather than chance, wherein values approaching 100% indicate increasing inconsistency across the studies (Higgins et al., 2003).

Following the MLE, multiple imputation creates several different plausible imputed data sets by replacing each missing value with two or more imputed values to represent the uncertainty on which value to impute, and it appropriately combines the results obtained. After this step, a standard meta-analysis is independently carried out for each set of imputed effect sizes. Finally, the results of these meta-analyses are pooled using a standard formula for multiple imputations (Li et al., 1991).

A forest plot of the effect sizes of all studies was obtained through the function “meta(smd)” for each contrast and for each pair of areas of interest. We next applied the Leave One Out Protection (LOO) (“leave1out(x)”). This function allows to carry out a sensitivity analysis, based on the estimation of the same MLE model, though with all studies except the first, then with all studies except the second, then with all studies except the third, and so on. If the result obtained is consistent (significance-wise) in the majority of the repetitions of the analysis, one can infer that the outcome obtained is replicable.

Table 2
The description of the studies that were included in the meta-analysis for healthy controls (HC) and Mild Cognitive Impairment patients (MCI) comparison.

First author	Tool	Montage (system)	Connectivity index	MCI diagnosis (criteria)	RS method (analyzed time)	Results	Frequencies bands and areas analyzed	Findings
Akrofi et al., 2009	EEG	16 (10–20)	COH	MCI (NS)	EC (selected 30 s artifact-free)	MCI ↓ theta in FOMCI ↓ beta in FP, FO	Delta: FT; FP; FO; TP Theta: FT; FP; FO; TP Alpha: FT; FP; FO; TPBeta: FT; FP; FO; TP	No significance for alpha and delta. Significant for beta and theta.
Gonzalez-Escamilla et al., 2015	EEG	59 (10–20)	PLI	aMCI (Petersen 1999)	EC (10 min of rs; selected 60 s artifact-free)	MCI ↓ in alpha TP	Alpha: FT; FP; FO; TP	The aMCI group showed decreased neural synchrony patterns mainly in temporo-parietal regions.
Handayani et al., 2018	EEG	14 (10–20)	COH + PLV	MCI (NS)	EC (20 min of rs)	MCI ↑ COH delta in FT MCI ↓ COH alpha in FT, FP, FOMCI ↓ COH beta in FT, FP, FO MCI ↑ PLV alpha in FOMCI ↓ PLV beta in FT, FP, FO	Delta: FT; FP; FO; TPAlpha: FT; FP; FO; TP Beta: FT; FP; FO; TP	COH and PLV were lower in MCI than in the healthy subjects in the temporo-parietal-occipital regions.
López et al., 2014	MEG	306 (102 magnetometers.204 planar gradiometers).	PLV	MCI (Petersen 2004)	EC (3 min)	MCI ↓ delta in FP MCI ↑ theta in TP, FO MCI ↓ alpha in FOMCI ↑ beta in TP	Delta: FT; FP; FO; TP Theta: FT; FP; FO; TP Alpha: FT; FP; FO; TP Beta: FT; FP; FO; TP	MCI display hypersynchronization in low-frequency bands and a lack of synchronization in alpha and beta
Meghdadi et al., 2021	EEG	20 (10–20)	COH	aMCI (DSM-V)	EC (5 min) + EO (5 min)	MCI ↓ delta in TP	Delta: FT; FP; FO; TP Theta: FT; FP; FO; TPAlpha: FT; FP; FO; TP	Decrease TP synchronization in delta bands, no effects in alpha and theta in the areas of our interest.
Moretti et al., 2008	EEG	19 (10–20)	COH	MCI not considering clinical subtype (Petersen 1997)	EC (10 min)	MCI ↓ COH in delta FP MCI ↓ COH in alpha FP MCI ↓ COH in beta FP	Delta: FT; FP; TP Alpha: FT; FP; TPBeta: FT; FP; TP	Decrease in COH only in FP in all frequency bands in MCI
Núñez et al., 2019	EEG	19 (10–20)	COH, PLI, MSCOH	MCI due to AD (NIA-AA)	EC (5 min)	MCI tendency to ↓ in AEC-alpha MCI ↓ in AEC-beta in temporal and parieto-occipital regions= in MSCOH and PLI	Alpha: FT; FP; FO; TPBeta: FT; FP; FO; TP	Statistically significant differences between groups were found in the alpha and beta bands.
Teipel et al., 2009	EEG	32 (10–20)	COH	aMCI (Petersen, 2004)	EC (10 min)	MCI ↓ COH in alpha TPMCI = COH in beta	Alpha: TPBeta: TP	Reduced temporo-parietal coherence in alpha band
Tóth et al., (2014)	EEG	33 (10–20)	PLI	MCI (Petersen, 2004)	EC (4 min) + EO (4 min)	MCI ↓ PLV in delta FT, FPMCI ↓ PLV in theta FP	Theta: FP, FT, TP,	Decreases inter-regional delta e theta connectivity between FT and FP areas.
Youssef et al., (2021)	EEG	64(10–10)	dwPLI	aMCI (Petersen 2004)	EC (5 min)	MCI ↓dwPLI in theta in FO, FT, FP, TP	Delta: FT; FP; FO; TP Theta: FT; FP; FO; TP Alpha: FT; FP; FO; TPBeta: FT; FP; FO; TP	Decrease in PLI only in theta bands in MCI
Jiang and Zheng (2006)	EEG	16 (10–20)	COH	aMCI (DSM-IV)	EC (10 min)	MCI = HC	Delta: TP Theta: TPAlpha: TP	No between group differences
Su et al., (2021)	EEG	16 (10–20)	PLV	aMCI (NS)	EC (5 min)	MCI = HC	Alpha: FT; FP; FO; TP	No between group differences

Abbreviations: eyes closed (EC); eyes open (EO); amnestic MCI (aMCI); not specified (NS); Frontal-Temporal areas (FT); Frontal-Parietal areas (FP); Frontal-Occipital areas (FO); Temporal-Parietal areas (TP); electroencephalogram (EEG); magnetoencephalogram (MEG); coherence (COH); phase-lag index (PLI); phase locking value (PLV); debiased weighted phase lag index (dwPLI); amplitude envelope correlation (AEC); magnitude squared coherence (MSCOH); seconds (s); minutes (min); resting state (rs/RS); decrease (↓); equal (=); Diagnostic and Statistical Manual of Mental Disorders (DSM); National Institute on Aging e la Alzheimer's Association (NIA-AA).

As a final step, to check for publication bias through the detection of any asymmetry in the funnel plot, we conducted a meta-regression of the effect sizes of the studies by their standard errors through the "metabias" function.

3. Results

3.1. Study selection

The keywords filled in each one of the databases queried returned a total of 4685 articles, of which 1220 from PubMed, 838 from Scopus, 2219 from Web of Science and 408 from PsychInfo, while 730 were retrieved by cross-reference methods. From the research of June 2023 (with different keywords) a total of 4109 articles were found, of which 112 from PubMed, 979 from Scopus, 2578 from Web of Science and 440 from Psychinfo. After removing duplicates, title and abstract of 3852 articles were independently screened and then cross-checked by GB and CF. This first skimming step allowed us to proceed with the full-text screening of 398 articles, 367 of which were excluded for the following reasons: they did not allow open access (n = 20), the study design did not match with our research question [(n = 166), due to the contrast analyzed (n = 140) or the employment of an active task (n = 32)], they investigated other diseases (n = 6), they carried out within-group contrasts (n = 11) or data were incomplete (n = 3). Where articles showed missing information, authors were contacted by email. Thus, 31 articles were assessed for eligibility, 12 of which were furtherly excluded by cross-checking due to the study design implemented. At last, 19 studies were selected for the quantitative meta-analysis. However, due to the small sample size, 8 articles have been discarded, obtaining 12 exploitable articles for the quantitative analysis. The characteristics of the studies meeting our inclusion criteria are shown in Table 2 and the literature search is depicted in the PRISMA Flowchart (Fig. 1).

Results of QA are reported in the supplementary material (Table S2).

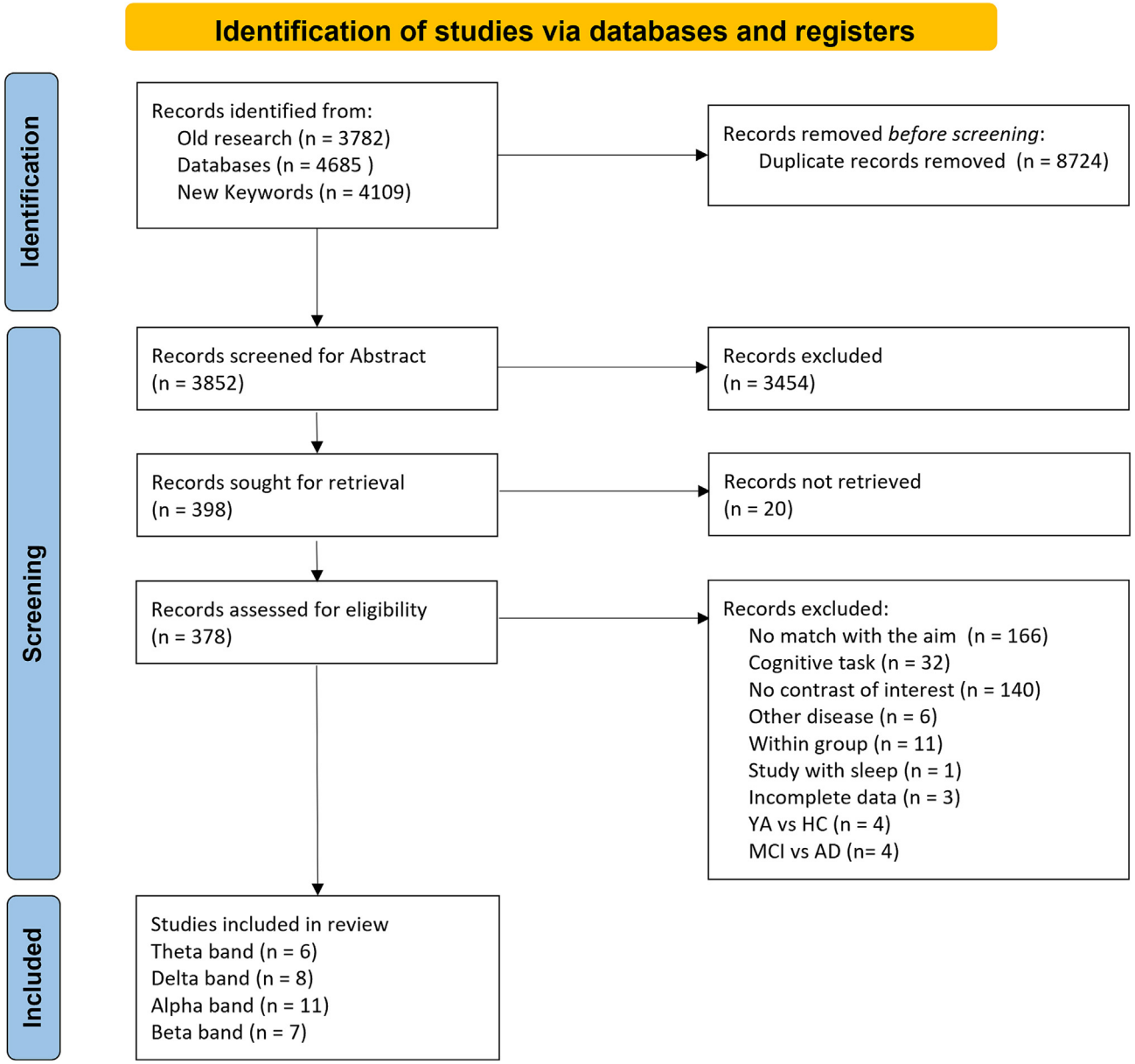

Fig. 1. The flowchart illustrates the study selection process following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for meta-analyses and systematic reviews. Abbreviations: healthy control (HC); Mild Cognitive Impairment (MCI); Alzheimer's Dementia (AD); young adults (YA).

3.2. Sample description

Sample characteristics are reported in Table 3. Demographic data of both HC (N = 327, 180 women; mean age 68.7 years, standard deviation (sd) 5.1 years; mean education 9.9 years, sd 1.3 years) and MCI patients (N = 379; 220 women; mean age 70.9 years, sd 4.1 years; mean education 8.6 years, sd 1.5 years) were included in the meta-analysis. The cognitive state of the sample was assessed by the Mini-Mental State Examination (MMSE) (Folstein et al., 1983) both for HC (mean score 28.6, sd 0.8) and MCI patients (mean score 25, sd 3.5). By applying independent sample t-tests between groups, the sample was found to be comparable for age ($p = 0.283$) and education ($p = 0.376$), but significant differences were found in MMSE score ($p < 0.001$). The diagnosis of MCI was based on NIA-AA (Jack et al., 2018), DSM-IV, DSM-V or Petersen (Petersen, 2004; Petersen et al., 1999) criteria.

3.3. Alpha band

The analysis showed a negative value in the comparison between the temporal and parietal (Fig. 2) and between the frontal and parietal (Fig. 3) areas (k = 11, of which 7 NSUEs, respectively, d = – 0.250, I^2= 1.11%, C.I. [-0.4317;-0.0749], $p < 0.01$ and d = -0.260, I^2= 34.54%, C.I. [-0.489;-0.0391], $p < 0.05$), thus indicating a decrease of alpha coupling between these areas in the MCI group compared to their healthy counterpart. No significant differences in alpha synchrony between Fronto-Temporal (k = 11, of which 8 NSUEs; d = -0.093, I^2= 0.70%, C.I. [-0.279; 0.092], p = 0.323) and Fronto-Occipital sites (k = 8, of which 6 NSUEs, d = -0.127, I^2= 1.37%, C.I. [-0.321;0.067], p = 0.200) were found. Leave-One-Out analyses replicated the results in all of the cases except for 3 studies (when discarding study 1 (d = -0.202, p = 0.094), when discarding study 5 (d = -0.246, p = 0.069, when discarding study 11 (d = -0.184, p = 0.062) considering the fronto-parietal areas (Fig. 4), suggesting that these three studies could have driven the outcome. On the contrary, the results were replicated in all the cases for the temporo-parietal coupling (Fig. 5), pointing out a high reliability of this outcome.

Finally, no publication biases were detected in any of the meta-analyses carried out for this frequency band.

3.4. Theta band

No significant fronto-parietal reduction of theta synchrony in MCI was detected by meta-analyzing the 6 studies, 5 of which NSUEs (d = -0.250, I^2 = 7.34%, C.I. [-0.52; 0.0], p = 0.053). In addition, the Leave-One-Out analysis found that when discarding study 1 (d = -0.279, p = 0.046), study 2 (d = -0.330, p = 0.030), study 5 (d = -0.302, p = 0.037) or study 6 (d = -0.294, p = 0.046), a moderate effect was found, suggesting that 4 studies out of 6 could have driven the results. No differences were found between fronto-temporal (k = 6, of which 5 NSUEs, d = -0.087, I^2 = 20.51%, C.I. [-0.39;0.22], p = 0.574), fronto-occipital (k = 6, 3 NSUEs, d = -0.0845, I^2 = 62.19%, C.I. [-0.45;0.28], p = 0.650) nor temporal-parietal areas (k = 6, 4 of which NSUEs, d = -0.020, I^2 = 59.75%, C.I. [-0.39;0.35], with no risk of publication bias in all cases.

3.5. Delta band

No delta synchrony alterations were found in any of the areas studied by summarizing the evidence of 8 studies (Fronto-Temporal: 6 NSUEs, d = -0.141, I^2 = 2.32%, C.I [-0.37; 0.09], p = 0.229; Fronto-Parietal: 5 NSUEs; d = -0.043, I^2 = 54.73%, C.I. [-0.38;0.35], p = 0.063; Fronto-Occipital: 7 NSUEs, d = -0.039, I^2 = 1.77%, C.I. [-0.28; 0.20], p = 0.744; Temporo-Parietal: 5 NSUEs, d = -0.015, I^2 = 69.36%, C.I. [-0.38;0.35], p = 0.937). No study was detected by the LOO analysis, and no publication bias emerged.

3.6. Beta band

No significant differences in beta synchrony were observed in the 7 studies considered of MCI subjects compared to HC in any pair of regions (Fronto-Temporal: 5 NSUEs, d = -0.0238, I^2 = 0.52%, C.I. [-0.27; 0.22], p = 0.775; Fronto-Parietal: 3 NSUEs; d = -0.203, I^2 = 0.63%, C.I. [-0.42; 0.01], p = 0.067; Fronto-Occipital: 4 NSUEs; d = -0.088, I^2 = 0.88%, C.I. [-0.33;0.15], p = 0.466; Temporo-Parietal: 3 NSUEs, d = -0.153, I^2 = 56.09%, C.I. [-0.49;0.18], p = 0.365). Lastly, no study was found to drive the outcome, and no potential reporting bias was observed.

4. Discussion

Identifying in-vivo biomarkers to diagnose Alzheimer's Disease at the prodromal stage is pivotal to developing new therapy protocols and possibly slowing down the progression of the disease (Pievani et al., 2011). Neurophysiological measures have been demonstrated as valid, cost-effective (for EEG), and readily accessible biomarkers for the early detection of brain alterations before the appearance of clinical symptoms (Rossini et al., 2020). In this framework, a powerful approach is provided by the analysis of functional connectivity, which can be computed from noninvasive M/EEG recordings with different methods quantifying linear and nonlinear relationships among the neural activity of distant brain regions (Stam, 2010). Capturing specific alterations of connectivity between brain regions could shed light on the effects of AD neuropathology on neurophysiological mechanisms underpinning neural excitation/inhibition, neurotransmission, as well as brain network dynamics (Courtney and Hinault, 2021; Voytek and Knight, 2015).

To our knowledge, this is the first meta-analysis to quantitatively summarize existing evidence of connectivity changes (in the main frequency bands) between specific couples of brain areas at rest using a recent technique that also includes Non-Statistically Significant Unreported effect sizes (Radua et al., 2015). This novel method avoids publication biases and allows for the identification

Table 3
Sample characteristics of healthy controls (HC) and Mild Cognitive Impairment patients (MCI). p-values lower than 0.05 were considered significant. Abbreviations: standard deviation (sd); Mini-Mental State Examination (MMSE); female (F); male (M).

	HC	MCI	p-value
Sample size (F/M)	327 (180/147)	379 (220/159)	
Age (mean years ± sd)	68.7 ± 5.1	70.9 ± 4.1	p = 0.283
Education* (mean years ± sd)	9.9 ± 1.3	8.6 ± 1.5	p = 0.376
MMSE (mean score ± sd)	28.6 ± 0.8	25 ± 3.5	P < 0.001

Note: * Data refer only to the studies that reported mean and sd; Student T-Test was computed for Age, while non-parametric Mann-Whitney Test was computed for Education and MMSE because it violates the assumption of normality.

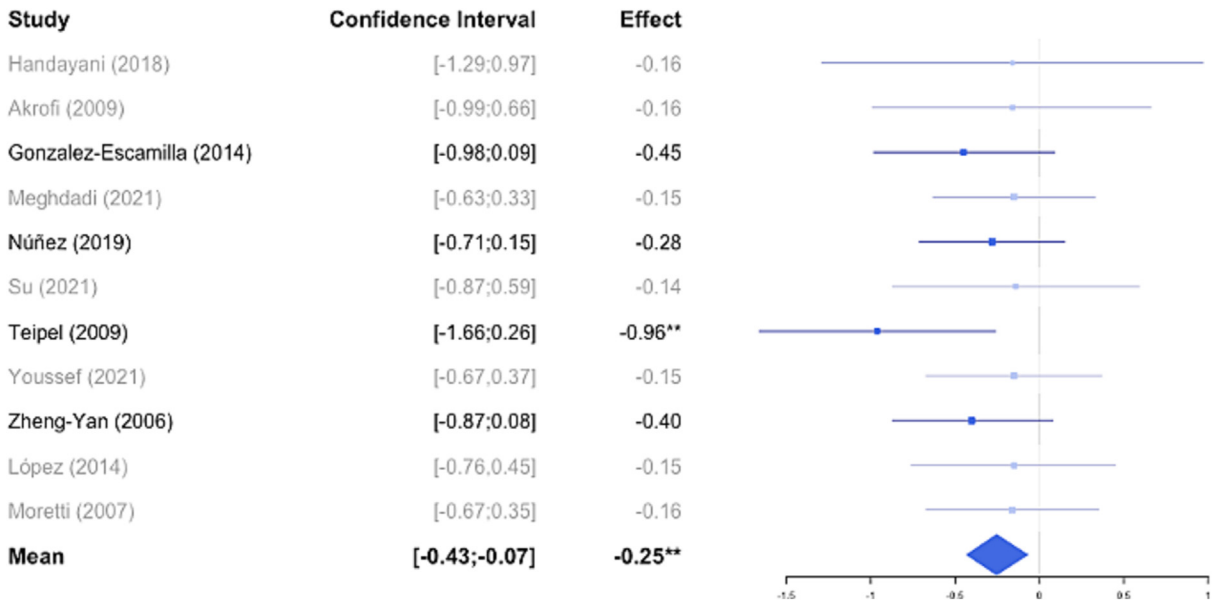

Fig. 2. Forest plot of Temporo-Parietal synchrony differences in α between MCI and HC. Values are weighted for the sample size. Asterisks represent p-values: *** = 0.001; ** = 0.01; * = 0.05.

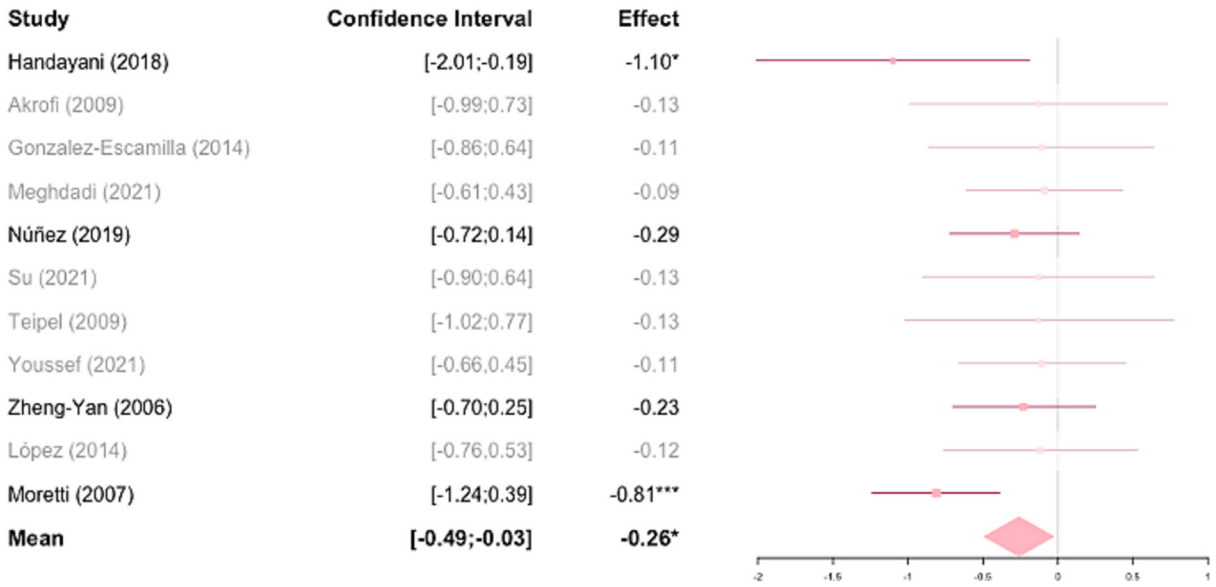

Fig. 3. Forest Plot of Fronto-Parietal synchrony differences in α between MCI and HC. Values are weighed for the sample size. Asterisks represent p-values: *** = 0.001; ** = 0.01; * = 0.05.

of potential patterns of synchrony alterations that characterize the MCI phase, expanding the current knowledge while increasing the strength of previous findings.

The forest plots, obtained by computing the standardized mean difference of the effect sizes of each study, showed an overall reduction of functional coupling in MCI patients compared to HC, in line with findings reporting a hypo-synchronization associated with MCI. Notably, we specifically observed a significant reduction of alpha synchrony between temporo-parietal areas. As the Leave-One-Out Analysis was significant in three cases out of eleven, the reported fronto-parietal alpha decrease is less consistent, and should be taken with caution.

A decrease in alpha global coherence has repeatedly been observed along the AD progression (for a review: Babiloni et al., 2016), and it is more evident in patients with a more severe cognitive impairment (Locatelli et al., 1998). Moreover, in line with our results, several studies have observed a specific reduction of temporal-parietal (together with fronto-parietal) alpha synchronization at rest also in MCI patients (Handayani et al., 2018; Gonzalez-Escamilla et al., 2015; Moretti et al., 2009; Teipel et al., 2009).

The medial temporal lobe, the prefrontal cortex (PFC) and posterior cingulate cortex (PCC) are hubs, among others, that are activated during wakeful states by a well-known resting state network (RSN) (van den Heuvel and Sporns, 2013) namely the default mode network (DMN) (Greicius et al., 2003; Gusnard et al., 2001; Raichle et al., 2001). Alterations of DMN have been established by MEG studies in cognitively normal individuals at-risk for Alzheimer's

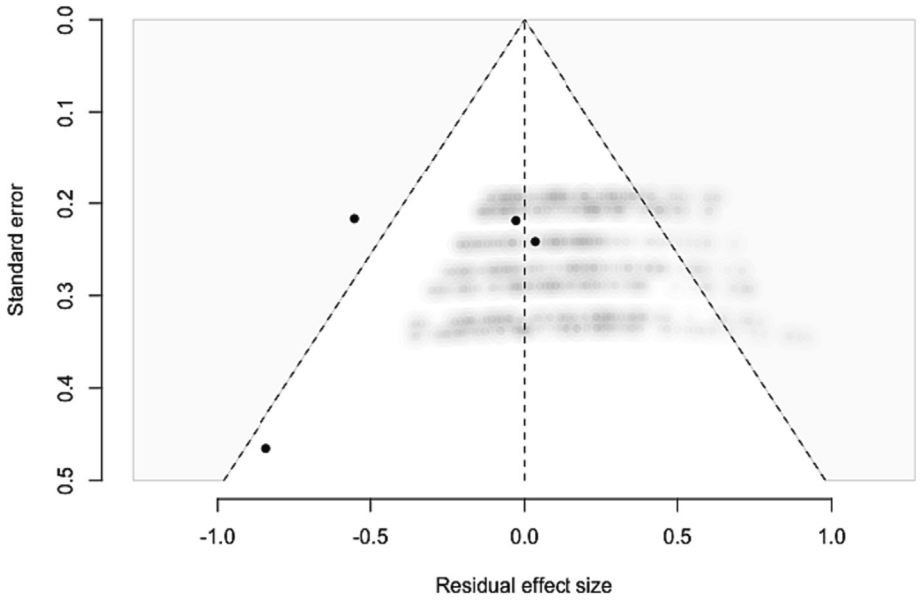

Fig. 4. Funnel Plot of the study results for Fronto-Parietal α synchrony differences between MCI and HC, expressed as the residual effect size (x-axis), and their standard error (y-axis), with each dot representing a single study. Larger studies with greater precision are displayed at the top and studies with lower precision at the bottom. The light gray shadow contains 95% of the imputations of the studies with NSUEs. Asterisks represent p-values: *** = 0.001; ** = 0.01; * = 0.05.

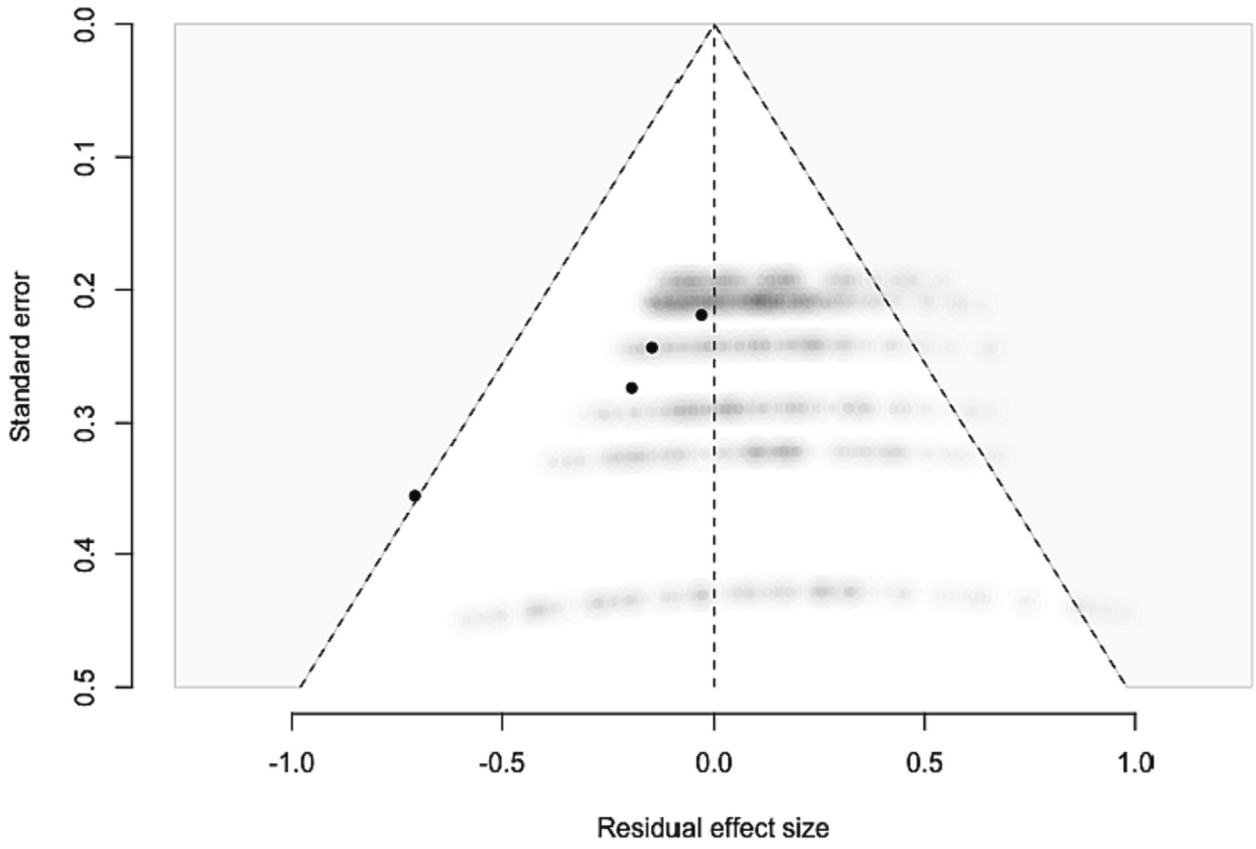

Fig. 5. Funnel Plot of the study results for Temporo-Parietal α synchrony differences in α between MCI and HC, expressed as the residual effect size (x-axis), and their standard error (y-axis), with each dot representing a single study. Larger studies with greater precision are displayed at the top and studies with lower precision at the bottom. The light gray shadow contains 95% of the imputations of the studies with NSUEs. Asterisks represent p-values: *** = 0.001; ** = 0.01; * = 0.05.

disease (Nakamura et al., 2017) suggesting the early susceptibility of this network, which thus deserves special attention in screening procedures at the earliest stage. This evidence seems to support the "system degeneration theory" (Greicius and Kimmel, 2012; Saper et al., 1987), according to which neurodegenerative diseases preferentially affect large-scale brain networks (Jones et al., 2016). Alpha coherence decrease is indeed mostly observed at first throughout temporal and parietal regions (Locatelli et al., 1998),

then it might spread to other network hubs lying in the frontal cortex, following the AD pathology progression (Braak and Braak 1991; Hardy and Higgins, 1992). This pattern could reflect an early degeneration of the cholinergic transmission between cortical and subcortical neurons (Chen et al., 2022) and can result in distortions of the temporal coordination of the distributed neural activity (Uhlhaas and Singer, 2006). For instance, a recent study by Ranasinghe and coll. (2020) established that alpha hypo-synchrony successfully predicted the density of neurofibrillary tangles in the angular gyrus, supporting the view of a link between neuropathology and EEG signals (Gaubert et al., 2019). Furthermore, a reduction of bilateral temporoparietal alpha coherence was found to be associated with the allele ε4 of the apolipoprotein E (Rossini et al., 2007), a major genetic risk factor for late onset's AD (Jelic et al., 1997).

Of note, DMN is considered to drive several internally oriented cognitive functions, such as episodic memory and mind wandering (Andrews-Hanna et al., 2010; Fox et al., 2015). A recent study exploiting MEG data (Higgins et al., 2021), reported that the DMN and alpha parietal network activity are related to *neural replay*, a key mechanism consisting of the spontaneous replay of items supporting memory consolidation and transferring knowledge from the hippocampus to the cortex (Dragoi and Tonegawa, 2011). Alpha rhythm is not only considered to be modulated by thalamus-cortical and cortico-cortical interactions supporting brain communications between cortical and subcortical structures, but it seems to also underlie the retrieval of the semantic information from the brain (Giustiniani et al., 2022; Pfurtscheller and Lopes Da Silva, 1999). Moreover, reduction of alpha coherence was found to be related with the immediate verbal recall score in patients with the diagnosis of Alzheimer's Dementia (Adler et al., 2003). We could therefore speculate that the temporoparietal alpha coherence decrease observed here could reflect an initial impairment by MCI subjects to form and store in memory recently acquired information.

From a therapeutic standpoint, the implementation of techniques such as transcranial magnetic stimulation (TMS) and EEG co-registration allows to jointly explore cortical reactivity and functional/effective connectivity (Nardone et al., 2021). As an example, Ferreri and coll. (2021) observed an inter-trial alpha coherence (ITS) decreases already at the MCI stage.

Patients with MCI show white matter hyperintensities (Targosz-Gajniak et al., 2009), hypoperfusion (Chandra et al., 2019) and gray matter loss in the posterior parietal cortex (for a review: Jacobs et al., 2012), which has a key role in memory retrieval dysfunction in MCI (Cabeza et al., 2008). Targeting TMS parietal cortex, Bonnì and coll. (2013) found that parieto-frontal cortico-cortical functional connectivity is altered in these patients, likely due to the alteration of the superior longitudinal fasciculus (SLF) connecting frontal and parietal cortices (Ferreri et al., 2016; Jacobs et al., 2012). This lack of connectivity between posterior parietal regions, temporal and frontal areas in MCI suggests that the DMN dysfunction could also be due to structural white matter changes (Babiloni et al., 2009; Jacobs et al., 2012), specifically in the SLF.

Overall, the present results report a global reduction of functional integration between cortical areas, which has been considered as an index of disconnection (Das and Puthankattil, 2020), thus suggesting that the cortical "disconnection syndrome" (Delbeuck et al., 2003) (i.e., the hypothesis claiming a reduction of functional integration between brain areas) could be observed even at the MCI stage in specific brain sites (Koenig et al., 2005; López et al., 2014; Stam et al., 2003; Youssef et al., 2021).

The electrophysiological assessment of the temporo-parietal functional synchronization (at least) in the alpha band is then useful to detect neurodegeneration processes in a first-level screening, playing a pivotal role in the detection of AD at prodromal stages. Altogether, alterations in temporoparietal synchrony for higher frequency bands have indeed proven to be highly sensitive and specific to AD neurodegeneration such as gray matter atrophy, loss of cortico-cortical connections (Whitwell et al., 2011), and temporo-parietal hypo-metabolism (Alexander et al., 2002; Tait et al., 2020), which are well-established neuropathological biomarkers of AD (Dubois et al., 2016; McKhann et al., 2011; Jack et al., 2018). Also, a mounting number of studies using machine learning observed that alpha 1 source in parietal and temporal areas were stronger in MCI converters than stable subjects (Rossini et al., 2006), and that the classification performance of alpha 2 bilateral temporo-parietal envelope correlation reached 98% (Dimitriadis et al., 2018). This flourishing line of research toward the discovery of a functional electrophysiological biomarker of AD will contribute to the early detection of the disease and thus to the implementation of disease-modifying therapies.

4.1. Limitations and future perspectives

The present work has some drawbacks. First, some of the results should be taken with caution, because of the (relatively) small samples of the retrieved studies and the LOO violation in alpha and theta fronto-parietal contrasts. Second, due to the heterogeneity in the electrode location and density of the M/EEG setup, different pairs of electrodes were selected for each brain area. To ensure as much as possible homogeneity of the spatial references between the studies, we decided to select only articles carrying out the analysis in the sensor space, which limits the spatial resolution of our findings. Importantly, despite these setup differences, the heterogeneity index calculated for the meta-analysis was low.

Finally, more studies are needed in order to assess whether tempo-parietal and fronto-parietal coupling in specific frequency bands can be predictive of neuropathology progression. Identifying functional biomarkers for AD, such as phase-coupling changes, may help devise new disease-modifying therapies and promote the implementation of new stimulation protocols, targeting specific sets of brain areas forming large-scale networks. Specifically, neurostimulation could induce plasticity and/or boost connectivity between those areas that exhibit weak coupling.

5. Conclusions

The present meta-analysis corroborates previous findings regarding the changes in synchronization between brain areas in MCI patients compared to HC. Here, we extend previous knowledge by reviewing and specifying synchrony alterations for the main frequency bands in several couples of areas, with a novel tool to compute a standardized mean difference that allows the inclusion of non-reported effect sizes. The high feasibility of electrophysiological measures could allow the early detection of brain pathological changes, thus providing new strategies to manage the disease at its prodromal stages.

Conflict of interest

The authors declare no conflict of interest.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2023.10.011.

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*References in bold and marked by * have been included in the quantitative analysis.*

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