

Alpha Power and Functional Connectivity in Cognitive Decline: A Systematic Review and Meta-Analysis

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Abstract.

Background: Mild cognitive impairment (MCI) is a stage between expected age-related cognitive decline and dementia. Dementias have been associated with changes in neural oscillations across the frequency spectrum, including the alpha range. Alpha is the most prominent rhythm in human EEG and is best detected during awake resting state (RS). Though several studies measured alpha power and synchronization in MCI, findings have not yet been integrated.

Objective: To consolidate findings on power and synchronization of alpha oscillations across stages of cognitive decline.

Methods: We included studies published until January 2020 that compared power or functional connectivity between 1) people with MCI and cognitively healthy older adults (OA) or people with a neurodegenerative dementia, and 2) people with progressive and stable MCI. Random-effects meta-analyses were performed when enough data was available.

Results: Sixty-eight studies were included in the review. Global RS alpha power was lower in AD than in MCI (ES = -0.30; 95% CI = -0.51, -0.10; $k = 6$), and in MCI than in OA (ES = -1.49; 95% CI = -2.69, -0.29; $k = 5$). However, the latter meta-analysis should be interpreted cautiously due to high heterogeneity. The review showed lower RS alpha power in progressive than in stable MCI, and lower task-related alpha reactivity in MCI than in OA. People with MCI had both lower and higher functional connectivity than OA. Publications lacked consistency in MCI diagnosis and EEG measures.

Conclusion: Research indicates that RS alpha power decreases with increasing impairment, and could—combined with measures from other frequency bands—become a biomarker of early cognitive decline.

keywords: Alpha rhythm, brain waves, dementia, electroencephalography, mild cognitive impairment

INTRODUCTION

The term mild cognitive impairment (MCI) is used to describe cognitive deficits beyond normal aging

but not severe enough to hamper day-to-day activities [1]. These mild deficits often, though not always, progress to dementia [2]. Estimated prevalence of MCI varies between 3 and 24% and is higher in older age groups [3]. With the world's population aging [4], the number of individuals experiencing pathological cognitive decline is also likely to rise [5]. It would be helpful to identify biomarkers that are sensitive to early stages of cognitive decline and that can be used

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as measures of disease state, disease progression, and treatment targets.

MCI is a heterogeneous condition with several different etiologies, presentations, and outcomes. While memory impairment was initially a necessary condition for MCI [6], the definition was later revised to include both memory (amnesic MCI, aMCI) and non-memory deficits (non-amnesic MCI, naMCI) [7]. These two subtypes can be broken down further depending on whether the impairment encompasses a single or multiple cognitive domains (single- and multiple-domain MCI) [2]. The majority of people with MCI will not experience further cognitive decline (stable MCI, sMCI) [8], but MCI can be progressive (pMCI). Though MCI has mostly been studied in relation to Alzheimer's disease (AD), it has also been recognized as a prodromal stage of other neurodegenerative dementias, including dementia with Lewy bodies and dementia due to Parkinson's disease [9–11], as well as frontotemporal dementia (FTD) [12]. Annual conversion rate is around 10% for dementia due to Parkinson's disease [13, 14], and from 5 to 20% for AD and dementia with Lewy bodies [8, 15–17]. Conversion rates depend on the subtypes of MCI considered [15, 18], and on whether sampling was clinic- or community-based [8, 19, 20]. However, even according to the lower estimates, people with MCI are at a higher risk of developing dementia than cognitively healthy older adults.

To develop interventions that delay or prevent progression from MCI to dementia, there is a need for affordable, widely accessible, and non-invasive measures of pathology. A promising neurophysiological marker is a change in rhythmic neural activity. These oscillations occur in several frequency bands ranging from slow (delta and theta) to fast (alpha, beta, and gamma) and can be recorded with electroencephalography (EEG). Two of the measures used to describe oscillatory signals are power and synchronization. Power is proportional to the rate of energy change at a specific frequency or frequency band [21]. Oscillations from two or more regions can be synchronized in phase or amplitude, which reflects functional connectivity between them [22, 23]. Power and synchronization of oscillations in different frequency bands are involved in various cognitive and motor processes [21, 24–27]. Activity in each of the bands has been associated with dementia [28–30], and a biomarker specific enough to distinguish between etiologies and outcomes of cognitive decline will likely combine information from several frequency bands and measures. Bands are

somewhat arbitrary, and changes in one band are not specific to a particular disorder [31, 32], meaning they need to be interpreted in the context of the whole spectrum. However, reviewing changes in more frequency bands would be beyond the scope of a single paper.

We have therefore decided to take the first step by focusing on the alpha band for three main reasons. First, alpha is the most prominent rhythm during quiet wakefulness [33]. Second, it has large amplitudes ranging from 10 to 50 μV [34]. This is in contrast to theta, beta, and gamma waves, which have smaller amplitudes at rest [34–36], and can be best identified using tasks with many repetitions. This makes measuring alpha activity in research and clinical practice highly feasible, as it does not require people with cognitive decline to perform challenging and tiresome tasks. Lastly, lower power and synchronization of alpha oscillations have consistently been associated with neurodegenerative dementias, especially AD [29, 37–39]. These decreases were found to correlate with lower cognitive scores [40, 41], higher atrophy of the hippocampus [42] and higher amyloid burden [43], as well as with genetic susceptibility for AD [44, 45]. Though alpha activity in other neurodegenerative dementias is less well-researched, there is evidence of lower alpha power in people with dementia due to Lewy body disorders [46–49]. Alpha power and synchronization are therefore an important part of the changes in the EEG spectrum associated with cognitive decline.

Though several studies have measured alpha power and synchronization in people with MCI, findings have not yet been integrated. We aim to consolidate findings on power and synchronization of alpha oscillations across stages of cognitive decline, including healthy aging, MCI, and dementia. We will include cross-sectional studies that compared people with MCI with cognitively healthy older adults and with people with a neurodegenerative dementia, as well as longitudinal studies that compared people with MCI who progressed to dementia and those whose cognitive status remained stable.

METHODS

Literature search

This review and meta-analysis were carried out according to PRISMA guidelines [50, 51]. We searched PubMed ($k=549$), Web of Science ($k=967$), EMBASE ($k=879$), PsychINFO ($k=222$),

and Cochrane ($k = 29$) for papers published until 24 January 2020. The search terms were: “*mild cognitive impairment*” AND (*eeg OR oscillations*). We used broad terms to ensure we captured all relevant papers—titles, abstracts, and keywords often only refer to significant differences in one frequency band, whereas non-significant findings in other bands are only briefly mentioned in the text.

Study selection

Two independent researchers (NL and DIL) reviewed abstracts and full texts. Disagreement was resolved by means of discussion.

The objectives of this paper and the inclusion criteria were framed in terms of the population of interest, comparators, outcomes, and study design (elements of the PICOS model). Abstracts were selected for further screening if they satisfied the following criteria: 1) at least one group with MCI, 2) a comparison group of cognitively healthy older adults or people with a neurodegenerative dementia, or a comparison of people with progressive and stable MCI, 3) used EEG to measure oscillations in awake resting state or during task performance, 4) reported results of alpha power or synchronization analysis, 5) sample size of at least 10 participants per group, and 6) paper published in English.

Studies were only included if the diagnosis of MCI was not related to a medical condition other than a neurodegenerative dementia. Studies on MCI due to cerebrovascular conditions, rapid eye movement sleep behavior disorder, diabetes, or depression were therefore excluded. We excluded conference abstracts, case studies, animal studies, computational models, and reviews and other publications without original data. Because PD itself has been associated with changes in EEG [52–54], we only included studies that compared people with MCI due to Parkinson’s disease (PD-MCI) with cognitively healthy PD patients (PD-CH).

If published data was insufficient or unclear, we contacted the original authors for additional information. When studies were based on overlapping datasets, we only included the most recent publication, the publication with the largest sample size, and/or the most prototypical study. Moreover, we prioritized publications with available means and standard deviations to maximize the amount of studies we could include in meta-analyses. Studies that fulfilled the inclusion criteria but were omitted due to overlapping samples are shown in

Supplementary Material 1. We allowed for overlap between studies when they measured different aspects of alpha oscillations. Furthermore, studies were excluded if published data was insufficient to determine whether any differences in alpha activity were found, or if there were inconsistencies within the report and original authors could not be reached or did not provide additional information upon request.

Data extraction

From every included paper, the first author (NL) extracted the following information: 1) first author and year of publication, 2) participant characteristics (diagnosis, sample size, mean age, sex), 3) diagnostic criteria for MCI and dementia, 4) length of follow-up for longitudinal studies, 5) recording conditions (eyes closed or open resting state, or task and cognitive domain), 6) measures of alpha power or synchronization, 7) frequency range, 8) electrodes or sources for which alpha was calculated, 9) whether findings were significant, 10) the direction of significant findings, and 11) the topographic location of significant findings. When available, means and standard deviations, or statistical values that could be used for meta-analysis, were also extracted. Otherwise, original authors were contacted and asked to provide this information. Original authors were also contacted to clarify any uncertainties.

Random-effects meta-analyses

Studies were grouped according to EEG measures (power or synchronization, rest or task-based; brief description of alpha measures can be found in Table 1), participant groups (MCI compared to cognitively healthy older adults, MCI compared to dementia, progressive compared to stable MCI), and alpha definition (full alpha band, lower alpha frequencies, upper alpha frequencies). Meta-analyses were only attempted when we had data of at least five comparable studies, as with a very small number of studies, quantitative analysis does not have added value over the description of individual study results. We were able to perform four meta-analyses: 1) power during awake rest in the full alpha band in people with MCI compared to cognitively healthy older adults, and 2) in people with AD compared to people with MCI; and 3) power during awake rest in lower and 4) upper alpha bands in people

Table 1
An overview of alpha measures included in this review and meta-analysis

Power at the level of electrodes (sensors) or reconstructed sources	
Absolute power	Amplitude of the oscillating waveform squared. It can be calculated for a narrow frequency band or the entire spectrum, and can be averaged over a set of electrodes.
Relative power	Absolute power in a narrow frequency band divided by total power.
Global field power	Spatial standard deviation across all electrodes that quantifies the amount of whole-brain activity in a frequency band.
Current source density	A measure of the strength of sources generating the current recorded by scalp electrodes.
ERS/ERD	Event-related synchronization/desynchronization. An increase (ERS) or decrease (ERD) in power in response to a stimulus.
Peak-to-peak amplitude	Difference between the highest and the lowest amplitude value.
Functional connectivity at the level of electrodes (sensors) or reconstructed sources	
Coherence	Degree of linear similarity between the phases of two signals. Based on real and imaginary parts of the cross-spectrum.
Imaginary coherence	Coherence based on the imaginary part of the cross-spectrum.
Lagged linear connectivity	Coherence between reconstructed activities of cortical sources. It attempts to overcome the problem of volume conduction.
Phase lag index	Degree of symmetry between the phase distributions of two signals. It attempts to overcome the problem of volume conduction.
Weighted phase lag index	Improved phase lag index. It attempts to overcome the problem of volume conduction.
Phase synchronization index	The distribution of phase differences between two signals.
Synchronization likelihood	The likelihood that two signals are in the same state at two different times. It detects linear and non-linear interdependencies.
Global field synchronization	The percentage of activity across all electrodes that can be explained by a single phase.
S-estimator	Synchronization strength based on the interdependent relationship between multi-channel time series in state space.
Global synchronization index	Improved S-estimator.
Global coupling index	Improved global synchronization index.
Amplitude envelope correlation	Synchronization between the magnitude (amplitude) of two signals independent of phase.
Source localization methods – estimate the likely location of the sources of EEG signals	
Beamforming	
Fast Fourier transform (FFT) dipole approximation	
Low resolution electromagnetic tomography (LORETA)	
Minimum norm estimate	
Multivariate autoregressive model-efficient fast independent component analysis (MVAR-EfICA)	

with MCI compared to cognitively healthy older adults.

We performed random-effects meta-analyses in Review Manager (RevMan) 5.3 [55]. For 12 out of 13 studies, we used means and standard deviations to calculate standardized mean difference (SMD). If results were reported for each scalp or brain region separately [56–60], we pooled means and standard deviations according to the formulas below [61]. For one study [62], the r value was converted into SMD. See Table 2 for an overview of measures included in meta-analyses.

$$M_i = \frac{M_i + (i - 1)NM_{i-1}}{iN}$$

$$SD_i = \frac{\sqrt{((i - 1)N - 1)SD_{i-1}^2 + (N - 1)SD_i^2 + \frac{N(i-1)}{2}(M_i^2 + M_{i-1}^2 - 2M_iM_{i-1})}}{iN - 1}$$

Formulas for pooled mean (above) and standard deviation (above) were adapted from the Cochrane

Handbook for Systematic Reviews of Interventions [61]. M is mean, SD is standard deviation, N is sample size, and i is iteration. Sample size was assumed to be the same for each scalp or brain region. The number of iterations is equal to the number of regions.

We calculated the overall effect size and 95% confidence intervals (CI). Heterogeneity among studies was examined with I^2 [63]. I^2 values of 25%, 50%, and 75% were considered low, moderate, and high, respectively [64]. We also calculated power for each study that was included in the meta-analysis with G*Power 3.1 [65]. The primary outcome measure was the difference in EEG power between two groups. Power was estimated given the alpha of 0.05, sample

sizes per group as reported in the original paper, and effect sizes as calculated in RevMan 5.3 [55].

Table 2

Overview of data included in meta-analyses. MCI diagnoses, power measures used to calculate SMD, and electrodes or sources across which means and standard deviations were pooled

Paper	Diagnosis	Power measure	Pooled electrodes/sources
Babiloni [56]	aMCI	LORETA; current source density	sources: central, frontal, parietal, occipital, temporal, limbic
Bonanni [70]	AD-MCI	global relative power	–
Caravaglios [62]	aMCI	global absolute power	–
Dauwels [71]	AD-MCI	global relative power	–
Huang [72]	MCI	FFT dipole approximation; global field power	–
Luckhaus [57]	aMCI	absolute power	electrodes: Fz, Cz, Pz
Michels [43]	aMCI	beamforming; power at first identified source (angular gyrus)	–
Musaeus [58]	MCI	relative power	electrodes: Fp1, Fp2, F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T3, T4, T5, T6, Fz, Cz, Pz
Pons [59]	aMCI	power at the maximum alpha frequency	electrodes: F3, F4, FT7, FT8, C3, C4, TP7, TP8, P3, P4, O1, O2
Poza [69]	AD-MCI	global relative power	–
Smailovic [73]	MCI	global field power	–
van der Hiele [79]	aMCI	global absolute power	–
Ya [60]	AD-MCI	? power	electrodes: F3, F4, C3, C4, P3, P4, T3, T4, O1, O2

MCI, mild cognitive impairment; aMCI, amnesic MCI; AD-MCI, MCI due to Alzheimer's disease; LORETA, low resolution brain electromagnetic tomography; FFT, fast Fourier transform; question mark indicates information was not reported.

Risk of bias assessment

Risk of bias in individual studies was assessed with a modified Newcastle-Ottawa scale. The modified scale and the assessment of each study are given in Supplementary Material 2.

Potential publication bias was assessed with funnel plot asymmetry. We did not perform Egger's regression test [66] because the number of studies in each meta-analysis was lower than 10 [67]. Funnel plots are given in Supplementary Material 3.

RESULTS

Study selection

A total of 2,646 records were identified, and after removing duplicates, 1,466 remained. Sixty-eight records were included in the systematic review, some of which reported on more than one measure of interest. The selection procedure is shown in Fig. 1.

Alpha power and functional connectivity during wakeful rest

Cross-sectional studies comparing people with MCI to cognitively healthy older adults and people with AD

Power. In most studies that investigated awake resting state alpha power, participants with MCI were diagnosed with the amnesic subtype (see Table 3

for details). Four studies included people with MCI due to AD (AD-MCI). AD-MCI was either diagnosed according to the 2011 clinical National Institute on Aging and Alzheimer's Association criteria (NIA-AA: [68]) [60, 69] or confirmed by later conversion to AD [70, 71]. Three studies did not specify the MCI subtype or ascribe MCI to a particular dementia, but did compare people with MCI to people with AD [58, 72, 73]. Sharma et al. [74] did not specify the MCI subtype or the type of dementia, and based their diagnoses solely on the Mini-Mental State Examination score. Jelic et al. [75] included participants with "objective memory disturbances", but their diagnostic criteria were in line with those that were later developed for aMCI [6]. In other studies, MCI was diagnosed according to widely accepted criteria (e.g., [6, 7, 68, 76]). In all of the studies, EEG was measured with eyes closed. Power was mostly reported as relative power, absolute power, or current source density (see Table 3 for details). For one study [60], it was not clearly stated whether power was relative or absolute.

In four studies, alpha power in the full band was lower in people with MCI than in cognitively healthy older adults (OA; Michels et al. [43], $n = 17$ aMCI, 17 OA; Musaeus et al. [58], $n = 117$ AD, 117 MCI, 138 OA; Bonanni et al. [70], $n = 50$ AD, 14 AD-MCI, 50 OA; Roh et al. [77], $n = 41$ AD, 38 aMCI, 39 OA), and in two of these, alpha power decreased with increasing impairment (Musaeus et al. [58], $n = 117$ AD, 117 MCI, 138 OA; Roh et al. [77], $n = 41$ AD, 38

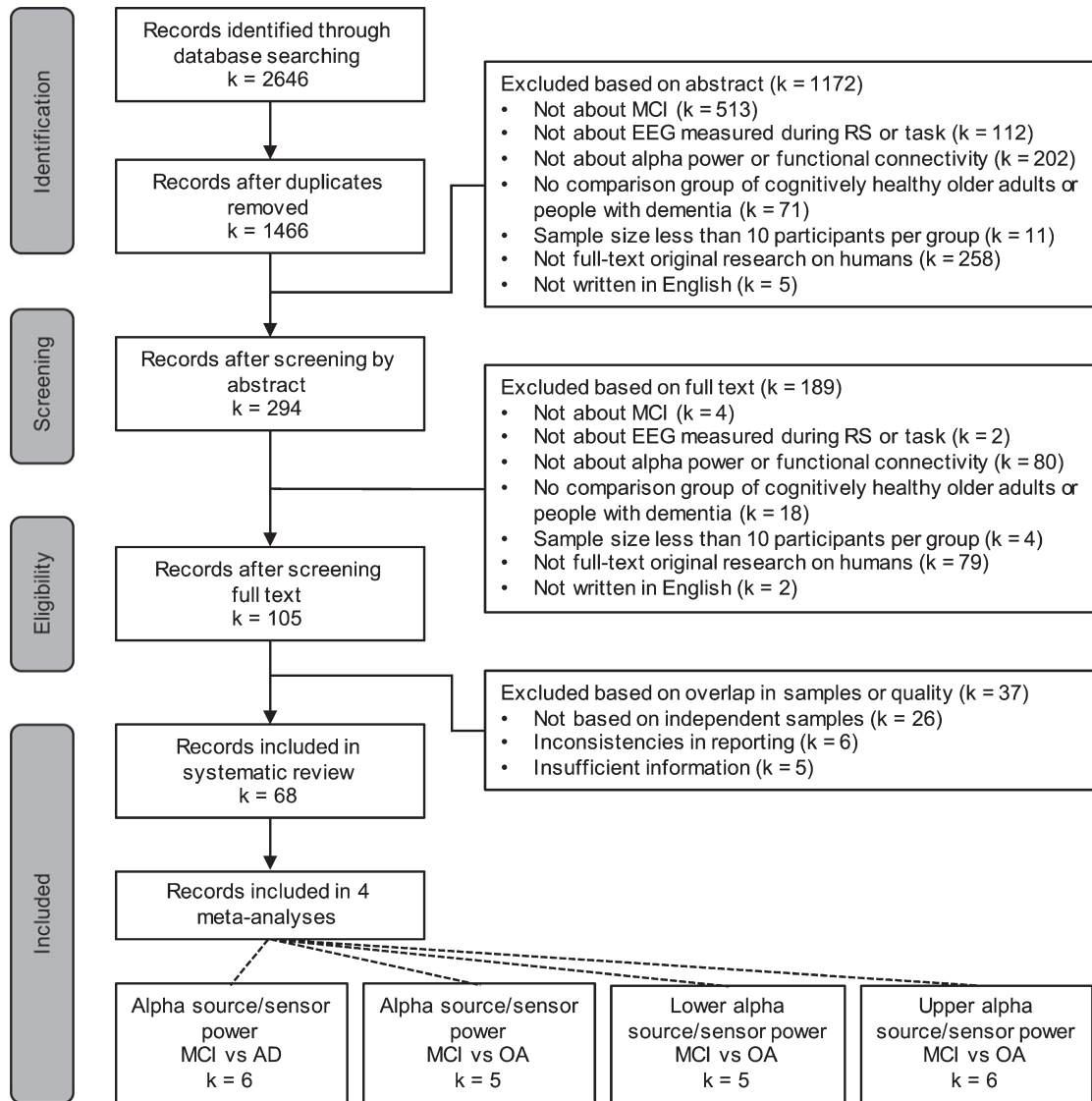


Fig. 1. PRISMA flow diagram. MCI, mild cognitive impairment; EEG, electroencephalography; RS, resting state; AD, Alzheimer's disease; OA, cognitively healthy older adults

aMCI, 39 OA). Three additional studies found lower alpha power in people with AD than in people with MCI (Huang et al. [72], $n = 38$ AD, 31 MCI, 24 OA; Smailovic et al. [73], $n = 197$ AD, 230 MCI; Jelic et al. [75], $n = 18$ AD, 19 aMCI, 16 OA). Though decreases were also reported for global measures [70, 72, 73] and for all areas of the scalp, they were most often found in posterior (temporal, parietal, and occipital) areas [43, 58, 72, 75, 77].

We performed separate meta-analyses comparing resting state power in the full alpha band in people with MCI and cognitively healthy older adults (Fig. 2; $k = 5$; $n = 198$ MCI, 258 OA), and in people with MCI

and people with AD (Fig. 3; $k = 6$; $n = 481$ AD, 499 MCI). The overall effect sizes indicated that people with MCI have lower resting state alpha power than cognitively healthy older adults ($ES = -1.49$; 95% $CI = -2.69, -0.29$; $p = 0.02$), and that people with AD have lower resting state alpha power than people with MCI ($ES = -0.30$; 95% $CI = -0.51, -0.10$; $p = 0.003$). However, because the meta-analysis comparing people with MCI and cognitively healthy older adults included studies with highly heterogeneous outcomes ($I^2 = 96\%$), the result should be interpreted with caution. The two studies that contributed most to the heterogeneity were Michels et al. [43] and

Table 3
Power in awake resting state at the level of electrodes and sources of neural activity in people with aMCI, MCI, and MCI due to AD

Paper	Groups	Diagnosis	<i>n</i>	Age (y)	Sex (% F)	EEG measure	Alpha (Hz)	Results MCI versus OA	AD versus MCI	Electrodes/ sources	Location of significant differences
Musaeus [58]	AD	DSM-IV-TR, McKhann [?]	117	75.5 (7.7 SD)	60.7	Welch's relative power (eyes closed)	9–12.99	↓ OA > MCI	↓ MCI > AD	electrodes: 19	OA > MCI: F7, T5, F8, T4, T6, O2 MCI > AD: F7, T3, T5, F8, T4, T6, P4, O2
	MCI OA	Winblad [7]	117 138	70.2 (8.1 SD) 66.6 (7.6 SD)	53 60.1						
Roh [77]	AD	McKhann [204]	41	73.8 (5.8 SD)	87.8	FFT relative power (eyes closed)	8–12	↓ OA > aMCI	↓ aMCI > AD	electrodes: 19	left and right parieto-occipital (P3/P7/O1, P4/P8/O2)
	aMCI OA	Petersen [6]	38 39	72.2 (5.7 SD) 72.7 (4.3 SD)	65.8 69.2						
Bonanni [70]	AD	McKhann [204] CSF biomarker (Aβ ₄₂ , tau, Ptau) positive	50	71.3 (4.4 SD)	60	FFT relative power (eyes closed)	9–12	↓ OA > AD-MCI	x	electrodes: 19	global averaged
	AD-MCI	Petersen [6], conversion	14	71.9 (9.7 SD)	50						
	OA		50	72.6 (5.4 SD)	48						
Michels [43]	aMCI	?, 6 APOE ε4 allele	17	72.1 (4.6 SD)	29.4	beamforming; source power (eyes closed)	8–13	↓ OA > aMCI	–	electrodes: 60 sources: whole brain	angular gyrus
	OA	5 APOE ε4 allele	17	71.8 (4.6 SD)	29.4						
Jelic [75]	AD	McKhann [204]	18	61.1 (5.5 SD)	66.7	FFT relative power (eyes closed)	8–13	x	↓ aMCI > AD	electrodes: 12	all regions: left and right frontal (F3/C3, F4/C4), left and right temporal (T3/T5, T4/T6), left and right parieto-occipital (P3/O1, P4/O2)
	aMCI	similar to Petersen [6]	19	61.5 (7.0 SD)	66.7						
	OA		16	64.3 (10.8 SD)	43.8						

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Table 3
(continued)

Paper	Groups	Diagnosis	<i>n</i>	Age (y)	Sex (% F)	EEG measure	Alpha (Hz)	Results MCI versus OA	AD versus MCI	Electrodes/ sources	Location of significant differences
Huang [72]	AD	McKhann [204]	38	62.7 (7.1 SD)	55.3	FFT relative power	8–11.5	x	↓ MCI > AD	electrodes: 16	all regions: left and right fronto-central (F3/C3, F4/C4), left and right temporal (T3/T5, T4/T6), left and right centro-parietal (C3/P3, C4/P4), and left and right temporo-occipital (T5/O1, T6/O2)
	MCI	similar to Petersen [6]	31	61.2 (8.0 SD)	51.6	FFT dipole approximation; global field power (eyes closed)		x	↓ MCI > AD	electrodes: 20 sources: whole brain	global
	OA		24	63.4 (9.8 SD)	62.5						
Poza [69]	AD	McKhann [205]	37	79.2 (6.9 SD)	64.9	CWT relative power (eyes closed)	8–13	x	x	electrodes: 19	
	AD-MCI OA	Albert [68]	19 29	76.5 (7.5 SD) 76.6 (7.2 SD)	57.9 69						
Sharma [74]	dementia	HMSE score < 18	15	61.1 (? SD)	?	Welch's absolute power (eyes closed)	8.6–12.6	x	x	electrodes: 21	
	MCI	HMSE score 18–24	16	58.4 (? SD)	?						
	OA		13	52.1 (? SD)	?						
Kwak [132]	AD	McKhann [204]	146	76.4 (8.1 SD)	64.4	FFT relative power (eyes closed)	8–13	x	?	electrodes: 20	
	aMCI	Petersen [76]	14	72.5 (6.0 SD)	71.4						
	OA		34	73.5 (8.4 SD)	47.1						

Smailovic [73]	AD	ICD-10	197	67.8 (9.2 SD)	63.5	FFT global field power (eyes closed)	8–11.5	–	↓ MCI > AD	electrodes: ?	global
	MCI	Winblad [7]	230	65.9 (8.2 SD)	52.6						
Luckhaus [57]	AD	McKhann [204]	42	69.1 (10.7 SD)	43.2	FFT absolute power (eyes closed)	8–11.5	–	x	electrodes: 3 Fz, Cz, Pz	
	aMCI	Petersen [6]	88	65.9 (9.6 SD)	52.3						
Scrascia [206]	mild AD	McKhann [205]	18	75.3 (1.7 SD)	44.4	Welch's absolute power (eyes closed)	8–12	–	x	electrodes: 19	
	moderate AD		8	77.0 (2.5 SD)	50						
	aMCI	Petersen [76]	12	74.3 (2.1 SD)	25						
Hsiao [207]	AD	DSM-IV, McKhann [204]	21	82.7 (7.5 SD)	71.4	minimum norm estimate; source power (eyes closed)	8–13	–	x	electrodes: 19 sources: sensori-motor network	
	aMCI	Petersen [1]	21	80.4 (5.6 SD)	61.9						
Vecchio [81]	AD	DSM-IV-TR, McKhann [205], MRI biomarker positive	174	73.2 (0.6 SE)	71.3	sLORETA; current source density (eyes closed)	8–10.5	↓ OA > aMCI	↓ aMCI > AD	electrodes: 19 sources: whole brain	parietal, occipital, limbic
	aMCI	Petersen [76]	154	71.5 (0.6 SE)	55.8						
	OA			50	72.9 (1.0 SE)		50	10.5–13	↓ OA > aMCI	↓ aMCI > AD	

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Table 3
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Paper	Groups	Diagnosis	<i>n</i>	Age (y)	Sex (% F)	EEG measure	Alpha (Hz)	Results MCI versus OA	AD versus MCI	Electrodes/ sources	Location of significant differences
Babiloni [80]	AD	DSM-IV, McKhann [204]	73	74.1 (1.0 SE)	47.9	FFT relative power	8–10	↓ OA > aMCI	↓ aMCI > AD	electrodes: 9	left, right, central parietal (P3, P4, Pz)
	aMCI	Petersen [76], Portet [208]	69	74.1 (0.8 SE)	55.1		10–12	x	x		
	OA		64	73.7 (0.9 SE)	50						
Babiloni [56]	AD	DSM-IV, McKhann [204]	108	71.0 (0.8 SE)	?	LORETA; current source density (eyes closed)	8–10.5	↓ OA > aMCI	↓ aMCI > AD	electrodes: 19 sources: whole brain	parietal, occipital, limbic, global
	aMCI	Petersen [76], Portet [208]	102	69.4 (1.0 SE)	?		10.5–13	x	x		
	OA		57	73.4 (0.9 SE)	?						
McBride [78]	AD	?, no <i>APOE</i> ε4 allele	17	76.7 (5.2 SD)	60	Welch's relative power (eyes closed)	7.5–9.5	x	x	electrodes: 30	
	aMCI	?, no <i>APOE</i> ε4 allele	16	74.6 (9.0 SD)	25		9.5–12.5	x	x		
	OA		15	75.7 (5.5 SD)	50						
Ya [60]	AD	Albert [68]	40	73.5 (7.3 SD)	37.5	? power (eyes closed)	8–10.9	x	x	electrodes: 10	
	AD-MCI	Albert [68]	40	71.9 (7.9 SD)	42.5		11–13.9	x	x		
	OA		40	70.4 (7.1 SD)	45						

Table 3
(continued)

Paper	Groups	Diagnosis	<i>n</i>	Age (y)	Sex (% F)	EEG measure	Alpha (Hz)	Results MCI versus OA	AD versus MCI	Electrodes/ sources	Location of significant differences
Dauwels [71]	AD-MCI	conversion, postmortem examination	22	71.9 (10.2 SD)	?	DFT relative power (eyes closed)	8–10	x	–	electrodes: 21	
	OA		38	71.7 (8.3 SD)	?		10–12	x			
van der Hiele [79]	aMCI	Petersen [6]	12	74.0 (6.0 SD)	41.7	FFT absolute power (eyes closed)	8–10.5	x	–	electrodes: 17	
	OA		16	72.0 (5.0 SD)	56.3		10.5–13	x			
Pons [59]	aMCI	Petersen [6]	30	66.8 (4.7 SD)	30	power at maximum alpha frequency (eyes closed)	7–9	↑ aMCI > OA	–	electrodes: 12	left and right central (C3, C4), parietal (P3, P4, TP8), occipital (O1, O2)
	OA		30	68.4 (6.1 SD)	30		9.1–11	↓ OA > aMCI			left and right occipital (O1, O2)
Caravaglios [62]	aMCI	Albert [68]	27	70.6 (6.6 SD)	70.3	FFT absolute power (eyes closed)	upper alpha individually determined	↑ aMCI > OA	–	electrodes: 21	all electrodes
	OA		15	67.3 (6.5 SD)	53.3						
Hsiao [94]	AD	DSM-IV, McKhann [204]	21	82.7 (7.5 SD)	71.4	minimum norm estimate; source power (eyes closed)	lower alpha individually determined	–	↓ aMCI > AD	electrodes: 19 sources: default mode network	left medial temporal cortex, right inferior parietal cortex, bilateral PCC
	aMCI	Petersen [1]	21	80.4 (5.6 SD)	61.9		upper alpha individually determined	↓ aMCI > AD			bilateral medial frontal cortex, ACC, inferior parietal cortex, PCC, precuneus, left medial temporal cortex

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Table 3
(continued)

Hsiao [94]	AD	DSM-IV, McKhann [204]	21	82.7 (7.5 SD)	71.4	minimum norm estimate; source power (eyes closed)	lower alpha individually determined	-	↓ aMCI > AD	electrodes: 19 sources; default mode network	left medial temporal cortex, right inferior parietal cortex, bilateral PCC
	aMCI	Petersen [1]	21	80.4 (5.6 SD)	61.9		upper alpha individually determined		↓ aMCI > AD		bilateral medial frontal cortex, ACC, inferior parietal cortex, PCC, precuneus, left medial temporal cortex

Arrows indicate whether power in the more cognitively impaired group was significantly lower or higher than in the less impaired group and crosses mark non-significant findings. Dashes indicate that differences between the two groups were not investigated, and question marks that information was not reported or was unclear. AD, Alzheimer's disease; MCI, mild cognitive impairment; aMCI, amnesic MCI; OA, cognitively healthy older adults; SD, standard deviation; SE, standard error; FFT, fast Fourier transform; DFT, discrete Fourier transform; CWT, continuous wavelet transform; (s)LORETA, standardized low resolution brain electromagnetic tomography; PCC, posterior cingulate cortex; ACC, anterior cingulate cortex; BA, Brodmann area; DSM, Diagnostic and Statistical Manual of Mental Disorders; ICD, International Classification of Diseases; CSF, cerebrospinal fluid; Ptau, phosphorylated-tau; HMSE, Hindi version of the Mini-Mental State Exam.

Bonanni et al. [70], both of which had very high effect sizes (-5.84 and -2.86 , respectively) indicating resting state alpha power was lower in people with MCI than in cognitively healthy older adults. Michels et al. [43] only compared power at the strongest source (angular gyrus), which likely inflated the result compared to other studies where power was compared globally [58, 69, 70, 72]. In addition, Bonanni et al. [70] only included participants who later converted to AD. Given the findings of longitudinal studies (see below) that found alpha power was lower in converters than non-converters, it is possible that participants in Bonanni et al. [70] had lower alpha power than participants in studies where converters and non-converters were grouped together.

Half of the studies in which lower and upper alpha bands were examined separately did not find significant differences between people with MCI and cognitively healthy older adults (Ya et al. [60], $n = 40$ AD, 40 AD-MCI, 40 OA; Dauwels et al. [71], $n = 22$ AD-MCI, 38 OA; McBride et al. [78], $n = 17$ AD, 16 aMCI, 15 OA; van der Hiele et al. [79], $n = 12$ aMCI, 16 OA). Meta-analyses for each band were also non-significant, and I^2 values indicated high heterogeneity between studies (lower alpha: Fig. 4; $k = 5$; $n = 206$ MCI, 181 OA; $ES = 0.23$; 95% $CI = -0.34, 0.81$; $p = 0.42$; $I^2 = 85\%$; upper alpha: Fig. 5; $k = 6$; $n = 233$ MCI, 196 OA; $ES = -0.05$; 95% $CI = -0.46, 0.36$; $p = 0.81$; $I^2 = 74\%$). Studies that did report significant differences had conflicting findings (Pons et al. [59], $n = 30$ aMCI, 30 OA; Caravaglios et al. [62], $n = 27$ aMCI, 15 OA; Babiloni et al. [80], $n = 73$ AD, 69 aMCI, 64 OA; Vecchio et al. [81], $n = 174$ AD, 154 aMCI, 50 OA) that could be explained by differences in methodology and the definition of alpha. Whereas studies by Babiloni et al. [80] and Vecchio et al. [81] had large sample sizes, studies by Pons et al. [59] and Caravaglios et al. [62] had smaller samples. In addition, results of the study by Pons et al. [59] could be affected by an overlap between alpha and theta activity. Though alpha band is usually defined as ranging from 8 to 13 Hz [82], Pons et al. [59] measured lower alpha power in the 7–9 Hz range, which includes frequencies belonging to the theta band. They measured power only at the individually determined peak alpha frequency in the 7–9 Hz range, and found that it was higher in people with MCI than in cognitively healthy older adults. For some people with MCI, the peak could have been in the theta band, which—contrary to alpha—was found to have higher power in MCI [58] and AD [29].

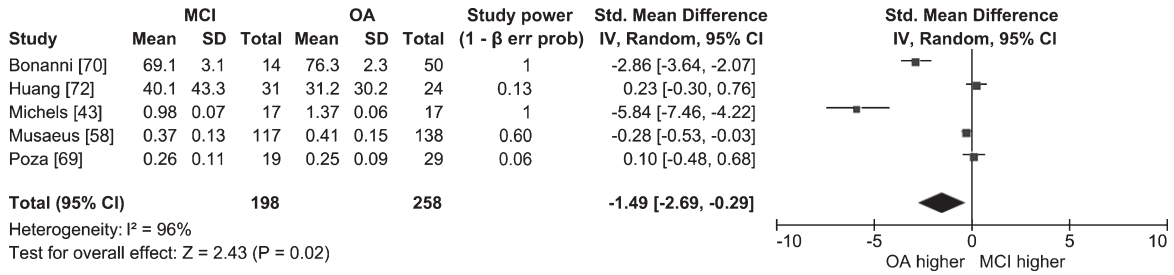


Fig. 2. Table and forest plot of effect sizes for power in awake resting state in the full alpha band in people with MCI versus cognitively healthy older adults (OA). The table shows mean, standard deviation (SD) and sample size (Total) for each participant group, and power for each study. Standardized mean difference and 95% confidence intervals (CI) for each study are shown in the table and in the forest plot as squares. The size of the square represents the weight of the study, and the whiskers the CI. Standardized mean difference was calculated by subtracting the mean alpha power of the OA group from that of the MCI group and dividing it by the standard deviation of alpha power among both groups. The overall effect size and 95% CI are shown in the table and in the forest plot as a diamond. The width of the diamond represents 95% CI. Statistical significance of the overall effect was calculated with the z-test.

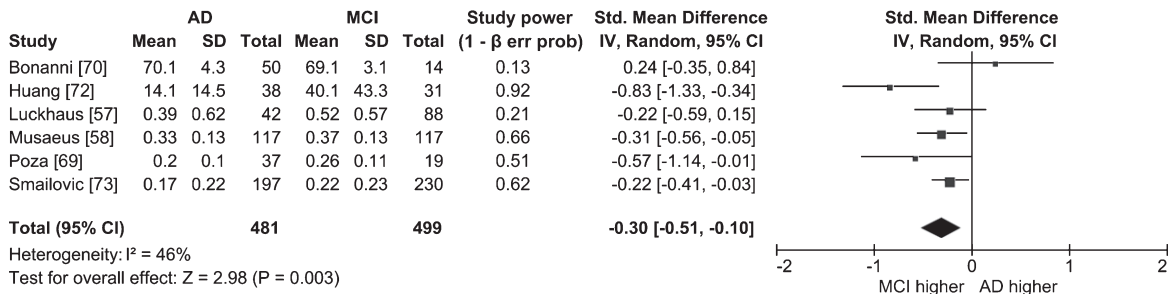


Fig. 3. Table and forest plot of effect sizes for power in awake resting state in the full alpha band in people with AD versus people with MCI. Standardized mean difference was calculated by subtracting the mean alpha power of the MCI group from that of the AD group and dividing it by the standard deviation of alpha power among both groups. For the explanation of the table and the plot, see Fig. 2.

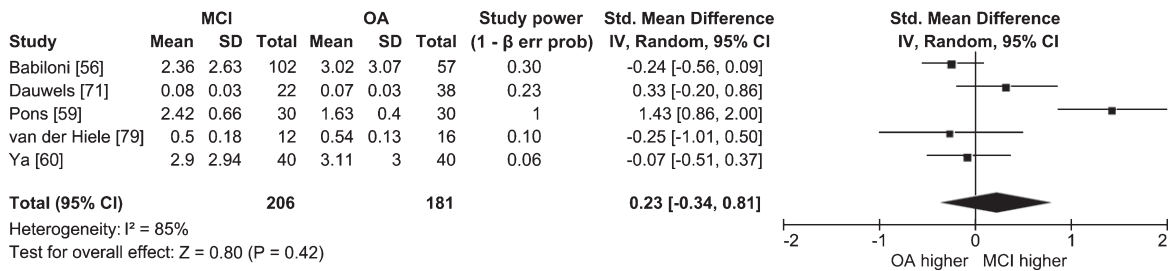


Fig. 4. Table and forest plot of effect sizes for power in awake resting state in the lower alpha band in people with MCI versus cognitively healthy older adults (OA). For the explanation of the table and the plot, see Fig. 2.

Overall, resting state alpha activity was lower in people with AD than in people with MCI, and in people with MCI than in cognitively healthy older adults. However, several studies did not report significant findings, indicating differences might be too subtle to be detected in smaller samples, or when the alpha band is split in half. Effect sizes were diverse in magnitude and sometimes in direction, which might reflect different EEG measures and sample characteristics.

Synchronization. A short explanation of functional connectivity measures can be found in Table 1. Thirteen studies included people with aMCI, three people with AD-MCI, and five did not specify the subtype (see Table 4 for details).

Five of the twelve studies that compared functional connectivity in the full alpha band between people with MCI and cognitively healthy older adults found lower connectivity in people with MCI (Michels et al. [43], *n* = 17 aMCI, 17 OA;

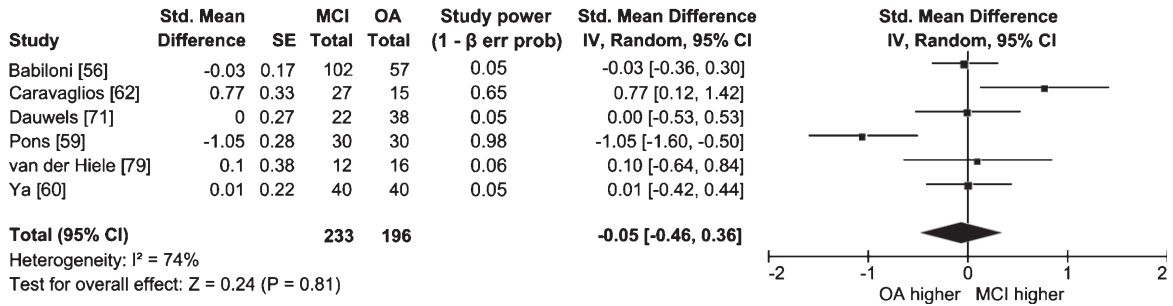


Fig. 5. Table and forest plot of effect sizes for power in awake resting state in the upper alpha band in people with MCI versus cognitively healthy older adults (OA). The table shows sample size (Total) for each participant group. For the explanation of the table and the plot, see Fig. 2.

Gonzalez-Escamilla et al. [83], $n = 29$ aMCI, 29 OA; Musaeus et al. [84], $n = 117$ AD, 117 MCI, 135 OA; Teipel et al. [85], $n = 16$ aMCI, 20 OA; Wen et al. [86], $n = 12$ aMCI, 12 OA). Connectivity was lower mainly within temporo-parietal areas [43, 83, 85] or between temporo-parietal and other areas [43]. The study with the largest sample (Koenig et al. [87], $n(\text{NY}) = 148$ AD, 51 MCI, 25 OA; $n(\text{Stockholm}) = 63$ AD, 41 MCI, 21 OA) did not find significant differences between people with MCI and cognitively healthy older adults, but there was significantly lower global connectivity in people with AD than in people with MCI. Lower connectivity in people with AD than in people with MCI was also reported by Smailovic et al. [73] ($n = 197$ AD, 230 MCI), Jelic et al. [75] ($n = 18$ AD, 19 aMCI, 16 OA), Musaeus et al. [84] ($n = 117$ AD, 117 MCI, 135 OA), and Núñez et al. [88] ($n = 45$ AD, 51 AD-MCI, 36 OA). In the studies that did not measure connectivity at the global level, differences between people with MCI and people with AD were mostly found in temporo-parietal areas [75, 84, 88].

In addition to finding the expected pattern of lower connectivity in more cognitively impaired groups, Musaeus et al. [84] also found higher connectivity in people with MCI than in cognitively healthy older adults, and in people with AD than in people with MCI. They used three different measures of connectivity and found that whereas coherence decreased with increasing impairment, the imaginary part of coherence and weighted phase lag index showed both lower and higher connectivity in more cognitively impaired groups.

Findings for lower and upper alpha bands were even less uniform than for the full band. Babiloni et al. [89] ($n = 75$ AD-MCI, 75 OA) found less posterior inter-hemispheric and global intra-hemispheric connectivity in people with AD-MCI than in cognitively healthy older adults in both lower and upper

alpha bands. Similarly, Xu et al. [90] ($n = 10$ aMCI, 10 OA) and Moretti et al. [91] ($n = 85$ MCI, 31 OA) found that people with MCI had less fronto-parietal connectivity in both bands. Xu et al. [90] additionally reported less inter-hemispheric frontal connectivity in the upper alpha band in people with aMCI compared to cognitively healthy older adults. However, in the study by Xu et al. [90], the frequency range for each band was not reported, meaning this study may not be comparable to others. Moreover, findings for the lower band differed based on the choice of the reference electrode.

Three studies reported higher connectivity in the lower alpha band in people with MCI than in cognitively healthy older adults. Moretti et al. [91] ($n = 85$ MCI, 31 OA) found more temporal inter-hemispheric connectivity in both bands, and Pons et al. [59] ($n = 30$ aMCI, 30 OA) more right occipito-central connectivity in the lower alpha band in people with MCI. In the study by Cantero et al. [92] ($n = 20$ aMCI, 20 OA), people with aMCI had higher connectivity between the thalamus, cuneus, and precuneus.

Compared to people with MCI, people with AD had less global connectivity in the lower alpha band (Babiloni et al. [93], $n = 33$ AD, 52 aMCI, 47 OA), and less connectivity between left posterior areas and other areas of the default mode network in both alpha bands (Hsiao et al. [94], $n = 21$ aMCI, 21 AD). Two studies with smaller sample sizes failed to find significant differences between the two groups in either band (Pijnenburg et al. [95], $n = 14$ AD, 11 aMCI; Stam et al. [96], 10 AD, 17 aMCI).

Findings on differences in alpha synchronization between people with MCI and cognitively healthy older adults and between people with MCI and people with AD are difficult to reconcile due to differences in analysis and reporting. Included studies differed in connectivity measures, and in electrode clusters

Table 4
Functional connectivity in awake resting state at the level of electrodes and sources of neural activity in people with aMCI, MCI, and MCI due to AD

Paper	Groups	Diagnosis	<i>n</i>	Age (y)	Sex (% F)	EEG measure	Alpha (Hz)	Results MCI versus OA	AD versus MCI	Electrodes/ sources	Location of significant differences
Musaeus [84]	AD	DSM-IV-TR, McKhann [204]	117	75.5 (7.7 SD)	60.7	coherence	8–12.99	↓ OA > MCI (↑ for one pair only)	↓ MCI > AD	electrodes: 19	widespread (see paper for details)
	MCI	Winblad [7]	117	70.2 (8.1 SD)	53	imaginary coherence		↓ and ↑ OA > MCI MCI > OA	↓ and ↑ MCI > AD AD > MCI		OA > MCI: mostly inter-hemispheric MCI > OA: mostly with right temporal areas MCI > AD: mostly with parieto-occipital areas AD > MCI: mostly between frontal areas (see paper for details)
	OA		135	66.4 (7.6 SD)	60.7	weighted phase lag index (eyes closed)		↓ and ↑ OA > MCI MCI > OA	↓ and ↑ MCI > AD AD > MCI		OA > MCI: widespread MCI > OA: mostly with fronto-central areas MCI > AD: mostly fronto-central, centro-occipital AD > MCI: left temporo-parietal (see paper for details)
Jelic [75]	AD	McKhann [204]	18	61.1 (5.5 SD)	50	coherence (eyes closed)	8–13	x	↓ aMCI > AD	electrodes: 12	left-right temporal, parietal (T3-T4, T5-T6, P3-P4)
	aMCI	similar to Petersen [6]	19	61.5 (7.0 SD)	73.7						
	OA		16	64.3 (10.8 SD)	43.8						
Koenig [87]	New York:					global field synchronization (eyes closed)	8–12	x	↓ MCI > AD	electrodes: 19	global
	AD	DSM-III-R, GDS stages 4–7	148	72.1 (? SD)	?						
	MCI	GDS stage 3	51	70.7 (? SD)	?						
	OA		25	67.1 (? SD)	?						
	Stockholm:										

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Table 4
(continued)

Paper	Groups	Diagnosis	<i>n</i>	Age (y)	Sex (% F)	EEG measure	Alpha (Hz)	Results MCI versus OA	AD versus MCI	Electrodes/ sources	Location of significant differences
Núñez [88]	AD	DSM-III-R, McKhann [204], SPECT biomarker positive	63	63.5 (? SD)	?						
	MCI	similar to Winblad [7]	41	61.0 (? SD)	?						
	OA		21	63.4 (? SD)	?						
	AD	McKhann [205]	45	79.5 [74.7 : 82.4]	55.6	amplitude envelope correlation (eyes closed)	8–13	x	↓ AD-MCI > AD	electrodes: 19	left-right temporal (F7/T3/T5-F8/T4/T6), left temporo-central (F7/T3/T5-Fz/C3/C4/Pz), right temporo-central (Fz/C3/C4/Pz-F8/T4/T6), fronto-central (Fp1/Fp2/F3/F4-Fz/C3/C4/Pz), centro-parietal (Fz/C3/C4/Pz-P3/P4/O1/O2), fronto-parietal (Fp1/Fp2/F3/F4-P3/P4/O1/O2), left and right temporo-parietal (F7/T3/T5-P3/P4/O1/O2, F8/T4/T6-P3/P4/O1/O2)
	AD-MCI	Albert [68]	51	77.2 [69.6 : 79.8]	58.8						
OA		36	75.9 [74.1 : 78.6]	69.4							
Smailovic [73]	AD	ICD-10	197	67.8 (9.2 SD)	63.5	global field synchronization (eyes closed)	8–11.5	–	↓ MCI > AD	electrodes: ?	global
	MCI	Winblad [7]	230	65.9 (8.2 SD)	52.6						
Hsiao [207]	AD	DSM-IV, McKhann [204]	21	82.7 (7.5 SD)	71.4	minimum norm estimate; coherence (eyes closed)	8–13	–	x	electrodes: 19	sources: motor network
	aMCI	Petersen [1]	21	80.4 (5.6 SD)	61.9						

Table 4
(continued)

van der Hiele [126]	AD aMCI OA	McKhann [204] Petersen [6]	16 18 22	78.0 (8.0 SD) 74.0 (5.0 SD) 70.0 (5.0 SD)	43.8 61.1 68.2	coherence (eyes closed)	8–13	x	x	electrodes: 21
Gonzalez-Escamilla [83]	aMCI OA	Petersen [6]	29 26	70.1 (6.8 SD) 66.5 (4.9 SD)	34.5 57.7	phase lag index (eyes closed)	alpha peak frequency ± 0.5	↓ OA > aMCI	–	electrodes: 40 left temporal-right parietal (FT7/T7/TP7-Cp6/CP4/Cp2/P8/P6/P4/P2), left-right parietal (Cp5/CP3/Cp1/P7/P5/P3/P1-Cp6/CP4/Cp2/P8/P6/P4/P2), right temporo-parietal (FT8/T8/TP8-Cp6/CP4/Cp2/P8/P6/P4/P2), within right parietal
Teipel [85]	aMCI OA	Petersen [1]	16 20	73.6 (7.8 SD) 67.0 (7.3 SD)	43.8 45	coherence (eyes closed)	8–12	↓ OA > aMCI	–	electrodes: 14 left-right central, temporal, parietal (C3-C4, T3-T4, T5-T6, P3-P4)
Wen [86]	MCI OA	DSM-IV	12 12	75.2 (7.1 SD) 73.0 (6.5 SD)	50 58.3	global coupling index, global synchronization index, S-estimator (eyes closed)	8–12	↓ OA > MCI	–	electrodes: 10 global
Michels [43]	aMCI OA	?, 6 APOE ε4 allele 5 APOE ε4 allele	17 17	72.1 (4.6 SD) 71.8 (4.6 SD)	29.4 29.4	beamforming; coherence (eyes closed)	8–13	↓ OA > aMCI	–	electrodes: 60 sources: primary motor cortex, primary visual cortex, PCC, angular gyrus, BA 46 whole brain
Ruiz-Gómez [209]	AD-MCI OA	McKhann [205]	51 51	85.5 (7.3 SD) 80.1 (7.1 SD)	70.6 49	weighted phase lag index (eyes closed)	8–13	x	–	electrodes: 19

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Table 4
(continued)

Paper	Groups	Diagnosis	<i>n</i>	Age (y)	Sex (% F)	EEG measure	Alpha (Hz)	Results MCI versus OA	AD versus MCI	Electrodes/ sources	Location of significant differences
Babiloni [93]	AD	DSM-IV, McKhann [204]	33	70.9 (1.73 SE)	75.8	coherence (eyes closed)	8–10	x	↓ aMCI > AD	electrodes: 19	global averaged
	aMCI	Petersen [1]	52	72.3 (0.75 SE)	51.9		10–13	x	x		
	OA		47	74.7 (0.90 SE)	46.8						
Babiloni [89]	AD-MCI	Albert [68], CSF/FDG-PET/MRI biomarker positive	75	70.1 (0.7 S E)	54.7	eLORETA; lagged linear connectivity (eyes closed)	lower alpha individually determined	↓ OA > AD-MCI	–	electrodes: 19 sources: whole brain	inter-hemispheric: parietal, occipital, temporal intra-hemispheric: global
	OA		75	70.1 (0.8 SE)	52		upper alpha individually determined	↓ OA > AD-MCI			inter-hemispheric: parietal, occipital, temporal intra-hemispheric: global
Moretti [91]	MCI	Petersen [76]	85	69.8 (7.9 SD)	65.9	coherence (eyes closed)	lower alpha individually determined	↓ intra-hemispheric OA > MCI ↑ inter-hemispheric MCI > OA	–	electrodes: 6	inter-hemispheric: temporal (T3-T4) intra-hemispheric: left and right fronto-parietal (F3-P3, F4-P4)
	OA		31	68.9 (5.1 SD)	35.5		upper alpha individually determined	↓ intra-hemispheric OA > MCI ↑ inter-hemispheric MCI > OA			inter-hemispheric: temporal (T3-T4) intra-hemispheric: left and right fronto-parietal (F3-P3, F4-P4)
Xu [90]	aMCI	Petersen [76]	11	75.50 (7.39 SD)	45.5	coherence (eyes closed)	?	↓ (vertex reference) OA > aMCI	x	electrodes: 21	fronto-occipital (Fpz-Oz)

Table 4
(continued)

	OA		14	74.04 (6.85 SD)	57.1		?	↓ (vertex, zero, average reference) OA > aMCI	x	within frontal, fronto-parietal (see paper for details)
Pons [59]	aMCI	Petersen [6]	30	66.8 (4.7 SD)	30	phase lag index (eyes closed)	7–9	↑ aMCI > OA	–	electrodes: right occipito-central (C4-O2) 12
	OA		30	68.4 (6.1 SD)	33.3		9.1–11	x		
Cantero [92]	aMCI	Petersen [1], 9 <i>APOE ε4</i> allele	20	68.4 (6.1 SD)	45	MVAR-EfICA; phase synchronization index (eyes closed)	7.5–10	↑ aMCI > OA	–	electrodes: thalamus, cuneus, precuneus 59 sources: whole brain
	OA	4 <i>APOE ε4</i> allele	20	66.8 (4.7 SD)	50		10.1–12.5	x		
Hsiao [94]	AD	DSM-IV, McKhann [204]	21	82.7 (7.5 SD)	71.4	minimum norm estimate; imaginary coherence	lower alpha individually determined	–	↓ MCI > AD	electrodes: left PCC-right precuneus, left PCC-left ACC sources: default mode network
	aMCI	Petersen [1]	21	80.4 (5.6 SD)	61.9	(eyes closed)	upper alpha individually determined	↓ MCI > AD		
Pijnenburg [95]	AD	McKhann [204]	14	76.4 (13.6 SD)	50	synchronization likelihood	8–10	–	x	electrodes: 19
	aMCI	Petersen [6]	11	78.4 (6.4 SD)	90.9	(eyes closed)	10–12		x	
Stam [96]	AD	McKhann [204]	10	76.2 (9.3 SD)	80	synchronization likelihood	6–10	–	x	electrodes: 21
	aMCI	Petersen [76]	17	77.4 (6.3 SD)	52.9	(eyes ?)	10–14		x	

Arrows indicate whether functional connectivity in the more cognitively impaired group was significantly lower or higher than in the less impaired group. When the original paper reported age range but not SD or SE, age range is included in square brackets. eLORETA, exact low resolution brain electromagnetic tomography; MVAR-EfICA, multivariate autoregressive model-efficient fast independent component analysis; GDS, Global Deterioration Scale; SPECT, single-photon emission computerized tomography; FDG-PET, fluorodeoxyglucose positron emission tomography; MRI, magnetic resonance imaging. For other abbreviations and the explanation of symbols, see Table 3.

or brain regions for which results are reported, precluding meta-analyses or direct comparisons. In two studies, results derived from the same sample differed depending on the reference electrode [90] and the measure of connectivity [84], raising questions about comparability of synchronization studies.

Cross-sectional studies on people with MCI due to neurodegenerative dementias other than AD

Power. Ten studies investigated alpha power in people with MCI due to Lewy body disorders, meaning either due to Parkinson's disease (PD-MCI) or due to dementia with Lewy bodies (DLB-MCI). All measured EEG at rest with eyes closed, and except three studies, all reported relative power (see Table 5 for details). Two studies (Caviness et al. [97], $n = 31$ PD-D, 28 PD-MCI, 75 PD-CH; Mostile et al. [98], $n = 46$ PD-MCI, 56 PD-CH) found that people with PD-MCI had lower alpha power than cognitively healthy PD patients. Lower alpha power was also found in people with DLB-MCI when they were compared to cognitively healthy older adults (Bonanni et al. [70], $n = 50$ DLB, 20 DLB-aMCI, 50 OA); however, the difference between the two groups in this study was extremely large (22.2% (± 10.6) of power was in the alpha band for people with DLB-MCI and 76.3% (± 2.3) for OA) and should be interpreted with caution. In other studies, alpha power in the full band did not differ significantly between people with PD-MCI and cognitively healthy PD patients (Caviness et al. [47], $n = 16$ PD-MCI, 42 PD-CH; Fonseca et al. [48], $n = 10$ PD-MCI, 15 PD-CH; Chaturvedi et al. [99], $n = 27$ PD-MCI, 43 PD-CH; He et al. [100], $n = 61$ PD-MCI, 74 PD-CH).

Three of the studies that split alpha into lower and upper frequencies found less lower alpha power in people with PD-MCI compared to cognitively healthy PD patients (Babiloni et al. [101], $n = 35$ PD-D, 50 PD-MCI, 35 PD-CH; Bousleiman et al. [102], $n = 41$ PD-MCI, 12 PD-CH) and in people with DLB-MCI compared to cognitively healthy older adults (Babiloni et al. [103], $n = 23$ DLB-MCI, 30 OA). Babiloni et al. also observed less upper alpha power in people with DLB-MCI compared to cognitively healthy older adults (Babiloni et al. [103], $n = 23$ DLB-MCI, 30 OA), but more upper alpha power in people with PD-MCI compared to cognitively healthy PD patients and in people with PD-D compared to those with PD-MCI (Babiloni et al. [101], $n = 35$ PD-D, 50 PD-MCI, 35 PD-CH). The latter study was the only one that investigated alpha power in PD-MCI in individually defined alpha bands. Given that aging

and PD duration have been associated with changes in alpha rhythms [104–106], this method might be more sensitive to changes due to cognitive impairment.

The only study on people with MCI due to FTD (FTD-MCI; Table 5) [107] ($n = 11$ FTD-MCI, 28 FTD) found that they had lower alpha power than people with FTD.

Synchronization. Three studies compared synchronization between people with PD-MCI and cognitively healthy PD patients (Table 6). Whereas two did not find any significant differences (Chaturvedi et al. [99], $n = 27$ PD-MCI, 43 PD-CH; Utianski et al. [108], $n = 13$ PD-MCI, 57 PD-CH), one found more synchronization in the upper alpha band in people with PD-MCI (Carmona Arroyave et al. [109], $n = 14$ PD-MCI, 22 PD-CH). The only study that compared people with DLB-MCI to cognitively healthy older adults found less synchronization in lower and upper alpha bands in people with DLB-MCI (Babiloni et al. [110], $n = 23$ DLB-MCI, 30 OA).

Longitudinal studies comparing people with MCI who progress to AD to people with MCI whose cognitive status remains stable

Power. We identified seven studies that compared alpha power in people with progressive and stable MCI (Table 7). In six of them, progression was defined as the diagnosis of clinical AD at follow-up [72, 111–115], and in one study as a 4-point increase in the total score on the cognitive subscale of the Alzheimer's Disease Assessment Scale [57].

Four studies found lower alpha relative power (Huang et al. [72], $n = 14$ AD-PMCI, 17 SMCI, mean follow-up after 2.1 years; Gouw et al. [111], $n = 83$ AD-PMCI, 59 AD-SMCI, median follow-up after 2.2 years; Poil et al. [114], $n = 25$ AD-PaMCI, 39 SaMCI, mean follow-up after 1.9 years), absolute power (Luckhaus et al. [57], $n = 16$ PaMCI, 72 SaMCI, follow-up after 1 year), or global field power of reconstructed sources (Huang et al. [72], $n = 14$ AD-PMCI, 17 SMCI, mean follow-up after 2.1 years) in people with progressive than in those with stable MCI. In three of these studies [57, 72, 111], significant differences were only found for posterior electrodes. The two studies that did not report significant differences had the smallest samples (Jelic et al. [112], $n = 14$ AD-PMCI, 13 SMCI, mean follow-up after 1.75 years; Musaeus et al. [113], $n = 11$ AD-PMCI, 13 SMCI, follow-up after 2 years) and may not have had enough power to detect between-group differences.

Table 5
Power in awake resting state at the level of electrodes and sources of neural activity in people with MCI due to Lewy body disorders and MCI due to FTD

Paper	Groups	Diagnosis	<i>n</i>	Age (y)	Sex (% F)	EEG measure	Alpha (Hz)	Results MCI versus PD-CH/OA	Dementia versus MCI	Electrodes/ sources	Location of significant differences
Caviness [97]	PD-D	Emre [210]	31	78.9 (6.6 SD)	26	FFT relative power (eyes closed)	8–12.9	↓ PD-CH > PD-MCI	↓ PD-MCI > PD-D	electrodes: ?	global averaged
	PD-MCI PD-CH	Litvan [10]	28 75	76.7 (6.6 SD) 74.4 (9.2 SD)	25 44						
Caviness [47]	PD-MCI	Petersen [6]	16	80.4 (8.8 SD)	?	FFT relative power (eyes closed)	8–12.9	x	–	electrodes: 15	
	PD-CH		42	74.6 (8.6 SD)	?						
Fonseca [48]	PD-MCI	Portet [208]	10	70.3 (? SD)	?	FFT relative power (eyes closed)	8.2–12.5	x	–	electrodes: 17	
	PD-CH		15	63.5 (9.6 SD)	?						
He [100]	PD-MCI	Petersen [76]	61	60.2 (10.6 SD)	47.5	? relative power (eyes closed)	8–13	x	–	electrodes: 12	
	PD-CH		74	59.2 (12.4 SD)	37.8						
Chaturvedi [99]	PD-MCI	Litvan [10], level II criteria	27	67.0 [53 : 84]	22.2	FT relative power (eyes closed)	8–13	x	–	electrodes: 214	
	PD-CH		43	67.0 [46 : 82]	39.5						
Mostile [98]	PD-MCI	Litvan [10], level II criteria	46	66.1 (8.1 SD)	45.6	Welch's absolute power LORETA ICA (eyes closed)	8–12	↓ PD-CH > PD-MCI	–	electrodes: 10	occipital (O1, O2)
	PD-CH		56	65.4 (8.7 SD)	48						

(Continued next page)

Table 5
(continued)

Paper	Groups	Diagnosis	<i>n</i>	Age (y)	Sex (% F)	EEG measure	Alpha (Hz)	Results MCI versus PD-CH/OA	Dementia versus MCI	Electrodes/sources	Location of significant differences
Bonanni [70]	DLB	McKeith [211]	50	70.3 (4.9 SD)	46	FFT relative power (eyes closed)	9–12	↓ OA > DLB-MCI	x	electrodes: 19	global averaged
	DLB-aMCI	Petersen [6], 1 core DLB symptom, conversion	20	74.1 (7.0 SD)	35						
	OA		50	72.6 (5.4 SD)	48						
Bousleiman [102]	PD-MCI	Litvan [10], level II criteria	41	?	?	Welch's relative power (eyes closed)	8–10	↓ PD-CH > PD-MCI	–	electrodes: 256	global averaged, left frontal, left central, left and right temporal, right occipital
	PD-CH		12	?	?		10–13	x			
Chaturvedi [99]	PD-MCI	Litvan [10], level II criteria	27	67.0 [53 : 84]	22.2	FT relative power (eyes closed)	8–10	x	–	electrodes: 214	
	PD-CH		43	67.0 [46 : 82]	39.5			10–13	x		
Babiloni [101]	PD-D	similar to Emre [210], impairment in 1 domain enough	35	73.8 (1.2 SE)	60	eLORETA; current source density (eyes closed)	lower alpha individually determined	↓ PD-CH > PD-MCI	x	electrodes: 19 sources: whole brain	occipital
	PD-MCI		Litvan [10]	50	71.5 (1.0 SE)		58				
	PD-CH		35	71.3 (1.2 SE)	51.4		upper alpha individually determined	↑ PD-D > PD-MCI	↑ PD-MCI > PD-CH	PD-MCI > PD-CH: temporal PD-D > PD-MCI: frontal, central, temporal	
Babiloni [103]	DLB-MCI	McKeith [211, 212], SPECT (DaTscan) biomarker positive	23	75.7 (1.4 SE)	39.1	eLORETA; current source density (eyes closed)	lower alpha individually determined	↓ OA > DLB-MCI	–	electrodes: 19 sources: whole brain	temporal, limbic, occipital

Table 5
(continued)

OA		30	74.7 (0.8 SE)	40	upper alpha individually determined	↓ OA > DLB-MCI	occipital
Moretti [107]	FTD	28	66.8 (9.1 SD)	?	Welch's global field power (eyes closed)	-	electrodes: 19
	FTD-MCI	11	64.8 (4.2 SD)	?	10.5-14		global averaged

PD, Parkinson's disease; PD-D, dementia due to PD; PD-MCI, MCI due to PD; PD-CH, cognitively healthy people with PD; DLB, dementia with Lewy bodies; DLB-(a)MCI, (amnesic) MCI due to DLB; FTD, frontotemporal dementia; FTD-MCI, MCI due to FTD; ICA, independent components analysis; GRN, granulin precursor gene. For other abbreviations and the explanation of symbols, see Tables 3 and 4.

Only one study investigated lower and upper alpha bands separately (Rossini et al. [115], $n = 24$ AD-PaMCI, 45 SaMCI, mean follow-up after 1.2 years), and found that people with MCI who eventually progressed to dementia had more power in posterior sources in the lower alpha band.

Synchronization. We only identified three studies that compared alpha synchronization in people with progressive and stable MCI (Table 8). All studies defined progression as a diagnosis of clinical AD at follow-up. Whereas Jelic et al. [112] ($n = 14$ AD-PMCI, 13 SMCI, mean follow-up after 1.75 years) did not find significant differences between the two groups in the full alpha band, Musaeus et al. [116] ($n = 11$ AD-PMCI, 13 SMCI, follow-up after 2 years) found both lower and higher connectivity in people who progressed to AD. Rossini et al. [115] ($n = 24$ AD-PaMCI, 45 SaMCI, mean follow-up after 1.2 years) reported higher lower and upper alpha connectivity in people who progressed to AD.

Alpha power and functional connectivity during task performance

Alpha power and functional connectivity during tasks of executive functions

Power. We identified 12 reports that compared changes in alpha power during tasks of executive functions. Seven studies used a task of working memory, five a task of attention, and one a task of inhibition (see Table 9 for details). All but two studies included participants with aMCI, and one [117] further divided the group into single (sd-aMCI) and multiple domain aMCI (md-aMCI). It should be noted that event-related synchronization (ERS) and event-related desynchronization (ERD) represent power increase and decrease, respectively, that is synchronized with the event of interest, and not changes in synchronization between two regions.

Several studies reported that people with aMCI had attenuated responses to task stimuli during working memory tasks compared to cognitively healthy older adults. People with aMCI were found to have less ERD during the processing of target stimuli in a 1-back task in the full alpha band (Fraga et al. [118], $n = 15$ AD, 21 aMCI, 27 OA) and during picture retention in the lower alpha band (van der Hiele et al. [79], $n = 12$ aMCI, 16 OA). They also had lower ERS in the full alpha band during the learning period of the Sternberg task (Fodor et al. [119], $n = 17$ aMCI, 21 OA), and during the processing of ignored distractors in the delayed-match-to-sample task (Deiber

Table 6
Functional connectivity in awake resting state at the level of electrodes and sources of neural activity in people with MCI due to Lewy body disorders

Paper	Groups	Diagnosis	<i>n</i>	Age (y)	Sex (% F)	EEG measure	Alpha (Hz)	Results	Electrodes/sources	Location of significant differences
Carmona Arroyave [109]	PD-MCI	Litvan [10], level I criteria	14	66.1 (7.4 SD)	28.6	coherence (eyes closed)	8–10	x	electrodes: 36	
	PD-CH		22	61.8 (8.0 SD)	36.4		10–13	↑ PD-MCI>PD-CH		left and right fronto-parietal (AF3/F1/F3/FC1/FC3-CP1/CP3/P1/P3, AF4/F2/F4/FC2/FC4-CP2/CP4/P2/P4)
Chaturvedi [99]	PD-MCI	Litvan [10], level II criteria	27	67.0 [53:84]	22.2	phase lag index (eyes closed)	8–13	x	electrodes: 214	
	PD-CH		43	67.0 [46:82]	39.5		8–10	x		
							10–13	x		
Utianski [108]	PD-MCI	Litvan [10]	13	77.0 (5.2 SD)	?	phase lag index (eyes closed)	8–10	x	electrodes: 21	
	PD-CH		57	74.9 (8.2 SD)	?		10–13	x		
Babiloni [110]	DLB-MCI	McKeith [211, 212], SPECT	23	75.7 (1.4 SE)	39.1	eLORETA; lagged linear connectivity (eyes closed)	lower alpha individually determined	↓ OA > DLB-MCI	electrodes: 19 sources: whole brain	whole brain
	OA	(DaTscan) biomarker positive	30	74.7 (0.8 SE)	40		upper alpha individually determined	↓ OA > DLB-MCI		whole brain

For abbreviations and the explanation of symbols, see Tables 3–5.

Table 7

Power in awake resting state at the level of electrodes and sources of neural activity in people with MCI who eventually progress to AD and in people with MCI whose cognitive status remains stable

Paper	Groups	Diagnosis	<i>n</i>	Age (y)	Sex (% F)	Follow-up (y)	EEG measure	Alpha (Hz)	Results	Electrodes/ sources	Location of significant differences
Gouw [111]	AD-PMCI	AD: ?; MCI: Albert [68]; both Aβ ₄₂ positive	83 (79 AD)	68.0 (8.0 SD)	52	≥1, median 2.2	FFT relative power (eyes closed)	8–13	↓ SMCI > PMCI	electrodes: 21	parietal (P3/P4/Pz), occipital (O1/O2), temporal lobe (T3/T4/T5/T6/A1/A2)
	AD-SMCI		59	68.0 (7.0 SD)	46						
Huang [72]	AD-PMCI	AD: McKhann [204]; MCI: similar to Petersen [6]	14	?	?	1–4, mean 2.1	FFT relative power	8–11.5	↓ SMCI > PMCI	electrodes: 16	right temporal (T4/T6), right temporo-occipital (T6/O2), left and right centro-parietal (C3/P3, C4/P4)
	SMCI		17	?	?						
Luckhaus [57]	PaMCI	MCI: Petersen [6]; progression: 4-point increase in ADAS-cog score	16	?	?	1	FFT absolute power (eyes closed)	8–11.5	↓ SMCI > PMCI	electrodes: 3 (Fz, Cz, Pz)	Pz
	SaMCI		72	?	?						
Poil [114]	AD-PaMCI	AD: McKhann [204]; MCI: Petersen [6]	25	69.0 [67:72]	44	≤2, mean 1.9	? relative power (eyes closed)	8–13	↓ SMCI > PMCI	electrodes: 23	median across F3, Fz, F4, T7, C3, Cz, C4, P3, Pz, P8, O1
	SaMCI		39	67.0 [65:71]	28.2						
Jelic [112]	AD-PMCI	AD: McKhann [204]; MCI: similar to Petersen [6]	14	58.2 (5.9 SD)	64.3	1–3.25, mean 1.75	FFT relative power (eyes closed)	8–13	x	electrodes: 12	
	SMCI		13	58.5 (7.9 SD)	69.2						

Table 7
(continued)

Paper	Groups	Diagnosis	n	Age (y)	Sex (% F)	Follow-up (y)	EEG measure	Alpha (Hz)	Results	Electrodes/ sources	Location of significant differences
Musaeus [113]	AD-PMCI	AD: McKhann [205]; MCI: Winblad [7]	11	?	?	2	Weich's relative power (eyes closed)	8–12.99	x	electrodes: 19	
Rossini [115]	SMCI AD- PaMCI	AD: McKhann [204]; MCI: Petersen [216, 76]	13 24	? 72.7 (1.1 SE)	? 50	mean 1.2 years	LORETA; current source density (eyes closed)	8–10.5	↑ PMCI > SMCI	electrodes: 19 sources: whole brain	central, parietal, occipital, temporal, limbic
	SaMCI		45	70.0 (1.1 SE)	64.4			10.5–13	x		

Arrows indicate whether power in people with progressive MCI was higher or lower than in people whose cognitive status remained stable. P(a)MCI, progressive (amnesic) MCI; S(a)MCI, stable (amnesic) MCI; AD-PMCI, MCI that progressed to Alzheimer's disease; AD-SMCI, stable MCI due to Alzheimer's disease. For other abbreviations and the explanation of symbols, see Tables 3 and 4.

et al. [117], $n = 16$ sd-aMCI, 27 md-aMCI, 36 OA). However, the latter was only true for people with md-aMCI. Three other studies did not find significant differences between people with aMCI and cognitively healthy older adults (McBride et al. [78], $n = 17$ AD, 16 aMCI, 15 OA; Goodman et al. [120], $n = 29$ AD, 100 MCI, 40 OA; van der Hiele et al. [121], $n = 11$ AD, 13 aMCI, 13 OA).

In addition to the differences in the magnitude of power increase or decrease, Fraga et al. [118] ($n = 15$ AD, 21 aMCI, 27 OA) also found differences in the direction of power change between cognitively healthy older adults and those with aMCI. While viewing the non-target stimuli of the 2-back task, frontal alpha activity was increased (ERS) in the former but decreased (ERD) in the latter group.

A diverging pattern of alpha reactivity has also been observed during a pre-response period of an omitted tone detection task of attention (Caravaglios et al. [62], $n = 27$ aMCI, 15 OA). Whereas upper alpha power decreased (ERD) for cognitively healthy older adults, it increased (ERS) for people with aMCI. On the other hand, Sharma et al. [74], ($n = 15$ dementia, 16 MCI, 13 OA), Kurt et al. [122], ($n = 22$ aMCI, 21 OA), and Yener et al. [123], ($n = 18$ aMCI, 18 OA); [124], ($n = 30$ aMCI, 28 OA) did not find significant differences between people with MCI and cognitively healthy older adults during tasks of attention. Sharma et al. [74] did find a difference between people with MCI and people with dementia, but the direction of the difference was unclear, and dementia and MCI were not diagnosed according to widely accepted criteria. The only study that focused on inhibition found that compared to cognitively healthy older adults, people with aMCI had lower ERD during the processing of go trials in the lower alpha band (Nguyen et al. [125], $n = 22$ aMCI, 22 OA).

None of the four studies that compared changes in alpha activity during tasks of working memory between people with MCI and people with AD reported significant differences between the two groups (McBride et al. [78], $n = 17$ AD, 16 aMCI, 15 OA; Fraga et al. [118], $n = 15$ AD, 21 aMCI, 27 OA; Goodman et al. [120], $n = 29$ AD, 100 MCI, 40 OA; van der Hiele et al. [121], $n = 11$ AD, 13 aMCI, 13 OA).

Synchronization. Both studies on alpha synchronization (Table 10) used a picture retention task of working memory. They did not find significant differences between people with aMCI and cognitively healthy older adults (van der Hiele et al. [126], $n = 16$ AD, 18 aMCI, 22 OA) or between people with aMCI

Table 8

Functional connectivity in awake resting state at the electrode level in people with MCI who eventually progress to dementia and in people with MCI whose cognitive status remains stable

Paper	Groups	Diagnosis	<i>n</i>	Age (y)	Sex (% F)	Follow-up (y)	EEG measure	Alpha (Hz)	Results	Electrodes	Location of significant differences
Jelic [112]	AD-PMCI	AD: McKhann [204]; MCI: similar to Petersen [6]	14	58.2 (5.9 SD)	64.3	1–3.25, mean 1.75	coherence (eyes closed)	8–13	x	12	
	SMCI		13	58.5 (7.9 SD)	69.2						
Musaeus [116]	AD-PMCI	AD: McKhann [205]; MCI: Winblad [7]	11	70.3 (6.6 SD)	18.2	2	coherence	8–12.99	↓ and ↑ SMCI > PMCI PMCI > SMCI	19	SMCI > PMCI: right fronto-temporal (F4-T6), left central-right temporal (C3-T6), left central-right occipital (C3-O2) PMCI > SMCI: right frontal (Fp2-F4) left central (C3-Cz)
	SMCI		13	72.4 (6.1 SD)	30.8						
Rossini [115]	AD-PaMCI	AD: McKhann [204]; MCI: Petersen [216, 76]	24	72.7 (1.1 SE)	50	mean 1.2 years	coherence (eyes closed)	8–10.5	↑ PMCI > SMCI	6	left, right, central fronto-parietal (F3-P3, Fz-Pz, F4-P4)
	SaMCI		45	70.0 (1.1 SE)	64.4						

Arrows indicate whether functional connectivity in people with progressive MCI was higher or lower than in people whose cognitive status remained stable. For abbreviations and the explanation of symbols, see Tables 3 and 7.

Table 9
Changes in power at the level of electrodes and sources of neural activity during task performance in people with aMCI, MCI, and MCI due to AD

Paper	Groups	Diagnosis	<i>n</i>	Age (y)	Sex (% F)	EEG measure	Time window (ms)	Task	Alpha (Hz)	Results MCI versus OA	AD versus MCI	Electrodes /sources	Location of significant differences
Working memory													
Fodor [119]	aMCI	Petersen [1]	17	69.2 (7.0 SD)	47	ERS/ERD	learning: 800–1500 retention: 600–1000	Sternberg	7–14	learning: ↓ ERS OA > aMCI	–	electrodes: 128	right central
	OA		21	64.9 (5.2 SD)	66.7	eLORETA; current source density				x		electrodes: 128 sources: whole brain	
Fraga [118]	AD	McKhann [204]	15	79.7 (1.3 SE)	33.3	ERS/ERD	–300–1700 in 2 s increments	n-back	8–12	1-back, match: ↓ ERD OA > aMCI	x	electrodes: 29	frontal (Fz, F4), central (C3, Cz, C4), occipital (O1, O2)
	aMCI	Winblad [7], Petersen [217]	21	79.9 (1.1 SE)	47.6					2-back, non- match: OA ERS, aMCI ERD			frontal (Fp1, Fpz, Fp2, F7, F3, Fz, F4)
	OA		27	77.6 (1.0 SE)	59.3								
Deiber [117]	sd-aMCI	Petersen [76], Petersen [218]	16	65.8 (5.4 SD)	43.8	ERS/ERD	encoding: 200–1000 in 10 ms increments	delayed-match- to-sample	7.5–12.5	ignored letters: ↓ ERS OA > md- aMCI	–	electrodes: 3 (P4 for attended faces, P7 for attended letters, C4 for ignored faces and letters)	C4
	md-aMCI		27	64.0 (5.3 SD)	55.6								
	OA		36	64.7 (6.6 SD)	66.7								
van der Hiele [121]	AD	McKhann [204]	11	75.0 (8.0 SD)	45.5	% change from eyes closed	/	picture retention	8–13	x	x	electrodes: 21	
	aMCI	Petersen [6]	13	73.0 (5.0 SD)	53.8								
	OA		13	73.0 (5.0 SD)	76.9								
Goodman [120]	AD	DSM- IV–TR, McKhann [204]	29	76.3 (6.3 SD)	48.3	post-stimulus power divided by pre-stimulus power	post-stimulus: 0–1500 pre-stimulus: –1500–0	n-back	7.5–12	x	x	electrodes: 64	
	MCI	DSM-5	100	71.9 (5.8 SD)	51.0								
	OA		40	72.5 (5.7 SD)	70.0								
van der Hiele [79]	aMCI	Petersen [6]	12	74.0 (6.0 SD)	41.7	% change from eyes closed	/	word and picture retention	8–10.5	picture retention: ↓ ERD OA > aMCI	–	electrodes: 17	all regions: left and right frontal (F7/F3, F4/F8), left and right temporal (T3/T5, T4/T6), left and right centro-parietal (C3/P3, C4/P4), occipital (O1/O2), midline (Fz, Cz, Pz)
	OA		16	72.0 (5.0 SD)	56.3				10.5–13	x			

Table 9

(continued)

McBride [78]	AD	?, no <i>APOE</i> ϵ 4 allele	17	76.7 (5.2 SD)	60.0	Welch's relative power	/	counting backwards	7.5–9.5	x	x	electrodes: 30	
	aMCI	?, no <i>APOE</i> ϵ 4 allele	16	74.6 (9.0 SD)	25.0								
	OA		15	75.7 (5.5 SD)	60.0				9.5–12.5	x	x		
Other executive functions													
Nguyen [125]	aMCI	Albert [68]	22	68.7 (7.7 SD)	63.6	ERS/ERD	0–600	inhibition; go/no-go	8–10		↓ ERD (go) OA > aMCI; go–no-go difference aMCI > OA	– electrodes: 9	parietal (P1/Pz/P2) frontal (F1/Fz/F2)
	OA		22	65.3 (6.8 SD)	72.7				11–13		go–no-go difference aMCI > OA		frontal (F1/Fz/F2)
Caravaglios [62]	aMCI	Albert [68]	27	70.6 (6.6 SD)	59.3	ERS/ERD	pre-motor 1: -1000–-500 pre-motor 2: -500–0 post-stimulus: 0–500	attention; omitted tone detection	upper alpha individually determined		pre-motor 2: OA ERD, aMCI ERS	– electrodes: 24	global
Sharma [74]	OA dementia	HMSE score < 18	15	67.3 (6.5 SD)	53.3								
	MCI	HMSE score 18–24	16	58.4 (? SD)	?	Welch's absolute power	/	attention; continuous performance test	8.6–12.6	x	?	electrodes: 21	global
Kurt [122]	OA		13	52.1 (? SD)	?								
	aMCI	similar to Petersen [6]	22	74.0 (7.0 SD)	40.9	peak-to-peak amplitude	0–500	attention; auditory oddball paradigm	8–13	x		– electrodes: 14	
Yener [123]	OA		21	70.3 (6.5 SD)	61.9								
	aMCI	Petersen [6], 4 later converted to AD	18	70.5 (5.6 SD)	38.9	peak-to-peak amplitude	0–300	attention; visual oddball paradigm	8–13	x		– electrodes: 12	
Yener [124]	OA		18	68.2 (5.6 SD)	50.0								
	aMCI	Albert [68]	30	70.5 (5.5 SD)	33.3	ERS/ERD (peak power)	0–400	attention; visual oddball paradigm	8–13	x		– electrodes: 12	
Prieto del Val [127]	OA		26	66.7 (4.9 SD)	50.0								
	aMCI	Petersen [6]	12	74.0 (6.0 SD)	41.7	% change from eyes closed	/	semantic memory; animal fluency	8–10.5	x		– electrodes: 17	
van der Hiele [79]	OA		16	72.0 (5.0 SD)	56.3				10.5–13	x			
Memory													
Prieto del Val [127]	AD-aMCI	Albert [68], 16 later converted to AD	34	69.0 (6.8 SD)	64.7	ERS/ERD	encoding and retrieval: 0–1000 ms	associative memory	8–12	x		– electrodes: 59	
van der Hiele [79]	OA		26	66.7 (4.9 SD)	50.0								
van der Hiele [79]	aMCI	Petersen [6]	12	74.0 (6.0 SD)	41.7	% change from eyes closed	/	semantic memory; animal fluency	8–10.5	x		– electrodes: 17	
van der Hiele [79]	OA		16	72.0 (5.0 SD)	56.3				10.5–13	x			

Arrows indicate whether the change in power in the more cognitively impaired group was significantly lower or higher than in the less impaired group. sd-aMCI, single domain aMCI; md-aMCI, multiple domain aMCI; ERS, event-related synchronization; ERD, event-related desynchronization. For other abbreviations and the explanation of symbols, see Tables 3 and 4.

Table 10
Functional connectivity during performance of a working memory task at the electrode level in people with aMCI

Paper	Groups	Diagnosis	<i>n</i>	Age (y)	Sex (% F)	EEG measure	Time window (ms)	Task	Alpha (Hz)	Results MCI versus OA	AD versus MCI	Electrodes
van der Hiele [126]	AD	McKhann [204]	16	78.0 (8.0 SD)	43.8	coherence	/	picture retention	8–13	x	x	17
	aMCI OA	Petersen [6]	18 22	74.0 (5.0 SD) 70.0 (5.0 SD)	61.1 68.2							
Pijnenburg [95]	AD	McKhann [204]	14	76.4 (13.6 SD)	50	synchronization / likelihood		picture retention	8–10	–	x	19
	aMCI	Petersen [6]	11	78.4 (6.4 SD)	90.9				10–12		x	

For abbreviations and the explanation of symbols, see Table 3.

Table 11
Changes in power at the level of electrodes and sources of neural activity during task performance in people with MCI who eventually progress to dementia and in people with MCI whose cognitive status remains stable

Paper	Groups	<i>n</i>	Diagnosis	Age (y)	Sex (% F)	Follow-up (y)	EEG measure	Time window (ms)	Cognitive domain/task	Alpha (Hz)	Results	Electrodes/ sources	Location of significant differences
Mazaheri [128]	AD-PaMCI	15	AD: McKhann [204]; MCI Petersen [1]	75.2 (7.1 SD)	37.5	≤3, mean 1.62	change from baseline	lexical and semantic processing: 500–1000	language comprehension; semantic judgment task	9–11	x	electrodes: Pz (lexical processing), Cz (semantic processing)	
Prieto del Val [127]	SaMCI	10		71.1 (7.5 SD)	40.0								
	AD-PaMCI	16	AD: DSM-IV, McKhann [?]; MCI: Albert [68]	69.7 (6.5 SD)	56.3	2	ERS/ERD	encoding and retrieval: 0–1000	associative memory	8–12	retrieval: ↓ ERD SMCI > PMCI	electrodes: 59	left and right temporo-parietal
	AD-SaMCI	18		68.4 (7.1 SD)	72.2		beam-forming; ERS/ERD	encoding and retrieval: 500–1000			encoding and retrieval: ↓ ERD SMCI > PMCI	electrodes: 59 whole brain	encoding: bilateral frontal and parietal lobes, left lateral and medial temporal lobe retrieval: similar as above plus right posterior lateral regions

For abbreviations and the explanation of symbols, see Tables 3, 7, and 9.

and people with AD (Pijnenburg et al. [95], $n = 14$ AD, 11 aMCI; van der Hiele et al. [126], $n = 16$ AD, 18 aMCI, 22 OA).

Alpha power and functional connectivity during other cognitive tasks

Only a few studies examined alpha power in people with MCI during tasks that tap into cognitive processes other than executive functions (Table 9). van der Hiele et al. [79] ($n = 12$ aMCI, 16 OA) did not find any differences between people with aMCI and cognitively healthy older adults during a task of semantic memory, and Prieto Del Val et al. [127] ($n = 34$ AD-aMCI, 26 OA, follow-up after 2 years) did not find any differences between the two groups during a task of associative memory. They did, however, find that people with aMCI who eventually progressed to AD had lower alpha ERD during encoding and retrieval of associative memories (Table 11; Prieto del Val et al. [127], $n = 16$ AD-PaMCI, 18 AD-SaMCI, follow-up after 2 years).

A study that compared alpha power in people with progressive and stable MCI during a task of language comprehension (Table 11) did not find significant differences between the two groups (Mazaheri et al. [128], $n = 15$ AD-PaMCI, 10 SaMCI, mean follow-up after 1.62 years).

DISCUSSION

The aim of this review and meta-analysis was to integrate findings of studies that compared power and functional connectivity of alpha oscillations between 1) people with MCI and cognitively healthy older adults, 2) people with MCI and people with a neurodegenerative dementia, and 3) people with MCI who progress to dementia and those whose cognitive status remains stable. Overall, there is evidence for 1) a gradual decrease of alpha power in awake resting state as people move along the continuum of cognitive decline, 2) lower alpha power in awake resting state in people with MCI who eventually progress to AD than in those whose cognitive status remains stable, and 3) lower alpha reactivity during tasks of executive functions in people with aMCI than in cognitively healthy older adults (see Fig. 6). There is also some evidence of lower functional connectivity in people with MCI than in cognitively healthy older adults, and in people with AD than in people with MCI. Findings of lower global resting state alpha power in people with AD than in people with MCI, and in people with

MCI than in cognitively healthy older adults were supported by meta-analyses. However, these results should be interpreted with caution due to the small number of studies in both meta-analyses, and highly heterogeneous outcomes with high I^2 in the analysis comparing people with MCI and cognitively healthy older adults.

Our review indicates that resting state alpha activity, globally and in posterior regions, reduces gradually as people progress from healthy aging to MCI to AD. Several studies that reported significant differences found lower alpha power in people with AD than in people with MCI, and in people with MCI than in cognitively healthy older adults [43, 58, 70, 72, 73, 75, 77, 80, 81, 94]. Though findings on MCI due to Lewy body disorders are scarce, they suggest that it might also be characterized by a lowering of resting state alpha power [70, 97, 98, 102, 103]. Moreover, four out of six longitudinal studies reported lower alpha power in people with MCI that eventually progressed to AD [57, 72, 111, 114]. In healthy people, alpha is the dominant resting state rhythm that is strongest in posterior parts of the brain [129, 130]. In people with MCI and those with AD, alpha activity was found to shift toward lower frequencies [29, 59, 62, 131–133], and in AD also toward more anterior brain regions [129, 134]. Consistent with these findings, studies that reconstructed sources of electrical activity found that the loss of alpha power in people with MCI was mostly localized to posterior regions [43, 56, 81, 94].

Lower resting state alpha power has been reported in several neurodegenerative diseases [135–138] and may be associated with cholinergic dysfunction. Due to its inverse relationship with neuronal activity [139–141], alpha was initially considered to reflect cortical idling or rest [142], but is now recognized to have an active role in inhibition, selective attention, and executive control [143, 144]. Alpha oscillations originate from thalamo-cortical and cortico-cortical interactions [145–147] that are modulated by the neurotransmitter acetylcholine [145, 148–150]. Cholinergic dysfunction has been described in neurodegenerative diseases such as AD, PD, dementia with Lewy bodies, Huntington's disease, and FTD [151–157], as well as in people with MCI, especially those who later progressed to AD [158–161]. Interestingly, cholinergic drugs that are used to treat symptoms of dementia were also found to affect oscillations in people with AD and dementia due to PD. Drug-induced changes included an increase in resting state alpha and beta power, and a

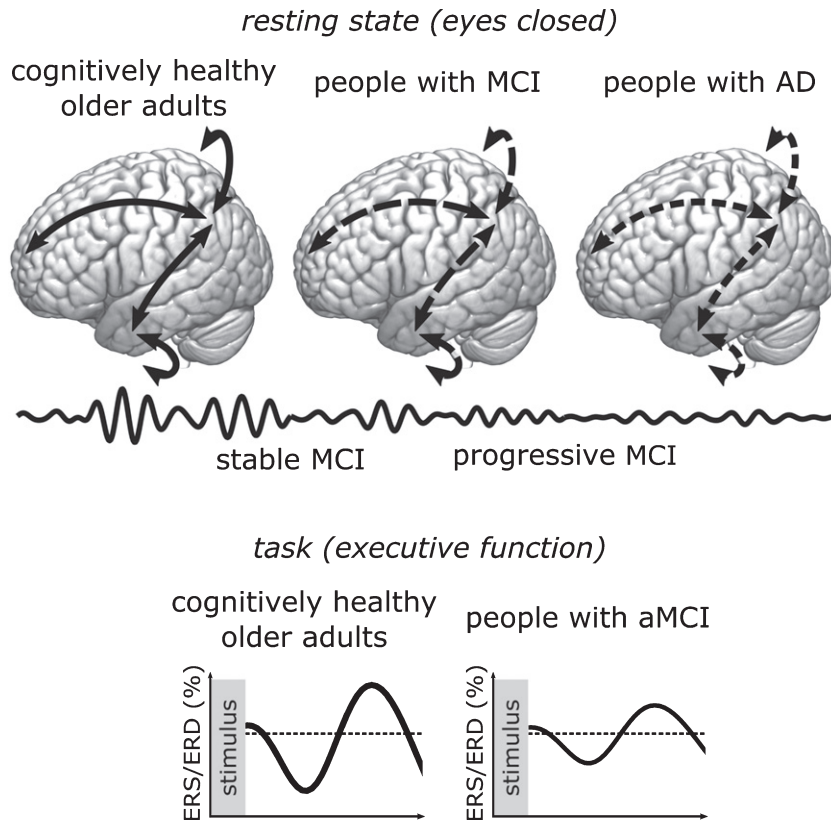


Fig. 6. Schematic summary of most consistent findings showing lower power of alpha oscillations and connectivity of parietal areas during rest in people who are further along the continuum of cognitive decline (top panel), and lower reactivity to task stimuli in people with aMCI compared to cognitively healthy older adults (bottom panel). Arrows represent functional connectivity, and the amplitude of waves the power of alpha oscillations. Dashed arrows represent lower functional connectivity.

decrease in theta and delta power [162–164], meaning that cholinergic drugs can counteract the slowing of oscillations that is characteristic of AD [29]. Cholinergic dysfunction could thus be related to observed changes in alpha activity, and in turn impairments in attention, inhibition, and executive functioning in people with neurodegenerative cognitive impairment.

Studies that measured alpha activity during task performance suggest that impaired executive functioning in people with aMCI [165] is underpinned by an inefficient recruitment of neural resources. Compared to cognitively healthy older adults, people with aMCI had lower event-related synchronization (ERS) [117, 119] and desynchronization (ERD) [79, 118, 125] during tasks of executive functions. Alpha ERS has been associated with the inhibition of task-irrelevant areas and learned responses, and ERD with cognitive processing [166], suggesting that people with aMCI have a reduced ability to recruit task-relevant areas and to inhibit task-irrelevant infor-

mation. This interpretation was supported by Fraga et al. [118] who found ERS in cognitively healthy older adults but ERD in people with MCI in response to stimuli that require response inhibition. Similarly, in a study by Caravaglios et al. [62], only cognitively healthy older adults showed a lowering of alpha power due to anticipatory attention. The studies that compared alpha reactivity between people with MCI and people with AD did not find any differences. Whereas task activation differs between cognitively healthy older adults and those that are experiencing cognitive decline, aMCI and AD might be characterized by similarly inefficient cognitive processing.

Studies on alpha synchronization found mostly lower, but also higher, resting state functional connectivity in people with MCI than in cognitively healthy older adults. AD has long been considered a disconnection syndrome [167, 168], and although connectivity in other neurodegenerative dementias is less well-researched, they have also been associated

with network disruption [169]. The pattern of amyloid deposition in AD overlaps with default mode network (DMN) topography [170], and there is evidence of reduced connectivity between regions of the DMN in people with AD [167, 169] and aMCI [171]. Similarly, Hsiao et al. [94] found lower coherence between the left posterior cingulate cortex and other areas of the DMN in AD than in MCI. Several other studies also reported lower synchronization within parietal and between parietal and frontal or temporal regions in people with MCI and AD [43, 75, 83, 85, 88–90].

There were some findings of higher connectivity in people with MCI compared to cognitively healthy older adults [59, 84, 91, 92], and in people with progressive compared to stable MCI [115, 116], which might suggest recruitment of compensatory mechanisms [172]. In fMRI studies, people with aMCI were found to have higher connectivity between the posterior cingulate cortex and frontal [173–175], parahippocampal, and hippocampal regions [174] than cognitively healthy older adults. Zhou et al. [176] compared people with the behavioral variant of FTD (bvFTD) and people with AD and found that these two groups were characterized by the opposite pattern of connectivity changes. While people with AD had lower connectivity in the DMN and higher connectivity in the salience network, people with bvFTD had enhanced DMN but reduced salience network connectivity. Hyper-connectivity between some areas might serve to compensate for the loss of connectivity caused by neurodegeneration and amyloid deposition between others [172–177].

Taken together, findings indicate that people with MCI and people with AD have disrupted alpha activity at rest and during task performance. Though findings on MCI due to Lewy body disorders are scarce, they suggest it could be characterized by similar changes in resting state alpha power. People with neurodegenerative cognitive decline may be less vigilant to incoming stimuli in the resting state, and less able to recruit relevant brain areas when performing a task. Exchange of information that is necessary for fast and efficient processing may be impaired due to hypoconnectivity of posterior regions, and possibly due to maladaptive compensatory hyperconnectivity.

Limitations and future directions

We identified several limitations at review- and outcome-levels that could have affected our results. Most had to do with the diversity in outcomes, which

is likely a consequence of the heterogeneous nature of MCI and the diversity of reported alpha measures. Moreover, though we took the first step in integrating findings of EEG studies across healthy aging, MCI, and dementia by focusing on the alpha band, changes in other frequency bands should not be overlooked.

We took several steps to avoid biased or spurious findings at the review-level. We used broad search terms to avoid missing any relevant results. We also contacted original authors if means and standard deviations were not reported, but were often unsuccessful. Despite our efforts, we cannot exclude the possibility that our results were affected by publication bias. Funnel plots (Supplementary Material 3), especially those for meta-analyses comparing alpha and lower alpha power in people with MCI and cognitively healthy older adults, were asymmetrical, but we cannot ascertain whether this is due to publication bias, spurious effects in smaller studies, or heterogeneity of outcomes [178].

Results of meta-analyses comparing people with MCI and cognitively healthy older adults need to be interpreted with caution due to highly heterogeneous outcomes and a small number of included studies. These meta-analyses had high I^2 values and included only five to six studies each, which could affect the estimation of the overall mean difference when using a random-effects model. A random-effects model takes the between-study variance into account and usually gives a more conservative estimation of significance when heterogeneity between outcomes is high [179–181]. However, when heterogeneity is high and the number of studies is small, the estimation of between-study variance is imprecise, which in turn affects the summary estimate [179]. Though the minimum number of studies for a random-effects model is not defined, it may be higher than five. Moreover, studies in a random-effects model are weighed more equally, meaning smaller studies can have a larger effect than they would in a fixed-effects model [178]. This could cause an inflated standardized mean difference in the meta-analysis comparing alpha power in people with MCI and cognitively healthy older adults. We therefore repeated the three meta-analyses with large heterogeneity with a fixed-effects model (Supplementary Material 4). Meta-analyses comparing lower and upper alpha power in people with MCI and cognitively healthy older adults remained non-significant. The meta-analysis comparing power in the full alpha band had a smaller effect size but remained significant.

High heterogeneity likely arose from diversity in EEG measures and samples in the original studies. To make outcomes more comparable, we combined means and standard deviations across electrodes or sources into a global measure. However, the number of electrodes or sources that data was available for ranged from three [57] to 19 [58]. Unfortunately, this pooling procedure was not suitable for measures of synchronization, as the data was often only available for certain electrode- or region-pairs. In a recent systematic review on the use of resting state EEG for the diagnosis and prognosis of AD and MCI, Cassani et al. [182] similarly identified large differences in experimental setups and reported EEG features between studies. We also observed that EEG was mostly recorded with a small number of electrodes, which could lead to imprecise measures of alpha power and connectivity in source space, and alpha connectivity in sensor space. Most studies that measured alpha at reconstructed sources used 19 or 20 electrodes [56, 72, 81, 89, 94, 98, 101, 103, 110, 115, 207], which is, according to COBIDAS-MEEG guidelines [82], not sufficient for precise source localization. Furthermore, when connectivity is measured in sensor space with a small number of electrodes and without spatial filters, it can lead to spurious connections. This could explain variable and inconsistent findings of studies that investigated alpha connectivity. Using a small number of electrodes saves time and effort, which is advantageous especially in clinical settings, but not ideal for source reconstruction and connectivity analyses.

Though most studies diagnosed MCI according to widely accepted criteria, samples likely differed in etiology, presentation, and the eventual outcome of impairment. Several studies compared people with MCI to people with AD, but only a few diagnosed AD-MCI according to the 2011 NIA-AA criteria [68], followed-up, or assessed amyloid biomarkers. It is possible that some people were mislabeled as having MCI due to AD while their impairment instead originated from Lewy body, vascular, or other pathology. Of the studies that included people with aMCI, only one [117] made a distinction between single (sd-aMCI) and multiple domain (md-aMCI) subtypes. Compared to people with sd-aMCI, those with md-aMCI were found to have lower resting state occipital alpha power [183] and lower ERS during encoding of attended faces [117]. There is some evidence suggesting that people with md-aMCI are further along the continuum of cognitive decline [184] and are more likely to progress to AD [185].

Cross-sectional studies inevitably grouped people with MCI who later developed different dementias, those who remained stable, and potentially those who reverted to healthy cognition [186]. According to our review of longitudinal studies, resting state alpha power may be lower in people who will progress to AD than in people with stable MCI. Moreover, as noted in our assessment of the quality of individual studies (Supplementary Material 2), some did not explicitly mention whether cognitively healthy older adults were free of cognitive complaints, meaning their results could be affected by the inclusion of people with subjective cognitive decline. Measures of alpha band could also be affected by factors other than cognitive impairment, such as drowsiness. However, all except two studies (Caravaglios et al. [62], van der Hiele et al. [79]) included in meta-analyses reported controlling participants' vigilance during resting state recording. In both of these studies, upper alpha power was higher in people with MCI than in cognitively healthy older adults. Given that alpha power, especially in upper alpha frequencies, is lower in drowsiness than in alert wakefulness [187], it is unlikely this affected the outcomes. Using more rigorous diagnostic criteria and following-up on participants, as well as standardizing methodology and reporting of EEG measures, would enhance comparability, enable cross-validation between studies, and increase the reliability of results.

While this paper focused on the alpha band, a valid diagnostic and prognostic biomarker will likely be a combination of multiple characteristics of the power spectrum. Theta and gamma bands are well-known for their involvement in memory [35, 188–190]. Activity in these bands, especially during task performance, was found to differ in people with MCI and cognitively healthy older adults [120, 125, 191–194], and activity in the theta band was found to predict progression to AD [112, 116, 195–197]. Task-related changes in delta power have also been identified as a potential biomarker of early cognitive decline [122, 123, 198–200]. Though the role of beta oscillations in MCI is less well-researched, some evidence suggests that beta activity differs in people with MCI and cognitively healthy older adults [119, 201, 202]. To account for the heterogeneity of MCI and for intra-individual differences in EEG activity [203], and to achieve good specificity, all of these changes will need to be taken into account. The present paper is therefore only the first step, and future reviews and meta-analyses should focus on findings from other frequency bands.

Conclusions

We investigated alpha power and functional connectivity in people at different stages of cognitive decline. Findings mostly indicated a lowering of resting state alpha power as people progress from cognitive health to MCI to AD. During task performance, people with MCI and AD had smaller alpha responses than cognitively healthy older adults. Studies on functional connectivity had mixed findings, reporting both lower and higher connectivity in people with MCI than in cognitively healthy older adults. Our review also highlights the diversity of EEG measures, alpha definitions, and cognitive profiles of participants in the studies conducted so far, and points toward the need to choose parameters that will allow for replicable and comparable research. If supported by a larger body of research, resting state alpha power could, perhaps combined with measures from other frequency bands, become a biomarker of early cognitive decline.

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SUPPLEMENTARY MATERIAL

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