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Global EEG coherence as a marker for cognition in older adults at risk for dementia

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Abstract

Quantitative electroencephalography (EEG) provides useful information about neurophysiological health of the aging brain. Current studies investigating EEG coherence and power for specific brain areas and frequency bands have yielded inconsistent results. This study assessed EEG coherence and power indices at rest measured over the whole skull and for a wide frequency range as global EEG markers for cognition in a sample at risk for dementia. Since global markers are more reliable and less error-prone than region- and frequency-specific indices they might help to overcome previous inconsistencies. Global EEG coherence (1–30 Hz) and an EEG slowing score were assessed. The EEG slowing score was calculated by low-frequency power (1–8 Hz) divided by high-frequency power (9–30 Hz). In addition, the prognostic value of the two EEG indices for cognition and cognitive decline was assessed in a 5-year follow-up pilot study. Baseline global coherence correlated positively with cognition at baseline, but not with cognitive decline or with cognition at the 5-year follow-up. The EEG slowing ratio showed no significant association, neither with cognition at baseline or follow-up, nor with cognitive decline over a period of 5 years. The results indicate that the resting state global EEG coherence might be a useful and easy to assess electrophysiological correlate for neurocognitive health in older adults at risk for dementia. Because of the small statistical power for the follow-up analyses, the prognostic value of global coherence could not be determined in the present study. Future studies should assess its prognostic value with larger sample sizes.

KEYWORDS
Alzheimer's disease, cognition, coherence, electroencephalography, functional connectivity, spectral power

1 | INTRODUCTION

With rising life expectancy, the diagnosis and treatment of age-related diseases are becoming significant and inevitable socio-economic topics. Age is the major risk factor for Alzheimer's disease (AD), which represents the most common cause of dementia. For many years, clinical assessments were exclusively informed by neuropsychological tests and by the history taken from patients and third parties. In recent years, neuropsychological assessment has been extended by

AD biomarkers (see Walsh, Drinkenburg, & Ahnaou, 2017; Weiner et al., 2013 for reviews). However, monitoring the continuum from healthy to pathological aging still remains challenging. Numerous studies suggest that quantitative electroencephalography (EEG) provides further insights into the neurophysiological correlates of pathological cognitive aging (see Babiloni et al., 2016 for a recent review). EEG is also a non-invasive, cost-effective tool.

One robust finding in AD is a decrease in EEG coherence as an index for reduced functional connectivity (see Babiloni et al., 2016; Dauwels, Vialatte, & Cichocki, 2010 for reviews). The most common finding has been a decrease in EEG coherence for faster frequency bands; that is, alpha and beta (e.g., Jelic et al., 1996; Knott, Mohr, Mahoney, & Ilivitsky, 2000; Wada, Nanbu, Kikuchi, et al., 1998). Results regarding theta band functional coherence are scarce, but consistently demonstrated a decrease in theta band power in patients with AD compared to controls (e.g., Adler, Brassen, & Jajcevic, 2003; Stevens et al., 2001). Results on changes in delta spectral coherence have been controversial: while some studies reported an attenuated delta spectral coherence in patients with AD compared to controls (e.g., Knott et al., 2000), others found an increase in delta spectral coherence in individuals with AD (Babiloni et al., 2009). Studies on coherence in mild cognitive impairment (MCI), as possible prodromal stage of AD, suggested that changes might already occur in this at-risk stage for dementia (e.g., Michels et al., 2017). Besides group comparisons, positive correlative associations have been reported between spectral coherence and cognitive performance, especially in the Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975), in subjects with AD as well as with MCI (e.g., Brunovsky, Matousek, Edman, Cervena, & Krajca, 2003; Dunkin, Osato, & Leuchter, 1995; Jelic et al., 1996; for controversial results see Babiloni et al., 2009; Knott et al., 2000, and for missing associations see Jiang, 2005; Leuchter et al., 1992).

In addition to the decrease in spectral coherence, a further robust finding in healthy aging and even more pronounced in AD is a shift in signal power from faster alpha and beta to slower delta and theta frequency bands, a process which is described as a slowing of the EEG activity (see Dauwels et al., 2010; Jeong, 2004 for reviews). Increased theta band activity (e.g., Brenner, Reynolds, & Ulrich, 1988; Coben, Danziger, & Storandt, 1985; Prichep et al., 1994; Soininen, Partanen, Pääkkönen, Koivisto, & Riekkinen, 1991) seems to be a salient index for AD, accompanied already in its early stage (Brenner et al., 1988; Kwak, 2006; Soininen et al., 1991) by a decrease in beta and alpha band activity (cf., Coben et al., 1985; Gianotti et al., 2007). An increased delta band activity seems to occur only in advanced stages of AD (e.g., Coben et al., 1985; Kwak, 2006; Prichep et al., 1994). Knowledge regarding changes in EEG power in individuals with MCI is very limited so far, but previous studies suggested that a significant slowing of EEG already begins in MCI and even before initial objective cognitive decline arises (e.g., Grunwald et al., 2002; Jelic et al., 1996, 2000; Kwak, 2006). Similar to the findings regarding spectral coherence, correlative associations have also been reported for spectral power and cognitive performance in individuals with AD and MCI (e.g., Alexander et al., 2006; Brenner et al., 1986; Gianotti et al., 2007; Kwak, 2006; van der Hiele et al., 2007), with elevated low-frequency power being associated with worse and high-frequency power with better cognitive performance (for missing associations, see, e.g., Moretti et al., 2004; Onishi, Suzuki, Yoshiko, Hibino, & Iguchi, 2005).

A wide range of literature regarding coherence and power changes in AD exists. The majority of studies have considered region-specific electrophysiological changes or changes in particular frequency bands (e.g., Prichep et al., 1994; Stevens et al., 2001). So far, only a few studies have investigated widespread (total) changes over the whole skull for spectral coherence and spectral power (Babiloni et al., 2009; Ihl, Brinkmeyer, Jänner, & Kerdar, 2000; Moretti et al., 2004), which in general support the above-mentioned findings for separate brain regions. Global electrophysiological changes for a wide frequency range as an index for cognition have not been investigated so far. However, global EEG markers for cognitive performance would be of high benefit for the clinical application as well as for scientific research, because averaging over multiple electrodes is more reliable and less error-prone than the use of multiple region- and frequency-specific measures and would allow a better comparison between study results.

To this date, only few longitudinal studies have investigated the prognostic value of EEG power and EEG functional connectivity in populations at risk for developing dementia (e.g., Jelic et al., 2000; Rossini et al., 2006), suggesting that EEG spectral coherence and power might be useful in the prognosis of cognitive decline in AD, but the research in this area is still in its infancy.

Thus, the aims of this study were twofold: (1) to examine global coherence (delta-beta, 1–30 Hz) and an EEG slowing score as markers for cognition in a at risk for dementia sample; thereby EEG slowing was defined as low-frequency power (delta and theta, 1–8 Hz) divided by high-frequency power (alpha and beta, 9–30 Hz); and (2) to examine the prognostic value of global coherence and EEG slowing for cognition in a 5-year follow-up pilot study within a sub-sample.

Based on previous results, we expected global coherence at baseline to be positively associated with cognition at baseline as well as 5 years later and with less cognitive decline at the 5-year follow-up. Because of the EEG slowing in pathological cognitive aging, we hypothesized that higher EEG slowing would be associated with lower cognition at baseline and at the 5-year follow-up and with more pronounced cognitive decline after a period of 5 years.

To give a deeper insight into the data, in additional analyses all associations with cognition were reported not only for the global EEG indices, but also for specific frequency bands and regions. As introduced earlier in this section, previous studies have investigated relations between coherence and cognition for localized coherence values; most often coherence changes in AD have been reported for the fronto-parietal and fronto-temporal area (see Babiloni et al., 2016 for a review). To enable the comparison with previous study results as well as between the global and localized scores, all baseline and follow-up associations with cognition were reported for the fronto-parietal and fronto-temporal area. For the main analyses, we used the overall cognition score comprising a composite score of episodic memory and attention/executive functions. Since it cannot be ruled out that these two cognitive domains are linked to coherence differentially, all EEG cognition analyses were also demonstrated for episodic memory and attention/executive functions separately.

In sum, in the supplemental material the following results scheme is presented for coherence: frequency band (delta, theta, alpha, beta) × cognitive domain (memory, attention/executive functions) × time (baseline, 5-year follow-up) and cognitive change × skull area (fronto-parietal, fronto-temporal). Additional analyses regarding EEG slowing values can be summarized as follows: frequency band (delta, theta, alpha, beta) × cognitive domain (memory, attention/executive functions) × time (baseline, 5-year follow-up) and cognitive change.

2 | METHOD

2.1 | Procedure and participants

The study was approved by the ethics committees of both study centers, University of Konstanz and Ulm University, Germany. The study was part of a controlled clinical trial investigating the effect of physical exercise and cognitive training on cognition as well as on biological and electrophysiological parameters (cf., Fissler et al., 2017; Küster et al., 2016, 2017; Laptinskaya et al., 2018). All participants provided written informed consent prior to study participation. Participants were recruited in the Memory Clinic of the University Hospital Ulm, Germany and the Center for Psychiatry Reichenau in Konstanz, Germany or via public advertisements. Inclusion and exclusion criteria for study participation are described in detail in Küster et al. (2016). In brief, participants had to be 55 years or older and report or show subjective or objective memory impairment. Further inclusion criteria were fluency in German language, stable anti-dementia and antidepressant medication, normal or adjusted-to-normal hearing, and independent living. Participants with probable moderate or severe dementia

(MMSE < 20) as well as a history of other neurological or psychiatric disorders (except mild to moderate depression) were excluded. One participant had to be excluded because of very noisy EEG data. The final baseline sample comprised 70 participants (mean age: 71.60 ± 6.16 years, range 60–88 years; mean education: 10.15 ± 1.96 years, range: 6–14 years; mean MMSE: 27.83 ± 2.31, range: 20–30).

A follow-up telephone interview was performed 5 years after study participation (M = 5.23 years, SD = 0.19) for participants of the Konstanz sample. We were able to reach twenty-nine participants, two of whom refused participation and another five had to be excluded, because they were no longer able to attend the telephone interview due to severe progression of cognitive and functional decline. Notably, one of the five participants was already excluded from the baseline analyses due to very noisy EEG data (see section "EEG Data Processing"). Four participants were not reachable. Finally, 22 complete data sets were available for the follow-up analyses. In the follow-up sample, the mean age was 70.91 years (SD = 7.81, range: 60–94 years). None of the final follow-up participants received a clinical AD diagnosis within the period between baseline and 5-year follow-up. As the MMSE is not suitable for a telephone interview setting, we used the modified version of the Telephone Interview for Cognitive Status (TICS-M; Brandt, Spencer, & Folstein, 1988; Gallo & Breitner, 1995) for cognitive functioning in the follow-up assessment, which can be administered using the telephone and showed high correlations with the MMSE test scores (Brandt et al., 1988). The sum-score in the TICS-M ranges from 0 to 50. The follow-up sample showed the following TICS-M sum scores: 36 ± 5.7 (M ± SD) in a range of 26–50. Gallo and Breitner (1995) identified a score of 33 as the cutoff value with the best specificity and sensitivity to distinguish cognitively healthy from cognitively impaired individuals.

2.2 | Neuropsychological assessment

All participants completed the following assessments: Alzheimer's Disease Assessment Scale–cognitive subscale (Ihl & Weyer, 1993); phonemic and semantic word fluency as well as Trail Making Test part A and B of the Consortium to Establish a Registry for Alzheimer's Disease–plus test battery (Welsh et al., 1994); the subtests digit span and digit-symbol coding of the Wechsler Adult Intelligence Scale (Tewes, 1991); the long-delay free recall scores of the adapted German version of the California Verbal Learning Test (German: Münchner Verbaler Gedächtnistest [MVGT, Munich Vebal Memory Test]; Ilmberger, 1988); and the working-memory subtest of the Everyday Cognition Battery (Allaire & Marsiske, 1999). All variables were z-standardized and entered into a principal component analysis. A detailed description of the principal component analysis at baseline as

well as at the 5-year follow-up can be found in Laptinskaya et al. (2018). Only the Everyday Cognition Battery–computation span with a_{ij} = .48 slightly missed the critical threshold of a_{ij} = .50. As a result, two component scores were built: the first one as an index for episodic memory and the second one as an index for attention/executive functions. Cognition was defined as the average of the episodic memory and the attention/executive functions composite score.

For the follow-up investigation, we selected tests from the baseline investigation which were suitable for assessments via telephone (for telephone tools for cognitive assessment, see, e.g., Castanho et al., 2014; Duff, Tometich, & Dennett, 2015), namely the adapted German version of the California Verbal Learning Test, the digit span forward and backward, and the Consortium to Establish a Registry for Alzheimer's Disease–plus subtests phonemic and semantic word fluency. The composite scores were built in the same manner as at baseline using the baseline weights for the available variables.

2.3 | EEG recording

EEG was recorded using a high-density 256-channel HydroGel™ Geodesic Sensor Net (HCGSN; Electrical Geodesics, Inc.; Eugene, Oregon, USA) with Cz (vertex) as reference and a sampling rate of 1000 Hz during data acquisition. A 50 Hz notch filter was applied to reduce line noise. During the 5 min resting state EEG, participants were sitting comfortably in an electrically shielded and sound-attenuated room. To avoid drowsiness artifacts, participants were instructed to keep their eyes open during EEG recordings. Furthermore, to avoid muscle and eye movement artifacts, participants were instructed to relax, and to blink as seldom as possible while fixating on one of the three points approximately at eye level on the opposite wall.

2.4 | EEG data processing

After recording, the data were imported into MATLAB (version 2015b; The MathWorks, 2015) and preprocessed using the FieldTrip toolbox (version 20151012; Oostenveld, Fries, Maris, & Schoffelen, 2011). According to our experience, the first as well as the last segments of EEG recordings are often contaminated by artifacts (cf., Schlögl et al., 2007). Hence, from the available 5 min EEG we used only the recordings from the second and the third minute for preprocessing. The data were bandpass filtered in the range of 1–30 Hz (24 dB/octave). Continuous data were cut into segments of a length of 1 second, resulting in 120 trials per participant. Noisy channels and artifact-contaminated segments were manually rejected. On average, 16 (SD = 16) channels were rejected for

every participant, especially the channels in the cheek areas and the lower part at the back of the head. Previous studies showed that the choice of the reference influences coherence analyses, a zero reference being the best choice (Fein, Raz, Brown, & Merrin, 1988; Rappelsberger, 1989). If the number of electrodes is high, the average common reference is typically close to zero (Nunez et al., 1997). For this reason, the data were re-referenced to the average of all artifact-free electrodes (M = 241; SD = 16). Finally, to exclude the contamination by the number of trials, 50 trials were randomly selected from the remaining epochs and used for subsequent analyses. One participant was excluded from the analyses because of very noisy EEG data, especially a high amount of eye artifacts (see also section "Procedure and Participants").

2.5 | Spectral coherence analyses

Functional connectivity was calculated using the spectral coherence method, which indicates the functional connectivity in brain activity between two cortical regions and is calculated as a function of frequency (Walter, 1968). The spectral coherence is a linear index for the coupling between signals without any information on the connectivity direction (Babiloni et al., 2016) and it can be interpreted analogously to a correlation coefficient as it represents the covariance of spectral energies originating from two skull regions (Knott et al., 2000). Spectral coherence analyses were conducted using the *bsmart* implementation for MATLAB (Cui, Xu, Bressler, Ding, & Liang, 2008). Since we were interested in functional connectivity across the entire brain, we calculated the spectral coherence for all electrode pairs and then averaged all of these values as an index for global coherence (1–30 Hz).

2.6 | Spectral power analyses

Frequency analysis was performed across all non-excluded electrodes (M = 241, SD = 16) using the fast Fourier transform (FFT) algorithm with Hanning window and a 1 Hz frequency resolution. The frequency bands were classified into delta (1–4 Hz), theta (5–8 Hz), alpha (9–13 Hz), and beta bands (14–30 Hz; cf., Babiloni et al., 2016; Schorr, Schlee, Arndt, & Bender, 2016). Low-frequency power was defined as the power in the range between 1 and 8 Hz, and high-frequency power as the power ranging from 9 to 30 Hz. Relative power represented spectral composition of the EEG. It was derived by dividing the power within each frequency band by the total power across all frequency bands (1–30 Hz). The relative power was used in all statistical calculations. As a marker for EEG slowing, we built a ratio score between relative low power in the

1–8 Hz frequency range and the relative high power in the 9–30 Hz frequency range, higher values indicated higher EEG slowing.

2.7 | Statistical analyses

All statistical analyses were performed using *R* (version 3.2.3; R Core Team, 2016) in *RStudio* (RStudio Team, 2015). As a first step, to investigate the associations between the EEG indices and cognitive performance at baseline ($n = 70$), we performed hierarchical linear regression models with the neuropsychological composite score for cognition as dependent variable. The first model (model 1) included only one EEG index as predictor. Since age depicts a risk factor for cognitive decline (e.g., Salthouse, 2009, 2012), we accounted for this covariate in our statistical analyses. Thus, we advanced the first model by age as a second independent variable following the EEG index, which was the independent variable that was entered into the model first (model 2). Both models described above were carried out separately for each EEG index as independent variables. To underpin the justification of age as covariate, we used ANOVA to compare model 2 with EEG parameter and age as independent variables to model 1 without age as additional predictor. We further compared both models by Akaike's Information Criterion (AIC). AIC has a profound information-theoretic foundation and aims at minimizing the expected Kullback–Leibler divergence between the model and the true underlying data-generating process (Burnham & Anderson, 2000), whereby lower values between nested models indicate a better model fit.

As additional analysis, associations between EEG indices and cognition at baseline were investigated for the different cognitive subscores (i.e., memory and attention/executive functions) and for different frequency bands (i.e., delta, theta, alpha, beta). Coherence associations with cognition were assessed for special long-range cortical networks (fronto-parietal and fronto-temporal). To investigate the associations between global EEG indices and cognitive subscores, the same hierarchical regression method was used as for the overall cognition score in the main analyses. To investigate the association between cognition indices and localized coherence and power values, we performed simple hierarchical linear regressions, and *p*-values were adjusted according to Holm's method for multiple comparisons. The number of comparisons was set to eight for coherence (four frequency bands × two cortical networks). For power results, the *p*-value was adjusted for four comparisons (four frequency bands).

As a second step, changes in cognitive performance, namely in cognition, episodic memory, attention/executive functions, as well as in single cognitive tests at baseline and at the 5-year follow-up were conducted with one-tailed *t*-tests for paired samples for those tests that were used at both time points (see section "Neuropsychological Assessment"). Test–retest reliability as a measure for data quality was assessed by correlations between baseline and follow-up scores. In the third step, we compared the baseline global coherence and the EEG slowing score in excluded participants in comparison to non-excluded participants ($n = 4$ vs. $n = 22$), as some participants were excluded from follow-up assessment because of pronounced cognitive decline (see section "Procedure and Participants").

To investigate group differences in EEG parameters, group comparisons were conducted with univariate analysis of variance (ANOVA).

Finally, we examined the prognostic value of global coherence and EEG slowing score ($n = 22$). For this purpose, we investigated the association between EEG indices and cognitive decline in cognition 5 years later as well as the cognitive performance in cognition at the 5-year follow-up. Cognitive decline was indexed by the difference score between cognition at baseline and cognition at the 5-year follow-up, with higher values indicating more pronounced cognitive decline. Again, we used hierarchical regression models to examine the association between EEG indices and cognitive decline in cognition as well as the cognitive performance 5 years later, the latter as dependent variable. Standardized regression coefficients of global coherence as well as the EEG slowing score predicting cognition were used as effect size measure for the associations between cognition and the EEG indices. The first model included one EEG marker only (model 1), and the second model accounted for age by including it as additional independent variable (model 2). The same way as for baseline analyses, we compared the model with only one EEG predictor to the model additionally including age as covariate via ANOVA and via AIC. Additionally, associations between EEG indices and cognitive decline at the five-year follow-up were investigated for the different cognitive subscores (i.e., memory and attention/executive functions) and for different frequency bands (i.e., delta, theta, alpha, beta). Besides that, coherence associations with cognitive decline were assessed for special long-range cortical networks (fronto-parietal and fronto-temporal). To investigate the associations between global EEG indices and cognitive decline, the same hierarchical regression method was used as for the overall cognition score. To investigate the association between cognition indices and localized coherence and power values, we performed simple hierarchical linear regressions, and *p*-values were adjusted according to Holm's method for multiple comparisons. The number of comparisons was set to eight for coherence (four frequency bands × two cortical networks). For power results, the *p*-value was adjusted for four comparisons (four frequency bands).

Collinearity between predictors was examined by computing the variance inflation factor (VIF) for each predictor's beta score and for the mean beta score as well as the

VIF tolerance score (1/VIF). Individual VIF scores > 10, a mean VIF score > 1, and a VIF tolerance score < 0.1 indicated beta score inflation by collinearity in the models (Bowerman & O'Connell, 1990; Menard, 1995; Myers, 1990).

Normal distribution of all models' residuals was confirmed using the Shapiro–Wilk test (*W* statistic) and visual inspection (Q–Q plots). The statistical significance level (α) was set to .05 for all analyses.

3 | RESULTS

3.1 | Associations between baseline EEG indices and baseline cognition

Global coherence was positively associated with cognition, $\beta = .31$, 95% CI [.09, .54], $p = .009$ (Table 1 and Figure 1). The association still remained significant after adjusting for age, $\beta = .25$, 95% CI [.03, .47], $p = .028$. Furthermore, age was significantly associated with cognition, $\beta = -.30$, 95% CI [−.52, −.08], $p = .01$. We did not find any significant associations between the EEG slowing score and cognition, $\beta = .01$, 95% CI [−.23, .25], $p = .921$. Adjusting for age did not change the results, but age was significantly associated with cognition, $\beta = -.35$, 95% CI [−.58, −.12], $p = .003$.

Baseline associations between global EEG indices and cognitive subscores, that is, memory and attention/executive functions, are depicted in Supplementary Table S1. The associations between global coherence and attention/executive functions were significant in model 1, including the EEG index only, $\beta = .28$, 95% CI [−.05, .51], $p = .019$. The association between global coherence and memory was significant at the trend level in model 1, $\beta = .22$, 95% CI [−.01, .46], $p = .064$. After adjusting for age, neither attention/executive functions nor memory was significantly associated with global coherence. Age was significantly associated with attention/executive functions, $\beta = -.30$, 95% CI [−.53, −.08], $p = .007$; as well as with memory, $\beta = -.26$, 95% CI [−.49, −.03], $p = .029$. Supplementary Table S2 shows the baseline associations between EEG indices for selective frequency bands as well as for special cortical networks and (overall) cognition, memory, and attention/executive functions. Before the correction for multiple comparisons, fronto-parietal coherence in the theta and in the beta band were positively associated with cognition, $\beta = .27$, 95% CI [.05, .50], $p = .022$ and $\beta = .26$, 95% CI [.03, .50], $p = .027$, respectively. Theta power was negatively associated with attention/executive functions, $\beta = -.29$, 95% CI [−.52, −.06], $p = .016$. After the adjustment for multiple comparisons, none of the associations reached statistical significance.

3.2 | Associations between baseline EEG indices and cognitive decline in cognition, as well as follow-up cognition

We found no significant difference in cognition between baseline and the 5-year follow-up, indicating no significant cognitive decline in this sub-sample. The results of the baseline follow-up comparisons in cognitive performance, which was subdivided into (overall) cognition, memory, attention/executive function and single cognitive tests, are presented in Table 2.

TABLE 1 Correlative associations between global coherence and EEG slowing with cognition at baseline (*n* = 70)

	Cognition						
	$M \pm SD$	ΔR^2	B	β	95% CI	p	AIC
Global coherence (1–30 Hz)							
Model 1		.10				**.009**	170.60
Global coherence	0.34 ± 0.16		1.62	.31	[.09, .54]	**.009**	
Model 2		.08				**.010**	165.73
Global coherence			1.32	.25	[.03, .47]	**.028**	
Age	71.60 ± 6.16		−0.04	−.30	[−.52, −.08]	**.010**	
EEG slowing (1–8 Hz/9−30 Hz)							
Model 1		<.01				.921	177.73
EEG slowing	3.28 ± 1.75		0.01	.01	[−.23, .25]	.921	
Model 2		.12				**.003**	170.68
EEG slowing			0.02	.04	[−.18, .27]	.704	
Age	71.60 ± 6.16		−0.05	−.35	[−.58, −.12]	**.003**	

Note: The EEG slowing score was calculated by low-frequency power (1–8 Hz) divided by high-frequency power (9–30 Hz). Higher values indicated more pronounced EEG slowing. Significant p-values are written in bold.
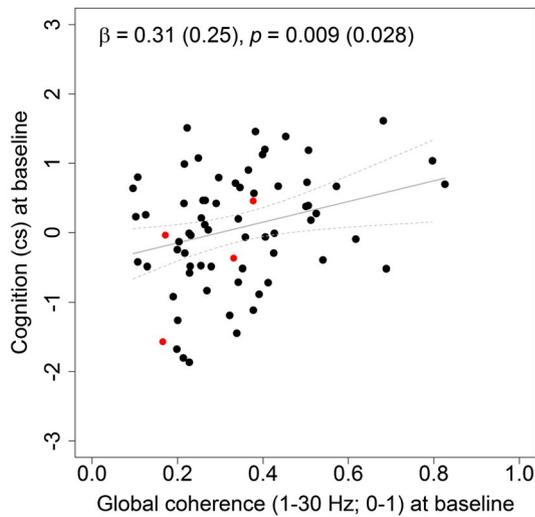
β = 0.31 (0.25), *p* = 0.009 (0.028)

FIGURE 1 Correlative association between global coherence at baseline and baseline cognition composite score (*n* = 70). *Note*. Values in brackets are adjusted for age. Dashed gray lines represent the 95% confidence interval. Red dots depict values of the participants from whom no 5-year follow-up data were available because they showed pronounced cognitive decline and were no longer able to attend the telephone interview

TABLE 2 Change in cognitive performance at the 5-year follow-up (*n* = 22)

	Change [95% CI]	t^a (21)	*p*	d^b
Cognition (global, cs)	−0.13 [-.44, .18]	0.88	.390	.19
Episodic memory (cs)	−0.05 [-.35, .26]	0.32	.752	.07
Attention/EF (cs)	−0.14 [-.55, .27]	0.73^c	.472	.16
MVGT enc. (0–80)	−1.14 [-5.79, 3.52]	0.51	.617	.11
MVGT rec. (0–16)	0.00 [-1.14, 1.14]	<0.01	>.999	.00
Digit span (0–28)	−0.38 [-1.69, 0.93]	0.61^d	.550	.13
Word fluency (w.)	−0.15 [-3.71, 3.41]	0.09^c	.931	.02

Note: EF, executive functions; MVGT enc., Münchner Verbaler Gedächtnistest [Munich Verbal Memory Test]—encoding (sum of words of the five learning trials); MVGT rec., Münchner Verbaler Gedächtnistest [Munich Verbal Memory Test]—long-delay free recall; digit span, total value from the forward and backward part; word fluency, total value of the episodic and phonemic word fluency; cs, composite score; w., words.

[a]*t*-value for one-tailed *t*-test comparison between baseline and 5-year follow-up.
[b]Cohen's *d*.
[c]*t* (19).
[d]*t* (20).

Test–retest reliability was high: it was *r* = .80 for the cognition score, *r* = .77 for the episodic memory score, and *r* = .81 for the attention/executive functions score. There were no significant differences in baseline global coherence and baseline EEG slowing score between the four cognitively strongly impaired participants excluded from 5-year follow-up and the non-excluded participants (see Supplementary Table S3).

We further investigated the association of each EEG parameter alone (model 1) and after accounting for age (model

2) with cognition at the 5-year follow-up as well as the cognitive decline after a period of 5 years. No significant association was found for baseline global coherence and cognitive change over a period of 5 years, β = −.31, 95% CI [−.73, .10], *p* = .154 (see Table 3 and Figure 2) or cognition at the 5-year follow-up, β = .08, 95% CI [−.35, .52], *p* = .716 (see Supplementary Table S4).

We did not find significant associations between EEG slowing and cognitive decline (see Table 3) as well as cognition at the 5-year follow-up (see Supplementary Table S4). Age was significantly associated with neither cognitive decline over a period of 5 years (see Table 3), nor with cognition at the 5-year follow-up (see Supplementary Table S4).

Associations between global EEG indices and cognitive decline in memory as well as in the attention/executive functions subscore are presented in Supplementary Table S5. Similar to the association between (overall) cognition and EEG indices, no significant correlations were found between global coherence and EEG slowing with memory and attention/executive functions. Supplementary Table S6 shows the associations between EEG slowing and coherence for selected frequency bands and selected cortical networks and (overall) cognition, memory, and attention/executive functions. Only the association between alpha power and memory was significant, β = −.50, 95% CI [−.27, .59], *p* = .017. After adjusting for multiple comparisons and age, no significant associations were found.

4 | DISCUSSION

In accordance with our hypotheses, global spectral coherence was positively associated with cognition at baseline (β = .31; see Table 1 and Figure 1). The association remained significant after adjusting for age, indicating that global coherence explained variance in cognition in addition to age. None of the region- and frequency-specific coherence measures significantly predicted cognition after adjusting for multiple comparisons and all specific measures showed lower effect sizes than the global coherence measure (βs ≤ .27).

The positive association between global coherence and cognition is in line with other studies which reported a coherence decrease in delta, theta, alpha, and beta rhythms in individuals with AD and MCI compared to healthy controls (e.g., Knott et al., 2000; Wada, Nanbu, Koshino, Yamaguchi, & Hashimoto, 1998; but see Brunovsky et al., 2003; Jelic et al., 1997; Wada, Nanbu, Kikuchi, et al., 1998 for increased delta spectral coherence in participants with AD). Our results are further in accordance with studies which reported positive associations between coherence and cognitive performance in individuals with AD and MCI for separate brain regions (e.g., Dunkin et al., 1995; Jelic et al., 1996; Knott et al., 2000) as well as for total coherence (measured over the whole skull) for separate frequency bands (Babiloni et al., 2009).

TABLE 3 Correlative associations between global coherence and EEG slowing and cognitive decline at the 5-year follow-up (n = 22)

	Cognition						
	$M \pm SD$	ΔR^2	B	β	95% CI	p	AIC
Global coherence (1–30 Hz)							
Model 1		.10				.154	49.57
Global coherence	0.35 ± 0.15		−1.46	−.31	[−.73, .10]	.154	
Model 2		.04				.339	50.48
Global coherence			−1.29	−.28	[−.70, .14]	.213	
Age	70.91 ± 7.81		−0.02	−.21	[−.63, .21]	.339	
EEG slowing (1–8 Hz/9−30 Hz)							
Model 1		.06				.265	50.46
EEG slowing	2.96 ± 1.83		−0.10	−.25	[−.67, .18]	.265	
Model 2		.06				.130	51.46
EEG slowing			−0.09	−.24	[−.66, .19]	.287	
Age	70.91 ± 7.81		−0.02	−.25	[−.67, .17]	.265	

Note: Decline in cognition is defined as the difference score in baseline cognition and cognition at the follow-up, higher values indicating more pronounced decline. The EEG slowing score was calculated by low-frequency power (1–8 Hz) divided by high-frequency power (9–30 Hz). Higher values indicated more pronounced EEG slowing.
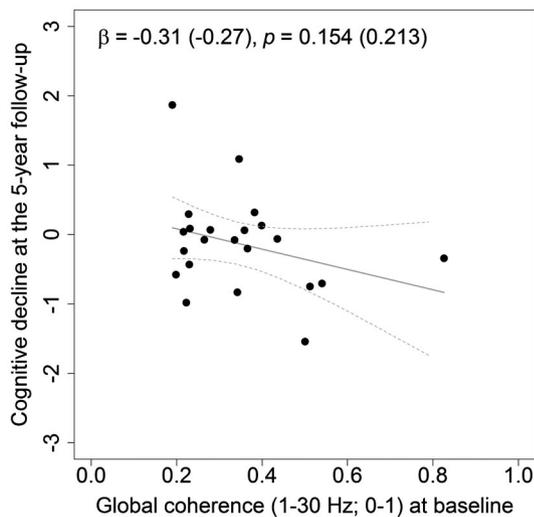
FIGURE 2 Correlative association between baseline global coherence and cognitive decline at the 5-year follow-up (n = 22). *Note.* Values in brackets are adjusted for age. Dashed gray lines represent the 95% confidence interval

Different biological mechanisms for the positive association between global coherence and cognition are conceivable. EEG coherence indicates the functional coupling between two brain regions (Wada, Nanbu, Koshino, et al., 1998). Thus, the *global* coherence describes the connectivity of brain networks across the whole brain. Accordingly, disturbances in global coherence reflect alterations in global information integrity in neural networks which are involved in cognitive processes. Since attenuation in global coherence has been demonstrated in AD, AD has also been described as

a "disconnection syndrome" (e.g., Bokde, Ewers, & Hampel, 2009). The disconnection hypothesis derives from the assumption that cognitive performance does not depend on one intact brain region only; it rather depends on the intact interplay between different brain regions (cf., Bokde et al., 2009). Thus, disturbances in functional and/or anatomical neuronal networks may lead to widespread cognitive impairment (cf., Morrison & Hof, 2002; Morrison, Scherr, Lewis, Campbell, & Bloom, 1986). An intact neuronal integrity between brain regions depends on various molecular mechanisms as well as sufficient energy provided by mitochondria as power stations in the (neuronal) cell (Ferrer, 2009). Cumulative evidence shows that mitochondrial function is disturbed in AD and this dysfunction is accompanied by many molecular changes; for example, oxidative stress, deregulation of Ca^{2+} homeostasis, promotion of the amyloid beta (Aβ) deposition, and neuro-inflammation. Those molecular changes may include and enhance neuronal cell exhaustion and neuronal death and may injure anatomical and functional connectivity (see Bhat et al., 2015; Zhao & Zhao, 2013 for reviews). As far as we know to date, no study has specifically investigated the association between mitochondrial function, functional connectivity, and cognition in the same (AD patients) sample; but some human and animal studies have investigated separate aspects of these associations. These studies suggest a negative impact of mitochondrial dysfunction on cognition (Hara et al., 2014) and its key role in cognitive decline in AD (Reddy, 2011). By these means, global EEG coherence might reflect impaired mitochondrial function resulting in an attenuated cognitive performance in older adults at risk for AD (for a review on mitochondrial function as possible target for the treatment

of AD see Stockburger, Eckert, Eckert, Friedland-Leuner, & Müller, 2018).

The positive association between spectral coherence and cognitive performance might be further explained by other shared neurobiological mechanisms apart from mitochondrial dysfunction. For instance, the loss of cholinergic neurons in AD and in AD mouse models is well documented (Davies & Maloney, 1976; Perez, Dar, Ikonomovic, DeKosky, & Mufson, 2007). Acetylcholine (ACh) activates cholinergic neurons and is one of the most important neurotransmitters in the human peripheral and central nervous system. ACh is responsible for the activation of muscle cells and is involved in numerous physiological and cognitive processes such as the stress response, the regulation of wakefulness and sleep, and memory and attention processes (Ferreira-Vieira, Guimaraes, Silva, & Ribeiro, 2016). Interestingly, previous studies indicated a positive association between EEG coherence in individuals with AD and reduced neuronal cholinergic activity (Wada, Nanbu, Koshino, et al., 1998). Thus, the EEG coherence–cognition relationship might be explained by a reduced cholinergic level in the brain, which influences both coherence and cognition. This assumption is supported by drug studies: While the administration of the ACh antagonist scopolamine has been associated with attenuated EEG coherence in delta and beta bands (Kikuchi, Wada, Koshino, Nanbu, & Hashimoto, 2000), the administration of acetylcholinesterase inhibitors has led to enhanced EEG coherence in the theta and gamma band (Ahnaou, Huysmans, Jacobs, & Drinkenburg, 2014). Notably, previous studies also indicated that ACh depletion and Aβ deposition interact with each other. Thus, their associations with coherence and cognition might be difficult to disentangle and should be regarded as a complex interplay between Aβ deposition, ACh function, spectral coherence, and cognition (for reviews, see, e.g., Contestabile, 2011; Craig, Hong, & McDonald, 2011; Schliebs & Arendt, 2011).

The additional analyses regarding coherence–cognition associations for separate frequency bands and separate cortical networks support our assumption that global coherence is a superior marker for cognition in comparison with coherence in region or frequency-specific cortical networks. In line with previous study results, we found a positive association between fronto-parietal coherence in the theta and beta band (cf., Babiloni et al., 2016 for a review), but both associations were no longer significant after correcting for multiple comparisons. No correction for multiple comparisons is needed for a global coherence score. In addition, effect sizes were lower for all region- and frequency-specific coherence markers (βs ≤ .27) than for the global coherence score (β = .31). It might be possible that there is a more precise coherence marker for cognition than the global coherence score, but it has not been found yet. Currently, a global coherence score seems to be a robust marker for cognition in healthy and pathological aging.

There were no significant associations between global EEG coherence at baseline and cognitive decline at the 5-year follow-up (see Table 3 and Figure 2). Studies investigating the prognostic value of EEG coherence on predicting cognition are very rare, and the results are mixed: While some authors report positive results (Rossini et al., 2006), others failed to find such associations (Jelic et al., 2000). Notably, the baseline and the follow-up assessment were carried out in different settings in this study (face-to-face, on telephone), which might be the reason for methodological inaccuracies regarding cognitive decline and missing associations with EEG coherence, especially within the small sample size. However, the high test–retest reliability of the cognitive outcomes supports the validity of the telephone-based assessment. Hence, we assume that the missing significance is due to the insufficient power for the follow-up analyses. For the sample size in the follow-up assessment (n = 22) and the observed effect size of β = .31 for the association between coherence and cognition at baseline, the power was low (42%). An intended power of 80% would require a sample size of n = 60. This knowledge might be used as a benchmark in future longitudinal studies.

We did not find a significant change in cognitive performance from baseline to the 5-year follow-up (see Table 2). However, during the 5-year period, five people showed very pronounced cognitive decline and were excluded from the 5-year follow-up since they were no longer able to operate a telephone. One of them also had very noisy EEG data and had to be excluded from baseline analyses. These participants might have been of special interest in evaluating the prognostic value of EEG coherence. Because the excluded participants did not differ in their baseline coherence from the non-excluded participants, there was no evidence that global coherence predicted cognitive decline, keeping the small sub-sample in mind. Refuting our expectation, no significant baseline associations were found between EEG slowing and cognition (see Table 1), which is contrary to the findings in the majority of studies indicating a slowing of EEG in individuals with AD and MCI (e.g., Baker, Akrofi, Schiffer, & Boyle, 2008; van der Hiele et al., 2007; Moretti et al., 2004; Riekkinen, Buzsaki, Riekkinen, Soininen, & Partanen, 1991; but see Onishi et al., 2005 for contrary results). The missing association is further contrary to the correlative association between power and cognitive performance reported by previous studies (Alexander et al., 2006; Claus et al., 2000; Garn et al., 2015; van der Hiele et al., 2007). Our results are in line with the findings reported by Moretti et al. (2004): The authors failed to find a correlative link between total power and cognitive performance, although they reported a significantly increased delta and significantly decreased alpha power in participants with AD in comparison with healthy controls.

The following limitations need to be considered when interpreting the results of this study: The sample size in the

5-year follow-up was rather small and could be a reason for the missing association between baseline EEG coherence and cognition 5 years later as well as cognitive decline over a period of 5 years. Thus, the follow-up data should be considered as pilot data and interpreted with caution. Longitudinal studies with larger sample sizes are needed to further evaluate the predictive value of global coherence for cognitive decline. This study investigated a sample at risk for developing dementia, and our results might not generalize to healthy adults without cognitive complaints.

5 | CONCLUSION

Our findings suggest that among older adults at risk for developing dementia, global EEG coherence might be a suitable marker for cognitive performance. Consequently, it might indirectly reflect disturbances in neuronal integrity accompanying cognitive deficits. We did not find evidence that global coherence predicts cognitive change. Subsequent studies with larger sample sizes are needed to determine the question, whether the association between global coherence and cognitive change indeed does not exist or the statistical power in the present study was insufficient. Global EEG markers would be of great benefit in clinical practice and in scientific research, because they seem to be more reliable as compared to region- and frequency-specific EEG coherence scores.

Global EEG coherence might be helpful to identify persons with pronounced deterioration in neuronal integrity who would benefit more from interventions focussing on neuronal integrity than persons with a cognitive syndrome but more intact functional connectivity.

CONFLICT OF INTEREST
The authors declare that they have no competing interests.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

Table S1 Correlative associations between global coherence and EEG slowing and cognition at baseline

Table S2 Correlative associations between localized coherence and EEG slowing and cognition at baseline

Table S3 Comparisons of global coherence and EEG slowing between subjects excluded from 5-year follow-up due to severe progression of cognitive and functional decline and non-excluded subjects

Table S4 Correlative associations between over-all coherence and EEG slowing with cognition at the 5-year follow-up ($n = 22$)

Table S5 Correlative associations between global coherence and EEG slowing and decline in cognition at the 5-year follow-up

Table S6 Correlative associations between localized coherence and EEG slowing and cognitive decline at the 5-year follow-up