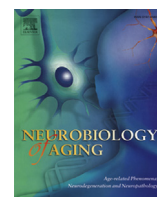


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## Quantitative EEG power and synchronization correlate with Alzheimer's disease CSF biomarkers



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### ABSTRACT

Synaptic dysfunction is the best anatomical correlate of early cognitive impairment in Alzheimer's disease (AD). Electroencephalography (EEG) directly reflects brain electrical activity at the level of synapses. The aim of the present study was to investigate correlations of quantitative EEG measures, global field power (GFP) and global field synchronization (GFS), with conventional cerebrospinal fluid (CSF) biomarkers of neurodegeneration in patients diagnosed with subjective cognitive decline ( $n = 210$ ), mild cognitive impairment ( $n = 230$ ), and AD ( $n = 197$ ). Decreased CSF amyloid  $\beta$ 42 significantly correlated with increased theta and delta GFP, whereas increased p- and t-tau with decreased alpha and beta GFP. Decreased CSF amyloid  $\beta$ 42 and increased p- and t-tau were significantly associated with decreased GFS alpha and beta. Subanalysis of the separate diagnostic groups demonstrated significant correlations between CSF biomarkers and generalized power and synchronization already in the subjective cognitive decline and MCI group. These results provide evidence that quantitative EEG measures are associated and possibly sensitive to distinct AD-like CSF biomarker profiles in cognitively impaired patients and are therefore promising early noninvasive markers of AD.

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### 1. Introduction

The identification and validation of reliable biomarkers of Alzheimer's disease (AD) that reflect both preclinical and early clinical stages of disease is a major research goal, considering it might provide a crucial opportunity for an intervention with disease-modifying drugs. Although AD diagnosis currently encompasses clinical stages only, the time between the initial brain changes and symptoms of clinically manifest disease is considered to represent the pathological-clinical continuum of AD (Sperling et al., 2011). According to Jessen et al., the prediction of dementia in AD supports

the model of AD continuum; that is, a transition from subjective cognitive decline through mild cognitive impairment (SCD and MCI, respectively) to dementia (Jessen et al., 2010, 2014). Indeed, a certain proportion of memory clinic referrals diagnosed with SCD and MCI at the baseline exhibit biomarker abnormalities such as decreased amyloid  $\beta$ 42 (A $\beta$ 42), increased total tau (t-tau) and phospho tau (p-tau) protein levels in cerebrospinal fluid (CSF) (Blennow, 2004), increased amyloid burden as assessed by positron emission tomography (PET) with Pittsburgh compound B (PiB-PET) (Amariglio et al., 2012; Forsberg et al., 2008), brain atrophy detected by magnetic resonance imaging (MRI), and decreased glucose metabolism by fluorodeoxyglucose PET (FDG-PET) (de Leon et al., 2007). These subjects are at high risk of developing further cognitive decline (Jessen et al., 2010, 2014).

Synaptic dysfunction in AD has recently gained increasing attention, especially since there has been evidence that synaptic

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loss is directly related to duration of dementia (Ingelsson et al., 2004) and is the best anatomical correlate of cognitive deficits in MCI and AD (Blennow et al., 1996; Goetzl et al., 2016; Scheff et al., 2011; Terry et al., 1991). Moreover, synaptic dysfunction is an early event in AD preceding cognitive decline and neuronal cell death (de Wilde et al., 2016; Selkoe, 2002), resulting in greater synapse loss compared with neuronal depletion in the same brain regions (Heinonen et al., 1995; Masliah et al., 1991). Consequently, given that biochemical and structural abnormalities appear later (Selkoe, 2002; Sperling et al., 2011) and are already characterized by reasonably valid and widespread CSF and imaging biomarkers in both research and clinical use, there is an urgent need for methods that mirror functional rather than just structural changes. Hypometabolism and/or hypoperfusion in the temporoparietal regions, assessed by functional imaging technologies, such as FDG-PET or single-photon emission computed tomography (SPECT), have been reported in patients with AD (Foster et al., 1984; Jagust et al., 1987). However, referred imaging modalities provide indirect evidence of synaptic dysfunction and neurodegeneration (Wicklund and Petersen, 2013) whose sensitivity and specificity remain unclear (Albert et al., 2017; Bhriaian and Lawlor, 2002).

One of the first measurements that directly reflects functioning of synapses in real time was the electroencephalography (EEG) consisting of scalp electric potential differences (Jelic, 2005; Michel, 2009). EEG offers several additional attractions: noninvasiveness, wide availability, low cost, high time resolution, and direct access to neuronal signaling in contrast to functional MRI or PET that detect indirect metabolic signals (Michel, 2009). In research settings, the most commonly used method is a computerized or quantitative EEG (qEEG) analysis that disentangles EEG signal in frequency, time, and space domain and gives information on connectivity and topography of neuronal networks (Jelic, 2005; Jelic and Kowalski, 2009). It has been postulated that both synapse and neuronal loss result in reduced brain functional connectivity and have an influence on EEG signals (Jelic, 2005). Slowing of fast-frequency bands (alpha and beta) and increase in slow-frequency bands (delta and theta) activity assessed by qEEG have been repeatedly reported in AD (Dierks et al., 1991; Jelic et al., 1996; Soininen et al., 1991). However, conventional fast Fourier transformation spectral analysis conducted in a vast number of qEEG analyses has a disadvantage of resulting in many parameters and reference-dependent topographical interpretation. Such properties represent shortcomings of conventional spectral power analysis when it comes to comprehensive correlative studies employing other biological measures. Global field power (GFP) is a reference-free method that reduces multichannel recordings to a single measure corresponding to the generalized EEG amplitude (Huang et al., 2000a; Jelic, 2005). Its computation takes into account all electrodes uniformly and therefore results in a global measure of scalp potential field strength (Michel, 2009). According to Huang et al., AD patients show an increase of delta and theta GFP as well as a reduction of alpha and beta GFP compared with the controls and MCI patients, respectively (Huang et al., 2000a). GFP and dipole source localization analysis in MCI, AD, and healthy controls showed a promising diagnostic and prognostic classification accuracy (Huang et al., 2000a). On the other hand, AD has been characterized as a “disconnection syndrome” as a result of neurodegeneration and neuronal loss, which affects coherent firing of corticocortical projections (Koenig et al., 2005; Morrison et al., 1996). In this context, global field synchronization (GFS) emerged as a novel qEEG measure of global functional connectivity of the brain. GFS as a single measure results from the multichannel analysis that does not

involve a priori selections and modeling of particular regions of interest, which is along with the postulated hypothesis of functional “disconnection syndrome” of broadly distributed neural networks. It resembles global amount of instantaneous phase-locked synchronization of oscillating neuronal networks across the scalp (Koenig et al., 2001, 2005). Decreased GFS in fast-frequency bands in a gradient-like pattern was indeed found in SCD, MCI, and AD compared to controls, supporting the hypothesis of early disruptions of brain functional connectivity in AD pathogenesis (Koenig et al., 2005).

Very few explorative clinical studies have tried to address the biological validity of qEEG measures and investigate their correlation with conventional markers of neurodegeneration in patients with different clinical stages of cognitive impairment. Only 1 study so far explored the relationship of qEEG parameters and conventional markers of neurodegeneration in patients with cognitive decline but involved only a modest number of subjects (Jelic et al., 1998).

The aim of the present study was to investigate the correlation of qEEG parameters GFP and GFS with conventional CSF biomarkers of core AD molecular pathology ( $A\beta$ , t-tau, and p-tau) in a large cohort of memory clinic patients with a wide range of cognitive impairment.

## 2. Subjects and methods

### 2.1. Study population

The study population consisted of 637 patients recruited at the memory clinic at the Karolinska University Hospital Huddinge, Stockholm, Sweden, (2007–2010 and 2013–2016) who underwent standard comprehensive assessment consisting of a clinical interview and examination, neuropsychological testing, screening blood tests, CSF biomarkers analyses, brain imaging with computed tomography (CT) or MRI, and digital resting-state EEG recording. The severity of cognitive deficits was assessed using Mini–Mental State Examination (MMSE) (Folstein et al., 1975). The patients were clinically diagnosed with AD ( $n = 197$ ) according to ICD-10 (World Health Organization, 1993), MCI ( $n = 230$ ) according to the criteria of Winblad et al. (2004), and SCD ( $n = 210$ ) in case they reported subjective complaints but had normal clinical investigation without any significant cognitive deficit (Jessen et al., 2010). Patients with other dementia diagnoses were excluded as well as those below 50 years of age, those with a time gap between baseline diagnosis and EEG recording longer than 6 months, major neurological comorbidity, epilepsy, psychiatric disorder, alcohol abuse, and chronic medication with any of the psychotropic drugs known to influence EEG activity.

### 2.2. Ethical approval

The study was approved by the local ethical committee of the Karolinska University Hospital Huddinge. The patients gave their written consent to register, store, and analyze clinical data and correlate these to biochemical, genetic, and clinical examination results for research purposes. The existing electronic database that includes patients investigated at the memory clinic has been reported to the Swedish Data Inspection Board and falls under the legislation on personal Data Act and Act on Ethical Review on research involving human subjects.

### 2.3. Lumbar puncture and CSF analysis

The CSF was obtained by lumbar puncture between the L3/L4 or L4/L5 intervertebral space while the patient was sitting in an upright position. All CSF withdrawals were performed in the morning using a 25-gauge needle and collected in 12 mL polypropylene tubes. CSF samples were centrifuged at 1000 rpm for 10 minutes, divided into polypropylene tubes of 1 mL, and frozen at  $-70^{\circ}\text{C}$  until further analysis. A $\beta$ 42, p-tau, and t-tau concentrations were simultaneously measured with the xMAP technology and the INNO-BIA AlzBio3 kit (Innogenetics), as previously described in detail (Olsson et al., 2005). Variables were transformed with zero-skewness logarithmic transformation (using the natural logarithm) to obtain nonskewed distributions.

### 2.4. EEG recordings

Resting-state EEGs were recorded on the Nervous System at the Department of Clinical Neurophysiology, Karolinska University Hospital-Huddinge. Electrodes were placed according to the standard 10/20 system with electrode impedances below 5 k $\Omega$  and a sampling rate of 256 Hz. The patients were seated in a sound-attenuated, normally lit room with their eyes closed. A technician monitored the entire EEG recordings to alert the patient (using acoustic stimulation) in case of drowsiness or sleep. Initial filter settings were a time constant of 1 second and low-pass filter frequency of 70 Hz. Digital EEG recordings were stored for further analysis offline.

### 2.5. Quantitative EEG analysis

A minimum of 20-second eyes-closed artifact-free epochs were selected after visual inspection and manual rejection of artifacts, episodes of drowsiness, and eyes-open periods. Any electroocular, electrocardiographic, and lateral eye-movement artifacts were eliminated by semiautomatic independent component analysis algorithm. Frequency analysis was performed using the fast Fourier transformation and Brain Vision Analyzer, version 2.0, software. Epochs of 2-second duration, which allowed a resolution of 0.5 Hz in the frequency spectrum, were averaged. GFP is a measure of global strength of scalp potential fields defined as the root mean of all squared potential differences between all electrode pairs. It therefore corresponds to the standard deviation of the potentials (Lehmann and

Skrandies, 1980; Michel, 2009). GFS was computed for each frequency bin using a principal component analysis of the 2-dimensional positions of the electrode entries in the sine-cosine diagram. The normalized difference between the resulting 2 Eigenvalues of the first and second principal components (per frequency) is a measure of cloud spread and corresponds to GFS. Its values range from 0 to 1 and represent the percentage of EEG activity that can be attributed to sources oscillating with a common phase at a given frequency; high GFS values assume predominance of single phase over all electrodes, whereas low GFS values indicate the absence of such a common phase (Koenig et al., 2001). GFP and GFS were averaged across epochs and within the conventional frequency bands: delta (1–3.5 Hz), theta (4–7.5 Hz), alpha (8–11.5 Hz), and beta (12–19.5 Hz). Obtained GFP values were transformed with zero-skewness logarithmic transformation to get nonskewed distributions for further statistical analysis.

### 2.6. Statistical analysis

Simple descriptive statistics in SPSS (IBM SPSS Statistics, version 23.0) software was used to present the distribution of the subjects in diagnostic groups, demographic characteristics (gender, age, and years of education), MMSE, and CSF biomarker values of the study population. The differences between GFS and logarithmically transformed GFP and CSF values across diagnostic groups were investigated by a 1-way analysis of variance (ANOVA). Games-Howell post hoc tests for unequal variance (Levene's test  $p < 0.05$ ) were performed, where significant group effects between CSF values were found. A multiple linear regression analysis of the whole study sample was performed in statistical software STATA, using GFP and GFS in conventional frequency bands as dependent and CSF values as independent continuous variables while controlling for age, gender, and MMSE. Subsequent statistical analysis of the 3 separate diagnostic groups was performed using linear regression model with the same independent and dependent variables, controlled for age and gender only. Beta coefficients indicate in which direction (positive or negative) and how much a dependent variable varies with an independent variable, when all other independent variables are held constant. The analysis was separately performed for each CSF (A $\beta$ 42, t-tau, and p-tau), GFP, and GFS frequency band measures. The level of significance was set at 5%.

**Table 1**  
Descriptive statistics and CSF biomarker values according to the diagnostic group

	SCD	MCI	AD
Number	210	230	197
Sex ratio (males/females)	79/131	109/121	72/125
Age, y	60.0 $\pm$ 6.1 (50–83)	65.9 $\pm$ 8.2 (50–87)	67.8 $\pm$ 9.2 (51–89)
Education, y	13.3 $\pm$ 3.6 (1–24.5)	12.1 $\pm$ 3.8 (3–22)	11.1 $\pm$ 3.6 (6–23)
MMSE <sup>a</sup>	28.7 $\pm$ 1.7 (23–30)	27.3 $\pm$ 2.1 (18–30)	23.0 $\pm$ 4.3 (7–30)
CSF biomarkers			
CSF A $\beta$ 42 (ng/L)	916.90 $\pm$ 248.85 (300–1650) <sup>b,c</sup>	713.63 $\pm$ 271.69 (229–1532) <sup>b,d</sup>	500.90 $\pm$ 123.55 (250–876) <sup>c,d</sup>
CSF p-tau (ng/L)	52.41 $\pm$ 21.52 (16–183) <sup>b,c</sup>	62.73 $\pm$ 28.60 (16–175) <sup>b,d</sup>	91.49 $\pm$ 37.57 (16–240) <sup>c,d</sup>
CSF t-tau (ng/L)	256.35 $\pm$ 121.37 (43–689) <sup>b,c</sup>	363.59 $\pm$ 210.32 (41–1140) <sup>b,d</sup>	628.70 $\pm$ 309.54 (103–1500) <sup>c,d</sup>

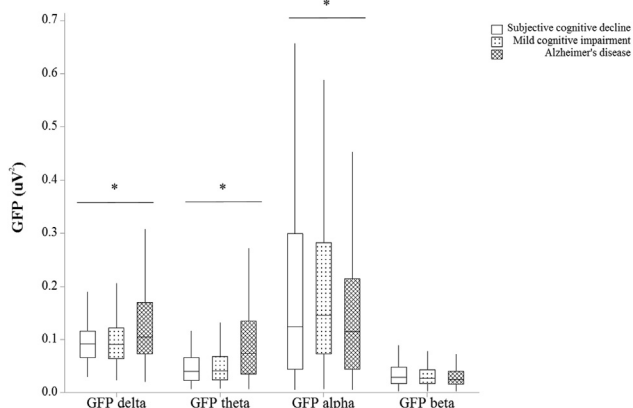
ANOVA over the diagnostic groups;  $p < 0.001$  for all CSF biomarkers. Games-Howell test for post hoc comparisons. Results are presented as means  $\pm$  standard deviation. Key: AD, Alzheimer's disease; ANOVA, analysis of variance; CSF, cerebrospinal fluid; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; SCD, subjective cognitive decline.

<sup>a</sup>  $n = 627$  (SCD = 206, MCI = 228, and AD = 193).

<sup>b</sup>  $p < 0.01$ , SCD versus MCI.

<sup>c</sup>  $p < 0.01$ , SCD versus AD.

<sup>d</sup>  $p < 0.01$ , MCI versus AD.



**Fig. 1.** Box plot of GFP (y-axis) in different frequency bands (x-axis). The box represents the interquartile range; the solid line within the box marks the median; and the upper and lower whiskers represent the upper and lower 25% of the distribution, respectively. Diagnostic groups are represented by different bar patterns. ANOVA over the diagnostic groups; \**p* < 0.05. Abbreviations: ANOVA, analysis of variance; GFP, global field power.

### 3. Results

#### 3.1. Demographics

Demographic data, MMSE scores, and CSF biomarker values of the study cohort are presented in Table 1. There is a shift toward younger patient population because the memory clinic at the Karolinska Hospital Huddinge is a referral center for subjects under 65 years of age in the Stockholm municipality. The mean age was higher in the AD group followed by the MCI group; the ratio of female compared with male patients was similar in all diagnostic groups. The mean MMSE score was 1.4 points and 5.7 points lower in MCI and AD, respectively, compared with the SCD group. There was a significant difference between all CSF biomarker levels across diagnostic groups (ANOVA/Games-Howell *p* < 0.01). The cutoff values for the conventional CSF markers were Aβ42 > 550 ng/L, p-tau < 80 ng/L, and t-tau < 400 ng/L.

#### 3.2. Association between GFP and CSF biomarkers

The GFP means and 95% confidence intervals (CIs) in conventional frequency bands across diagnostic groups are shown in Fig. 1. There were statistically significant differences in GFP between diagnostic groups as determined by 1-way ANOVA in delta (*p* = 0.003), theta (*p* < 0.001), and alpha (*p* = 0.026) frequency band.

**Table 2**  
Relationship between CSF biomarkers and GFP in 4 frequency bands

CSF biomarker	GFP delta	GFP theta	GFP alpha	GFP beta
Aβ42	−0.304 <sup>a</sup>	−0.514 <sup>b</sup>	0.170	0.002
p-tau	−0.107	−0.076	−0.409 <sup>b</sup>	−0.278 <sup>b</sup>
t-tau	−0.048	0.011	−0.222 <sup>a</sup>	−0.175 <sup>b</sup>

Multiple linear regression analysis controlled for age, gender, and MMSE. Data presented as β coefficients. The dependent variables are zero-skewness logarithmically transformed GFP in different frequency bands, whereas independent variables are zero-skewness logarithmically transformed CSF biomarker values. This means that the β coefficients just indicate in which direction (positive or negative) and how strong the associations are.

Key: CSF, cerebrospinal fluid; GFP, global field power; MMSE, Mini-Mental State Examination.

<sup>a</sup> *p* < 0.01.  
<sup>b</sup> *p* < 0.001.

**Table 3**  
Relationship between CSF biomarkers and GFP across the diagnostic groups

CSF biomarker	Frequency band	SCD	MCI	AD
Aβ42	GFP delta	0.010	−0.351 <sup>a</sup>	−0.329
	GFP theta	0.095	−0.449 <sup>a</sup>	−0.465
	GFP alpha	0.329	0.176	0.136
	GFP beta	−0.149	0.002	−0.226
p-tau	GFP delta	0.026	−0.143	−0.438 <sup>b</sup>
	GFP theta	−0.006	−0.311	−0.404
	GFP alpha	−0.364	−0.626 <sup>c</sup>	−0.311
	GFP beta	−0.150	−0.320 <sup>b</sup>	−0.305 <sup>a</sup>
t-tau	GFP delta	−0.046	−0.060	−0.239 <sup>a</sup>
	GFP theta	−0.104	−0.151	−0.147
	GFP alpha	−0.317	−0.337 <sup>b</sup>	−0.130
	GFP beta	−0.161	−0.162 <sup>a</sup>	−0.198 <sup>a</sup>

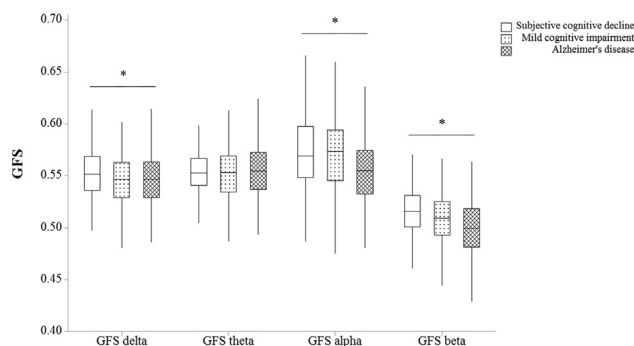
Multiple linear regression analysis controlled for age and gender. Data presented as β coefficients. The dependent variables are zero-skewness logarithmically transformed GFP in different frequency bands, whereas independent variables are zero-skewness logarithmically transformed CSF biomarker values. This means that the β coefficients just indicate in which direction (positive or negative) and how strong the associations are.

Key: AD, Alzheimer's disease; CSF, cerebrospinal fluid; GFP, global field power; MCI, mild cognitive impairment; SCD, subjective cognitive decline.

<sup>a</sup> *p* < 0.05.  
<sup>b</sup> *p* < 0.01.  
<sup>c</sup> *p* < 0.001.

A multiple linear regression model, controlling for age, gender, and MMSE, showed a significant negative association of CSF Aβ42 and GFP in the delta (*p* = 0.001) and theta (*p* < 0.001) frequency band, that is, lower Aβ levels were associated with higher delta and theta power (Table 2.). Separate linear regression analyses for the 3 diagnostic groups showed significant negative correlations between CSF Aβ42 and GFP delta and theta in the MCI group (*p* = 0.016 and *p* = 0.025, respectively) (Table 3).

Multiple regression analysis revealed a similar association of CSF p- and t-tau levels with power in fast-frequency bands; higher p-tau and t-tau significantly correlated with decrease of GFP in alpha (p-tau: *p* < 0.001; t-tau: *p* = 0.003) and beta frequency bands (p-tau: *p* < 0.001; t-tau: *p* < 0.001) (Table 2.). Statistical analysis for the 3 groups separately showed a significant inverse association between p- and t-tau and GFP alpha (p-tau: *p* < 0.001; t-tau: *p* = 0.005) and beta (p-tau: *p* = 0.005; t-tau: *p* = 0.04) in the MCI group and GFP delta (p-tau: *p* = 0.008; t-tau: *p* = 0.04) and beta (p-tau: *p* = 0.013; t-tau: *p* = 0.022) in the AD group (Table 3).



**Fig. 2.** Box plot of GFS (y-axis) in different frequency bands (x-axis). The box represents the interquartile range; the solid line within the box marks the median; and the upper and lower whiskers represent the upper and lower 25% of the distribution, respectively. Diagnostic groups are represented by different bar patterns. ANOVA over the diagnostic groups; \**p* < 0.05. Abbreviations: ANOVA, analysis of variance; GFS, global field synchronization.



**Table 4**  
Relationship between CSF biomarkers and GFS in 4 frequency bands

CSF biomarker	GFS delta	GFS theta	GFS alpha	GFS beta
A $\beta$ 42	0.002	0.001	0.024 <sup>b</sup>	0.013 <sup>b</sup>
p-tau	0.002	−0.001	−0.015 <sup>b</sup>	−0.005
t-tau	0.001	−0.001	−0.010 <sup>b</sup>	−0.004 <sup>a</sup>

Multiple linear regression analysis controlled for age, gender, and MMSE. Data presented as  $\beta$  coefficients. The dependent variables are GFS in different frequency bands, whereas independent variables are zero-skewness logarithmically transformed CSF biomarker values. The  $\beta$  coefficients indicate in which direction (positive or negative) and how strong the associations are.

Key: CSF, cerebrospinal fluid; GFS, global field synchronization; MMSE, Mini-Mental State Examination.

<sup>a</sup>  $p < 0.05$ .

<sup>b</sup>  $p < 0.001$ .

### 3.3. Association between GFS and CSF biomarkers

The GFS means and 95% CI in conventional frequency bands across diagnostic groups are shown in Fig. 2. There were statistically significant differences in GFS between group means as determined by 1-way ANOVA in the delta ( $p = 0.012$ ), alpha ( $p < 0.001$ ), and beta ( $p < 0.001$ ) frequency bands.

Multiple linear regression, controlling for age, gender, and MMSE, showed a significant positive correlation between CSF A $\beta$ 42 and GFS alpha ( $p < 0.001$ ) and beta ( $p < 0.001$ ), that is, lower CSF A $\beta$  values were associated with lower fast-frequency GFS (Table 4). The following separate analyses of the diagnostic groups revealed a significant direct correlation between CSF A $\beta$ 42 and GFS alpha ( $p = 0.002$ ) and beta ( $p = 0.034$ ) in the MCI group and GFS alpha ( $p < 0.001$ ) in the AD group (Table 5).

CSF p-tau and t-tau exhibited significant negative correlation with GFS alpha (p-tau:  $p < 0.001$ ; t-tau:  $p < 0.001$ ) and beta (t-tau only;  $p = 0.017$ ), that is, increase in p- and t-tau levels was associated with decreased GFS in fast-frequency bands (Table 4). The multiple regression analysis for the groups revealed a negative association between CSF p- and t-tau and GFS alpha in the MCI (p-tau:  $p < 0.001$ ; t-tau:  $p < 0.001$ ) and GFS beta in the SCD group (p-tau only;  $p = 0.012$ ) (Table 5).

**Table 5**  
Relationship between CSF biomarkers and global field synchronization between diagnostic groups

CSF biomarker	Frequency band	SCD	MCI	AD
A $\beta$ 42	GFS delta	0.002	0.002	0.000
	GFS theta	0.009	−0.003	0.012
	GFS alpha	0.016	0.022 <sup>b</sup>	0.045 <sup>c</sup>
	GFS beta	0.009	0.010 <sup>a</sup>	0.009
p-tau	GFS delta	−0.001	0.002	0.006
	GFS theta	−0.002	−0.003	−0.002
	GFS alpha	−0.014	−0.023 <sup>c</sup>	0.000
	GFS beta	−0.013 <sup>a</sup>	−0.002	0.001
t-tau	GFS delta	0.002	0.000	0.003
	GFS theta	0.000	−0.004	−0.001
	GFS alpha	−0.008	−0.015 <sup>c</sup>	−0.002
	GFS beta	−0.006	−0.003	−0.001

Multiple linear regression analysis controlled for age and gender. Data presented as  $\beta$  coefficients. The dependent variables are GFS in different frequency bands, whereas independent variables are zero-skewness logarithmically transformed CSF biomarker values. The  $\beta$  coefficients indicate in which direction (positive or negative) and how strong the associations are.

Key: AD, Alzheimer's disease; CSF, cerebrospinal fluid; GFS, global field synchronization; MCI, mild cognitive impairment; SCD, subjective cognitive decline.

<sup>a</sup>  $p < 0.05$ .

<sup>b</sup>  $p < 0.01$ .

<sup>c</sup>  $p < 0.001$ .

## 4. Discussion

This study is unique with respect to the large population of memory clinic patients being investigated with a comprehensive assessment battery including EEG and spinal taps, which are rarely performed routinely in patients without clinical evidence of dementia or objective cognitive impairment. The most important finding is the correlation of general EEG slowing and reduced synchronization with lower CSF A $\beta$ 42 and higher p- and t-tau levels. To our knowledge, no studies so far have reported the association between different, yet complementary, qEEG measures of generalized power and global functional connectivity and AD-associated CSF markers of neurodegeneration in a large patient cohort with wide spectra of cognitive impairment.

Similar changes in the pattern of EEG power spectra have been repeatedly reported in AD; namely an early increase in theta and decrease in beta, a subsequent decrease in alpha and a late increase in delta band power, resulting in general EEG slowing (Coben et al., 1985; Dierks et al., 1991). A previous study conducted in the same memory clinic cohort presented a correlation of lower CSF A $\beta$ 42/p-tau ratio and higher t-tau with slower background activity and a higher degree of episodic EEG abnormalities (Kramberger et al., 2013), based on visual analysis only. Although these results are consistent with our findings in the context of general slowing of EEG activity, visual assessment includes interobserver variations that should be taken into consideration. Stomrud et al. investigated the relationship between qEEG frequency analysis and conventional CSF biomarkers obtained in 33 subjects over 4 years. They reported a strong association of p-tau/A $\beta$ 42 and t-tau/A $\beta$ 42 with an increase of relative theta power and slowing of cognitive speed but included healthy elderly individuals only (Stomrud et al., 2010). Our findings provide evidence that lower CSF A $\beta$ 42 and higher p- and t-tau values correlated with increased EEG slowing in the entire memory clinic cohort. We have excluded the effect of significant group differences in qEEG measures by controlling for MMSE values in the correlative analyses of the whole study population. Therefore, our results support referred findings irrespective of the severity of cognitive deficit such as group diagnosis.

Moreover, relationships among CSF markers of AD neuropathology and EEG frequencies displayed distinct patterns, with A $\beta$ 42 exhibiting significant association with global power in slow (delta and theta) while p- and t-tau in fast (alpha and beta) frequencies only. These discrepancies may be explained by sensitivity of spectral EEG activity toward different neuropathological changes.

The widely accepted explanation for the reduction in CSF A $\beta$ 42 found in AD patients is that aggregation and retention of A $\beta$  into plaques lead to reduced diffusion of A $\beta$  into the CSF (Mottet et al., 1995). One of the studies aiming to investigate the role of amyloid accumulation in aging and dementia included subjects with Down's syndrome (DS) who overexpress amyloid precursor proteins due to 21-trisomy (Tanzi et al., 1987). According to their results, both DS and AD patients had increased delta and theta power compared with controls, but DS had preserved alpha and beta power as opposed to AD (Soininen et al., 1993).

One of the possible mechanisms underlying the observed relationship between A $\beta$ 42 and increased slow EEG activity might be the relation of A $\beta$  and cholinergic deficits in the AD brain. Previous studies have demonstrated that A $\beta$  disrupts muscarinic signaling (Huang et al., 2000b; Kelly et al., 1996) and negatively affects acetylcholine synthesis and release (Hoshi et al., 1997; Kar et al., 1998; Vaucher et al., 2001). Concurrently, decrease in cortical cholinergic activity is associated with increase of slow EEG activity (Riekkinen et al., 1990; Spehlmann and Norcross, 1982). Thus, the negative effect of A $\beta$  on cholinergic transmission in the brain could indirectly cause increase in slow-frequency activity.

On the contrary, our results indicate that CSF p- and t-tau protein levels were selectively associated with EEG fast frequencies. Previous studies have demonstrated that both CSF p- and t-tau presumably indicate the extent of neuronal damage and degeneration since they inversely correlate with gray matter density in temporal, parietal, and frontal lobes (Thomann et al., 2009) and hippocampal volume (Herukka et al., 2008) and predict whole-brain and regional atrophy in cognitively impaired and AD patients (Tarawneh et al., 2015). Meanwhile, qEEG studies have shown that alpha amplitude negatively correlated with the hippocampal atrophy and cortical gray matter in the MCI and AD subjects (Babiloni et al., 2009, 2013, 2015). Although thalamic neuronal networks possibly contribute to the production of fast rhythms, it has been postulated that alpha and beta are predominantly generated in the cortex itself and propagated through intracortical connections (da Silva, 2009). We suggest that EEG activity, specifically fast rhythms, are somewhat associated with neuronal loss evidenced by brain atrophy and increased CSF tau protein levels. Overall, qEEG parameters that have plausible sensitivity toward different neuropathological changes in the AD brain could serve as a noninvasive method for distinguishing patients with isolated amyloid pathology from amyloid-negative primary age-related tauopathies (Crary et al., 2014).

On the other hand, hypothesis of early disruption in brain functional connectivity in AD patients suggests that a measure of global brain functional connectivity could be used as a supportive marker of early AD: A previous study based on computerized qEEG analysis demonstrated that global synchronization correlated with MMSE and Clinical Dementia Rating scales of cognitive impairment in AD patients (Park et al., 2008). Our results show that lower CSF A $\beta$ 42 and higher t-tau levels correlated with decreased global synchronization in alpha and beta, whereas higher p-tau with decreased synchronization in alpha band only. This is in line with previous reports that decrease of alpha and beta synchronization mirrors particular neuropathological changes, such as neuronal loss, synaptic dysfunction, degeneration of associative fibers, and possibly cholinergic dysfunction, and has a specific significance in AD (Koenig et al., 2005; Stam et al., 2003). In addition, the importance of high-frequency synchronization for cognition has recently been emphasized because different studies reported most pronounced correlations between global synchronization and degree of cognitive decline in alpha and beta bands (Koenig et al., 2005; Ma et al., 2014; Park et al., 2008; Stam et al., 2003).

The following subanalyses of separate diagnostic groups demonstrated correlations of qEEG global power with AD-like CSF biomarker changes in MCI and AD patients, whereas with global EEG synchronization such correlation was present already in the SCD group. These significant associations across different frequencies were particularly abundant in the MCI group. It has been proposed that AD biomarker abnormalities obtain sigmoid-shaped courses over time and reach a “plateau” by the time of the clinically developed dementia (Sperling et al., 2011). The steep part of the referred dynamic curve, associated with MCI, represents the highest rate of the biomarker changes, which might explain the robust relationship between CSF and qEEG markers in this prodementia stage of the disease. Both analyses seem to yield less prominent relationships in the AD group, possibly due to the referred “plateau effect”, that is, rather constant CSFA $\beta$ 42, p-tau, and t-tau levels over time in patients with dementia (Le Bastard et al., 2013). Interestingly, CSF p- and t-tau levels inversely correlated with GFP delta in the AD group only, implying less pronounced EEG slowing once the critical level of neurodegeneration and neuronal loss has been reached.

Our findings support the hypothesis that qEEG measures of global power and synchronization are potential surrogate markers

of early AD because they significantly correlate with AD-like CSF biomarker abnormalities already in the SCD and MCI group of patients. It has been postulated that combinations of conventional CSF biomarker abnormalities characteristic of AD are predictive of future dementia development in MCI patients (Hansson et al., 2006; Visser et al., 2009). In addition, global power and dipole source localization analysis in MCI, AD, and healthy controls showed a promising diagnostic and prognostic classification accuracy (Huang et al., 2000a). Thus, the observed correlations restricted to our cross-sectional study indicate that qEEG parameters have a prognostic potential that should be further explored through longitudinal studies including both healthy and cognitively impaired individuals. Another limitation of this study was lack of a healthy control group because of the constraint in obtaining CSF from healthy individuals and use of global, nonlocal qEEG measures only. It would be of great relevance to extend this study and include alternative neuroimaging modalities of synaptic dysfunction and other neuropathological hallmarks of AD. MRI and PET topographical markers have been shown consistently to predict the development of AD dementia in MCI cohorts (Aguilar et al., 2014; Morris et al., 2009) and to correlate with disease severity (Jack et al., 2002; Nordberg et al., 2010). In this context, interpretation of EEG scalp field and source topographies and employment of novel measures of brain functional connectivity would yield valuable add-on to such correlative studies.

In conclusion, our study demonstrates plausible correlation of qEEG power and synchronization with AD profiles of CSF abnormalities in a large memory clinic cohort along different stages of cognitive impairment, making them promising noninvasive markers of synaptic dysfunction due to neurodegeneration.

#### Disclosure statement

The authors have no actual or potential conflicts of interest.

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