Slowing of EEG correlates with CSF biomarkers and reduced cognitive speed in elderly with normal cognition over 4 years

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Abstract

Background: Cerebrospinal fluid (CSF) biomarkers and quantitative EEG show particular patterns of change in Alzheimer's disease (AD) and reflect neuropathologic processes and cerebral function, respectively. The changes precede cognitive decline and should be visible already in preclinical stages. We therefore aimed to investigate their relationship in cognitively healthy individuals. **Method:** Thirty-three (33) elderly individuals with repeated normal scores on cognitive tests over 4.5 years underwent EEG recording with quantitative frequency analysis and analysis of CSF total tau (T-tau), phosphorylated tau (P-tau) and β-amyloid$_{1-42}$ (Aβ42). **Results:** CSF T-tau and P-tau correlated with relative EEG theta power ($r_s > 0.545$; $p < 0.01$), but not with relative alpha, beta or delta power. The combined P-tau/Aβ42 ratio exhibited an even stronger correlation with relative theta power ($r_s = 0.622$; $p < 0.001$), especially in the right posterior quadrant of the head ($r_s = 0.643$; $p < 10^{-4}$). Slowing of cognitive speed correlated with increased relative theta power, foremost in the posterior quadrants ($r_s > 0.503$; $p < 0.01$), and high P-tau/Aβ42 ratio ($r_s > 0.462$; $p < 0.01$). **Conclusions:** Our results suggest that already in cognitively healthy elderly subjects, biochemical changes in CSF, and the possible underlying neuropathologic processes it reflects, have an effect on cerebral function as visualized by the EEG rhythm and cognitive speed. It hereby suggests that CSF biomarkers and EEG theta activity might indicate early abnormal degenerative changes in the brain.

Keywords: Alzheimer disease; Dementia; Mild cognitive impairment; Early diagnosis; Cerebrospinal fluid; Biological markers; Tau protein; Amyloid beta-protein; Electroencephalography; Theta rhythm; Control group; Cognition; AQT

1. Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder where post-mortem studies have suggested disease-onset up to 20-30 years prior to diagnosis [42]. AD is believed to evolve in specific patterns [15] and in the last decade mild cognitive impairment (MCI) has gained acceptance as a prodromal state with cognitive impairment and pronounced increased risk of developing AD [4,19]. Diagnostic markers including cerebrospinal fluid (CSF) biomarkers, hippocampal atrophy on MRI, and temporo-parietal abnormalities on functional imaging with PET or SPECT have repeatedly been deviant already in the MCI stage [19]. Therefore, these biological markers have been given the status of supportive features in the newly proposed version of the NINCDS-ADRDA criteria for AD diagnosis [15]. It has furthermore been suggested that the biomarkers are affected already in the preMCI state, thus before measurable cognitive deterioration [17,55]. Increased knowledge of potential preclinical biomarkers is important since new disease-modifying treatments have already entered into clinical trials and are probably most effective early in disease progression, before irreversible changes are too widespread.

In CSF, the tau protein (T-tau), the phosphorylated tau protein (P-tau) and the β-amyloid$_{(1-42)}$ (Aβ42) are the most validated biomarkers for AD [3].The tau protein is responsible for axonal stability and transportation and elevated levels in CSF follows neuronal degeneration in AD but also in Creutzfeldt-Jacob's Disease (CJD) and transiently in acute stroke [3,24]. Abnormal hyperphosphorylation of tau protein constitutes a major component of the neurofibrillary tangles observed in AD [9]. Hence, elevated P-tau reflects the loss of neurons with a pathologic phosphorylation state seen in AD [26]. In contrast to T-tau, normal P-tau

levels are seen in CJD and acute stroke [24]. Aβ42 is a result of an alternative cleavage of amyloid precursor protein (APP) and it has a high tendency to aggregate and form plaques. Decreased levels are seen in CSF of subjects with AD but also in some other dementias and neurologic diseases [3]. The combination of both elevated T-tau and P-tau together with decreased Aβ42 differentiate and predict AD with good accuracy [23].

Diffuse low frequent activity on quantitative EEG is seen in AD and correlates with disease stage [1,11,44]. Increase of relative theta power by itself or in combination with changes in other frequencies has in several studies differentiated early forms of AD from controls, and has showed intermediate characteristics in MCI [11,29,30,33,44,48]. A suggested sequence of changes in EEG frequencies during AD development could be extrapolated from current published data on MCI samples. First an increase of theta power is seen, followed by a decrease of beta power, decrease of alpha power and at last increase of delta power [30,44]. Furthermore administration of anti-cholinergic substances [40] or acetylcholinesterase inhibitors [7,31] leads to enhancement and reduction, respectively, of the AD-related changes in EEG frequencies as described above. Moreover, the changes have in some studies been restricted to theta power alone [7,31].

Several biomarkers and diagnostic tools correlate with changes in EEG frequencies predominantly in AD cohorts. Hippocampal atrophy on MRI [21], abnormal cerebral blood flow [36,46], autopsy-confirmed neuron loss [45], activity of daily living functions [39] and memory function [44,57] have all correlated with slowing of EEG rhythm. Furthermore, a previous study reported a correlation between tau protein and slowing of EEG global field

power in a healthy control group [28]. The authors requested further studies investigating the relationship between CSF biomarkers and EEG rhythm, however no other study has to our knowledge been published. We therefore aim to investigate whether the levels of cerebrospinal fluid biomarkers are associated with EEG frequency in cognitively healthy elderly.

2. Methods and material

2.1. Subjects

The included subjects are cognitively normal, elderly subjects recruited by the memory clinic at Malmö University Hospital, Sweden to constitute a normal control group in dementia studies and they have been followed over a period of 4.5 years. They were recruited in 2002 through advertisements 3.5 years prior to baseline of this study and they were examined thoroughly, including medical history, somatic and psychiatric examination, and cognitive testing. Inclusion criteria for this control group in 2002 were intact ADL functions, no memory complaints and cognitive tests results within expected normal range. Exclusion criteria were active physical or mental disease, which could affect the cognitive status, including pathology on CT, fulfilment of criteria for AD [37] or other dementia types and fulfilment of criteria for MCI [41]. Remaining individuals at baseline of this study in 2005 underwent an EEG followed by CSF collection, which was performed within a year after the EEG. Cognitive testing was made at baseline prior to the EEG investigation and at the time of the CSF collection. The same cognitive test battery and assessments have been used throughout the 4.5 years and include mini-mental state examination (MMSE) [18], Alzheimer's disease assessment scale (ADAS-cog) [47], clock-drawing, cube-drawing and a

quick test for cognitive speed (AQT) [27]. Individuals were excluded if they performed subnormal results on MMSE (score of 26 or lower) at any of the cognitive test occasions, since the cognitive status of these could be questioned. Fulfilment of criteria for dementia disorder or MCI during the study period also led to exclusion. The study was approved by the regional ethics committee at Lund University, Lund, Sweden. The subjects gave their written consent to participate.

2.2 EEG procedure

EEG was recorded for 20 minutes with a Nervus (Viasys Healthcare Inc, Madison WI) equipment from 19 electrodes, according to the 10-20 system and a sampling frequency of 256 Hz, high pass filter 0.16 Hz and low pass filter at 500 Hz. In order to certify that the analysis was performed on EEG recorded with the patient fully awake, 10 sec epochs of artefact free EEG were selected in the eyes-closed situation within 5-20 sec after interaction with the patient either by verbal communication, or following eye closure on command. Post-interaction epochs were used in order to optimize and standardize the influence of fluctuation in arousal, which predominantly causes variability in the theta activity. Furthermore, several 10 s epochs were analysed and then based on alpha stability one epoch was selected for further calculations. Quantification of the EEG data reconstructed in CA mode, 2 sec epochs (Hamming filter), was performed by using commercially available software (Nervus Reader 3.4, Viasys Healthcare Inc Madison, WI). By FFT analysis, peak frequency of posterior dominant activity, log absolute power and relative power of delta (0.5-4 Hz), theta (4-8 Hz), alpha (8-13 Hz), beta (13-32 Hz) were calculated for each quadrant of the skull: left anterior (F3,F7,T3, C3), right anterior (F4, F8, T4,C4), left posterior (P3,T5,O1), right posterior

(P4,T6,02). In this study average values for all four quadrants are presented as well as values for each quadrant.

2.3. Baseline lumbar puncture and cerebrospinal fluid assays

Lumbar puncture was performed in the sitting position. The CSF samples were obtained in the L3/L4 or L4/L5 interspaces. After disposal of the first 1 ml of CSF, the consecutive 10 ml were collected in plastic (polypropylene) tubes to avoid absorbance of β-amyloid by the tube wall. All CSF samples were mixed gently to avoid possible gradient effects. No CSF sample contained more than 500 erythrocytes/µl. The CSF samples were centrifuged at 2,000 *g* at 4˚ C for 10 min to eliminate cells and other insoluble material, and were then immediately frozen and stored at -80˚ C pending biochemical analyses, without being thawed or refrozen. At the same time serum samples were collected. The CSF samples were analysed for total tau (T-tau), tau phosphorylated at threonine 181 (P-tau) and Aβ42 with xMAP technology using the INNO-BIA AlzBio3 kit (Innogenetics, Ghent, Belgium) using the same batch of reagents [38]. The results are presented in ng/l. The CSF/serum albumin ratio was calculated for evaluation of the blood-brain barrier function.

2.4. Statistical analysis

Statistical analysis was performed using the SPSS software (version 14.0.1 for Windows, SPSS Inc., Chicago, I11, USA). Non-parametric tests were used when the variable was not normally distributed. Spearman rank correlation coefficient was used to test the degree of correlation between EEG rhythms and CSF biomarkers, as well as the influence by cognition and age. Mann-Whitney Test was used to evaluate influence of gender and Kruskal-Wallis

Test the influence of ApoE-ε4 allele. Longitudinal change in cognition between baseline and follow-up on a group level was analysed with paired-samples T test. Outliers versus non-outliers were compared with Mann-Whitney U test. The level of significance was set to $p < 0.05$.

3. Results

3.1. Demographics

From the initial 35 individuals at baseline of this study, two individuals were excluded after performing a score of 26 or lower on MMSE. No individual developed a dementia disorder or MCI during the study period. Demographic and cognitive data for the 33 individuals participating in this study are presented in table 1. At follow-up the mean MMSE score was 0.7 points lower on a group level ($p < 0.001$) whereas other cognitive test results did not change significantly.

3.2. EEG and CSF results

EEG mean peak frequency and relative power for each frequency band on a group level are shown in table 2. Noticeable are one outlier and three extreme outliers seen in the theta frequency band (figure 1), considering all individuals being cognitively normal. In a clinical setting these individuals would be regarded as having pathologic EEG recordings. However, no significant differences in cognitive results were detected when comparing the outliers with the rest of the study sample ($p > 0.05$; Mann-Whitney U). Within the EEG variables two correlation patterns were outlined. Firstly, there were significant correlations between low mean peak frequency, high relative theta power and low relative beta power ($r_s > \pm 0.576$;

p <0.001). Secondly, there were significant correlations between low relative alpha power and high relative delta power (r_s = -0.726; p <10^{-5}).

The CSF biomarker levels are presented in table 2. Aβ42 had a normal distribution in contrast to T-tau and P-tau and did not correlate to them. However, a very significant correlation between the P-tau and T-tau (r_s = 0.938; p = 10^{-6}) was observed.

Increase of relative theta power correlated with higher age (r_s = 0.435; p <0.05) and male sex (p <0.01; Mann-Whitney U), which also correlated to relative beta power (p <0.05; Mann-Whitney U). The other EEG frequencies and CSF biomarkers were not significantly associated with sex, age or prevalence of the APOE-ε4 allele (p >0.05; Spearman's rho, Mann-Whitney U, Kruskal-Wallis Test).

3.3 EEG and CSF correlations

Relative theta power was the only EEG variable correlating with any of the CSF biomarkers as shown in table 3. The correlation was somewhat stronger with P-tau (r_s = 0.556; p <0.001) than T-tau (r_s = 0.545; p <0.01). However no significant correlation was seen between Aβ42 and relative theta power. The combination of tau protein and Aβ42 has earlier been proposed to predict AD [3,23]. We therefore calculated a ratio value of P-tau/Aβ42 and T-tau/Aβ42, respectively. These combinations correlated stronger with relative theta power than the biomarkers alone as seen in table 3. The combination including P-tau (r_s = 0.622; p <0.001) correlated more strongly with relative theta power than the one including T-tau (r_s = 0.575; p <0.001). The distribution of the individuals is seen in figure 2.

When sub-analysis for relative theta power of each quadrant of the head was performed, there was a correlation with P-tau/Aβ42 and T-tau/Aβ42 in all quadrants (r_s > 0.492; p

<0.01). However, this correlation was more pronounced in the right posterior quadrant and for P-tau/Aβ42 (r_s =0.643; p <10^{-4}). Thereafter, the strengths of the correlations between P-tau/Aβ42 and relative theta power were in the following order; the left posterior (r_s = 0.591; p <0.001), the right anterior (r_s = 0.575; p <0.001), and the left anterior quadrant (r_s = 0.510; p <0.01) (figure 3).

All correlations reported in the results above remained significant even if calculated without relative theta power outliers (data not shown).

3.4 EEG and CSF correlations in relation to cognition

Increase of relative theta power correlated significantly with slower results on colour-naming in baseline AQT, the test of cognitive speed, (r_s = 0.443; p < 0.01). Increase in the right posterior and the left posterior quadrants correlated stronger than the global value with colour-naming (r_s > 0.503; p <0.01) in baseline AQT, but also with the more complex task of colour-form-naming (r_s >0.372; p <0.05). Higher P-tau/Aβ42 and T-tau/Aβ42 ratio further correlated with slower results on colour-naming in baseline AQT (r_s > 0.462; p <0.01). The correlations remained with colour-naming in follow-up AQT one year later for relative theta power in the right and left posterior quadrants (r_s > 0.390; p <0.05) as well as for P-tau/Aβ42 and T-tau/Aβ42 ratio (r_s > 0.369; p <0.05).

4. Discussion

This cross-sectional study of healthy and cognitively normal elderly provides evidence that high tau protein and low Aβ42 in combination directly correlate with an increase in relative theta power on EEG. The AD-associated combination of CSF biomarkers correlates stronger with slowing of the EEG than the biomarkers do separately. Moreover, the connection

between CSF biomarkers and theta frequency are seen over all four scalp quadrants, but predominantly in the posterior quadrants and on the right side. The AD-associated combinations of CSF biomarkers and increase in relative theta power, foremost in the posterior quadrants, also correlates with slowing of cognitive speed.

In this study, CSF collection was done in healthy individuals outside a clinical setting, which is uncommon due to reluctance of performing lumbar puncture without medical indication. In addition, we required repeated normal range scores on general cognitive screening tests of those participating to assure stable cognition. The one-year time period between EEG testing and CSF analysis allows cross-sectional comparison, since longitudinal studies on CSF biomarkers have reported remarkably stable values over this time period [5,8,13], although a decrease in Aβ42 has been reported when followed 3-4 years [25,56]. Furthermore, only one earlier study has investigated the relation between CSF biomarkers and EEG frequencies [28]. Considering the presumed several decade long preclinical phase of AD, our study might provide interesting contributions to the knowledge of the very early stages of AD pathogenesis.

In the EEG calculations relative power values were used since absolute values vary more between healthy individuals than the intra-individual frequency distribution does. In this study we have used 10 sec epochs during maximal wakefulness in the eyes closed recording situation for EEG quantification in order to avoid fluctuating wakefulness as a confounding factor. The optimal length of epochs needed for analysis is still discussed within EEG methodology. Therefore, analysis of 1-minute epochs in the present EEG material was also performed and these show similar correlation as reported above (data not shown).

An increase in theta power is seen early in the EEG pattern associated with AD development [11,29,30,33,44,48]. Thus, a wide range of relative theta power and even outliers with clinically pathological values could be expected in a cognitively healthy study sample as ours, and might reflect very early and mild brain pathology. Furthermore, the correlation of relative theta and beta, and mean peak frequency seen in our study, has previously been reported in mild AD and has been shown to predict AD-progression in MCI cases [11,43]. On the other hand, other studies on MCI and AD have reported no significant EEG alterations [20,32] or EEG alterations occurring mainly in the alpha activity [1,11,29]. It has been discussed whether changes in different frequency components of the EEG reflect different AD-associated pathological mechanisms [34]. It should be kept in mind that a decrease in high frequency (beta, alpha) components of the EEG spectrum would by definition lead to an increase of the relative theta power. Increased relative theta power is not specific for AD and can be seen in normal aging [16,49] or other conditions of encephalopathy such as encephalitis, acute stroke and head trauma. However, an effort to minimize the occurrence of these conditions has been made by applying the exclusion criteria, as specified in the method section.

Several theories of the originate cause for increasing theta activity in AD have been proposed. A cholinergic dysfunction is one of the mechanisms associated with slowing of the EEG rhythm [30,40,54], due to the influence of cholinergic [7,31] and anti-cholinergic substances [40] in humans as well as hippocampal theta rhythm alterations by cholinergic transmissions in animal models [10,35,51]. The possible involvement of hippocampus is further supported by the correlation of medial temporal lobe atrophy and increase in neocortical theta activity in human studies [21]. Another mechanism associated with slowing

of the EEG is progressive cortical hypoperfusion [36,46], where disturbed connections in autoregulation or regulation from deeper areas on vessels could be a possible contributor. Irrespectively of the specific theory behind increased theta power, all mentioned theories above could be related to neuronal degeneration, which is reflected by tau protein increase in the CSF as suggested by the present study. Transentorhinal areas and later hippocampus, amygdala and neocortical association areas, which are associated with theta activity, also present the first signs of tau-pathology in AD [6]. However, cross-sectional studies have both rejected [50] and confirmed [12,13] correlation between CSF tau and MTL/hippocampal atrophy. The strong correlation between T-tau and P-tau further suggest an abnormal phosphorylation state of the degenerated neurons, which is a progressive neurodegenerative hallmark mostly connected to AD [3,26,52]. The additive effect of combining CSF tau with CSF Aβ42 for the prediction of future development of AD has been reported in several previous studies [3,17,23,55]. However, our current findings suggest that Aβ42-associated changes in the brain do not, by themselves, correlate with the theta regulating mechanisms. In normal elderly and MCI patients it is not uncommon for Aβ42 and tau protein to show different patterns of relationship. Aβ42-associated pathology is for example not as correlated to hippocampal volume loss as tau pathology in early stages and Aβ-deposition on Pittsburgh compound B-PET differentiate controls from MCI and AD better in dorso-frontal regions [3,14]. Thus regions not as associated with theta activity as discussed above. Aβ42 pathology is also suggested not to be as directly related to neuronal loss and damage as tau pathology in cross-sectional analyses [3,14]. Instead CSF Aβ42 might reflect more of a degenerative process leading to neuronal dysfunction, hereby its better ability to predict cognitive decline in normal elderly [22,53] including the current group [55].

In the only preceding study on tau protein and EEG rhythm, Jelic et al (1998) reported that higher T-tau levels correlated with lower alpha/theta ratio (i.e. slowing of EEG) in healthy controls [28]. Our findings reproduce these results and further strengthen the observation of possible AD-associated pathology already in healthy individuals. Hereby, pathological mechanisms prevailed in AD, bridge and erase the created cognition-based arbitrary division of normal and non-normal aging of the brain. The stronger correlation between CSF biomarkers and theta activity in posterior areas is also in accordance with the classical pattern of AD pathology distribution, where mainly temporal and parietal regions are affected. In addition, previous studies have reported similar stronger correlations between variables indicating AD and relative theta power in posterior regions of the brain [36,44].

EEG rhythm is a biomarker visualizing cerebral function. Another measurement of cerebral function is cognition and in the present study slowing of cognitive speed correlates with AD-associated changes in both CSF and EEG. The posterior localisation of the correlation on the EEG agrees with the cerebral area responsible for the cognitive speed measured by AQT [58]. Meta-analysis of cognitive decline in AD has further presented perceptual speed as one of the first cognitive entity affected [2]. Overall, cognitive decline becomes visible later than biomarkers in AD development [15]. It is therefore reasonable that the other general screening tests (MMSE, ADAS-cog, clock-drawing and cube-drawing) do not correlate with the results in our study.

5. Conclusions

In this study we show that biochemical changes in CSF, and the neuropathologic processes it reflects, are related to cerebral function visualized by EEG rhythm and cognitive speed in

cognitively healthy elderly. The patterns of both the CSF biomarkers and the EEG activity furthermore resemble those observed in the development of AD. Hereby, our results suggest that CSF biomarkers and EEG theta activity might indicate early abnormal degenerative changes in the brain.

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6.2. Disclosure statement

The authors declare no conflicts of interest.

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Tables

Table 1

Demographics and cognitive assessments

	Baseline	Follow-up
Number	35	33[†]
Age, mean (±SD)	76 (± 7.9)	77 (± 8.1)
Sex (F/M)	24 / 11	23 / 10
MMSE score, mean (±SD)	29.4 (± 0.7)	28.7 (± 1.2)***
MMSE score range	28 - 30	27 - 30
APOE-ε4 heterozygot, N (homozygote)	9 (1)	8 (1)

[†]2 individuals were excluded because of MMSE scores of < 27 at follow-up, *** p <0.001

Table 2

EEG frequencies and CSF biomarkers values

	Mean (±SD)	Median (25th - 75th pcntle)
EEG[†]		
Mean peak frequency, Hz	9.97 (± 1.63)	10.0 (9 - 11)
Relative power - Delta, %	22.5 (± 12.1)	21.0 (13.5 - 27.1)
Relative power - Theta, %	18.5 (± 11.2)	14.4 (12.2 - 21.0)
Relative power - Alpha, %	35.0 (± 14.3)	30.1 (26.2 - 45.8)
Relative power - Beta, %	24.0 (± 9.7)	23.6 (16.9 - 30.8)
CSF biomarkers		
CSF T-tau, ng/l	402.8 (± 195.4)	366.0 (256.0 - 534.0)
CSF P-tau, ng/l	65.2 (± 27.8)	61.0 (44.5 - 85.0)
CSF β-amyloid$_{1-42}$, ng/l	646.1 (± 168.4)	617.0 (511.0 - 761.0)

[†] Average values for all four scalp quadrants

Table 3

Spearman rank correlation coefficient for correlation of EEG frequencies and CSF biomarkers

	CSF biomarkers				
EEG[†]	T-tau, ng/l	P-tau, ng/l	$A\beta_{1-42}$, ng/l	P-tau/$A\beta_{1-42}$	T-tau/$A\beta_{1-42}$
Mean peak frequency	-0.234	-0.256	0.109	-0.303	-0.239
Relative power - Delta	0.113	0.167	0.089	0.152	0.137
Relative power - Theta	0.545**	0.556***	-0.178	0.622***	0.575***
Relative power - Alpha	-0.38	-0.105	0.094	-0.167	-0.132
Relative power - Beta	-0.120	-0.068	0.181	-0.193	-0.196

[†] Average values for all four scalp quadrants, ** $p < 0.01$, *** $p < 0.001$

Figure Legends

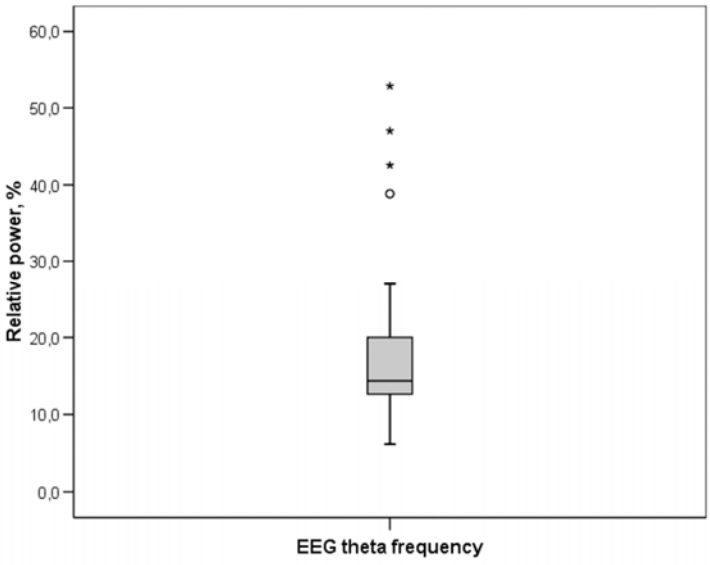

Figure 1

Box-plot of average EEG relative theta power for all four scalp quadrants with median value and the interquartile range. Circles define outliers between 1.5 and 3 times the interquartile range. Stars define extreme outliers over 3 times the interquartile range.

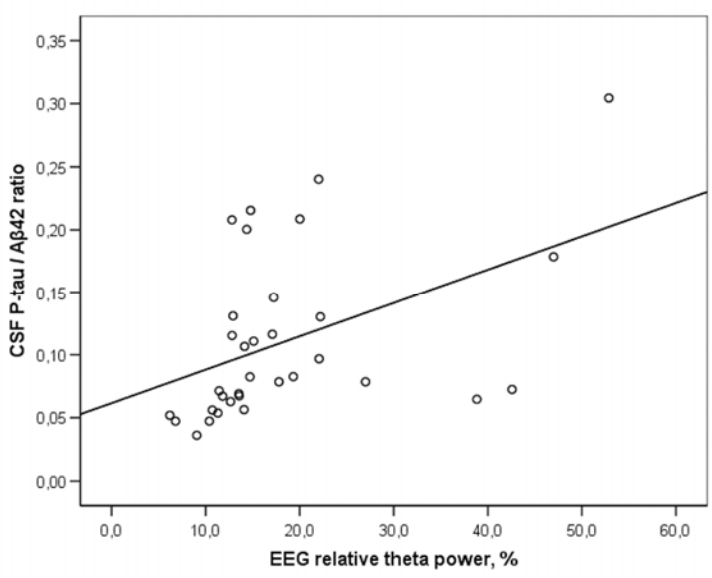

Figure 2

Distribution of CSF P-tau/Aβ42 ratio in relation to average EEG relative theta power for all four scalp quadrants. The regression curve is indicated. ($r_s = 0.622$; $p < 0.001$)

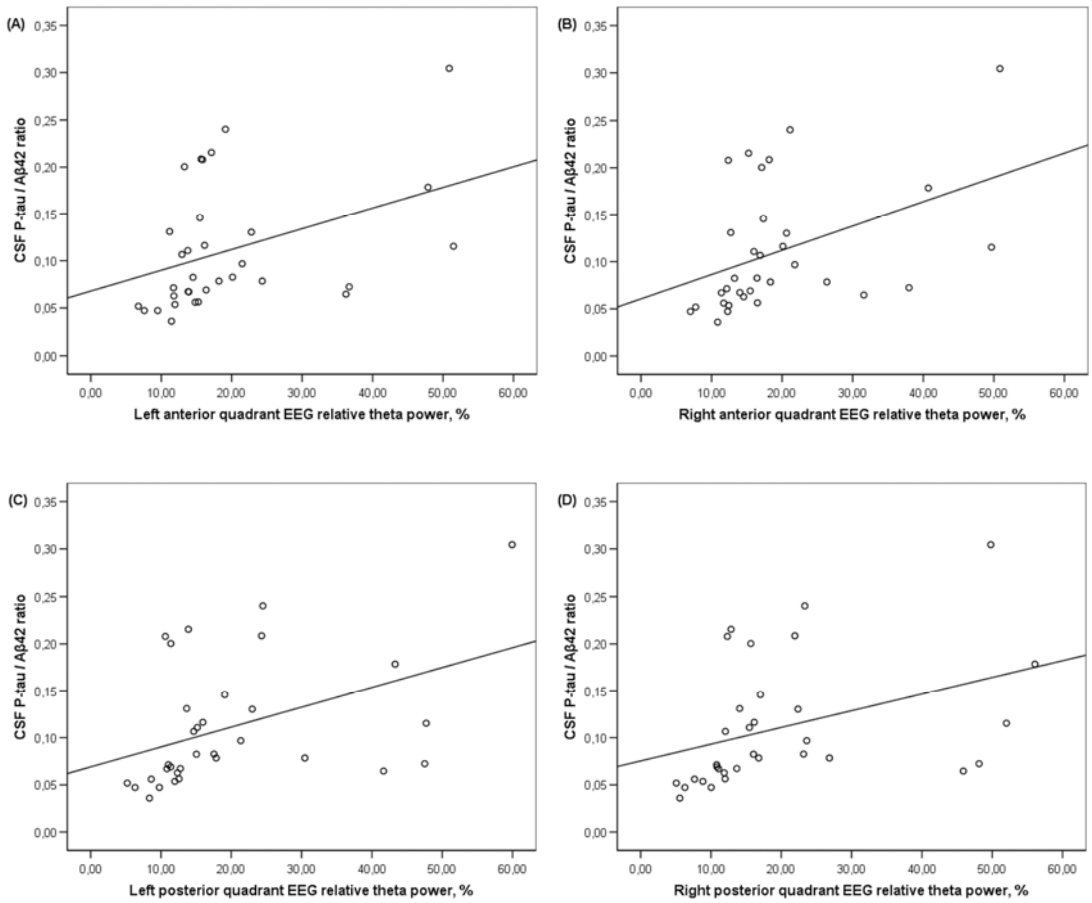

Figure 3

Distribution of CSF P-tau/Aβ42 ratio in relation to relative theta power level in (A) the left anterior quadrant (r_s = 0.510; p <0.01); (B) the right anterior quadrant (r_s = 0.575; p <0.001); (C) the left posterior quadrant (r_s = 0.591; p <0.001); (D) the right posterior quadrant (r_s =0.643; p <10^{-4}). The regression curve is indicated.