

# EEG evidence of compensatory mechanisms in preclinical Alzheimer's disease

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Early biomarkers are needed to identify individuals at high risk of preclinical Alzheimer's disease and to better understand the pathophysiological processes of disease progression. Preclinical Alzheimer's disease EEG changes would be non-invasive and cheap screening tools and could also help to predict future progression to clinical Alzheimer's disease. However, the impact of amyloid- $\beta$  deposition and neurodegeneration on EEG biomarkers needs to be elucidated. We included participants from the INSIGHT-preAD cohort, which is an ongoing single-centre multimodal observational study that was designed to identify risk factors and markers of progression to clinical Alzheimer's disease in 318 cognitively normal individuals aged 70–85 years with a subjective memory complaint. We divided the subjects into four groups, according to their amyloid status (based on <sup>18</sup>F-florbetapir PET) and neurodegeneration status (evidenced by <sup>18</sup>F-fluorodeoxyglucose PET brain metabolism in Alzheimer's disease signature regions). The first group was amyloid-positive and neurodegeneration-positive, which corresponds to stage 2 of preclinical Alzheimer's disease. The second group was amyloid-positive and neurodegeneration-negative, which corresponds to stage 1 of preclinical Alzheimer's disease. The third group was amyloid-negative and neurodegeneration-positive, which corresponds to 'suspected non-Alzheimer's pathophysiology'. The last group was the control group, defined by amyloid-negative and neurodegeneration-negative subjects. We analysed 314 baseline 256-channel high-density eyes closed 1-min resting state EEG recordings. EEG biomarkers included spectral measures, algorithmic complexity and functional connectivity assessed with a novel information-theoretic measure, weighted symbolic mutual information. The most prominent effects of neurodegeneration on EEG metrics were localized in frontocentral regions with an increase in high frequency oscillations (higher beta and gamma power) and a decrease in low frequency oscillations (lower delta power), higher spectral entropy, higher complexity and increased functional connectivity measured by weighted symbolic mutual information in theta band. Neurodegeneration was associated with a widespread increase of median spectral frequency. We found a non-linear relationship between amyloid burden and EEG metrics in neurodegeneration-positive subjects, either following a U-shape curve for delta power or an inverted U-shape curve for the other metrics, meaning that EEG patterns are modulated differently depending on the degree of amyloid burden. This finding suggests initial compensatory mechanisms that are overwhelmed for the highest amyloid load. Together, these results indicate that EEG metrics are useful biomarkers for the preclinical stage of Alzheimer's disease.

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**Abbreviations:** A− = amyloid-negative; A+ = amyloid-positive; INSIGHT-preAD = Investigation of Alzheimer's Predictors in Subjective Memory Complainers; MCI = mild cognitive impairment; MSF = median spectral frequency; N− = neurodegeneration-negative; N+ = neurodegeneration-positive; PSD = power spectral density; SUVR = standardized uptake value ratio; wSMI = weighted symbolic mutual information

## Introduction

Alzheimer's disease is the most common form of dementia, as it accounts for an estimated 60–80% of cases. The pathophysiological process of Alzheimer's disease begins many years before the onset of symptoms (Bateman *et al.*, 2012; Villemagne *et al.*, 2013). It is essential to diagnose Alzheimer's disease as early as possible because patients will be more likely to benefit from disease-modifying treatments if treated early in the disease course, before major brain damage has occurred (Sperling *et al.*, 2011). It is therefore important to develop biomarkers that are sensitive to this early, 'preclinical' stage of Alzheimer's disease even before mild cognitive impairment (MCI) occurs. At the preclinical stage subjects are cognitively unimpaired but show evidence of cortical amyloid- $\beta$  deposition, which is considered to be the most upstream process in the pathological cascade of Alzheimer's disease (Jack *et al.*, 2013) and is measured by amyloid PET or decreased amyloid- $\beta_{1-42}$  and amyloid- $\beta_{1-42}$ /amyloid- $\beta_{1-40}$  ratio in the CSF. Amyloid- $\beta$  deposition can be associated with pathologic tau deposits, measured by tau PET or elevated CSF phosphorylated tau and to neurodegeneration that is revealed by elevated CSF total tau,  $^{18}\text{F}$ -fluorodeoxyglucose ( $^{18}\text{F}$ -FDG) PET hypometabolism in an Alzheimer's disease-like pattern and atrophy on MRI (Jack *et al.*, 2018). Biomarkers for Alzheimer's disease are important not

only for identifying individuals at high risk of preclinical Alzheimer's disease, but also to better understand the pathophysiological processes of disease progression.

The Investigation of Alzheimer's Predictors in Subjective Memory Complainers (INSIGHT-preAD) study is an ongoing longitudinal observational study that was designed to identify risk factors and markers of progression to clinical Alzheimer's disease in 318 cognitively normal individuals with a subjective memory complaint (Dubois *et al.*, 2018). Among the several multimodal assessments, EEGs were performed every 12 months. In our study we focused on the analysis of baseline EEG, aiming to identify electrophysiological biomarkers, including functional connectivity, that are sensitive to the preclinical stage of Alzheimer's disease. EEG has many advantages as it is a non-invasive, cheap and reproducible technique that directly measures neural activity with a good temporal resolution.

There is already a rich literature on the use of EEG biomarkers in MCI and Alzheimer's disease, such as spectral measures and synchronization between brain regions (Babiloni *et al.*, 2016). Patients with Alzheimer's disease or MCI usually show slowing of oscillatory brain activity, reduced EEG complexity and reduced synchrony (Grunwald *et al.*, 2001; Jeong, 2004; Babiloni *et al.*, 2010; Stam, 2010). Decreased alpha power correlated with hippocampal atrophy and lower cognitive status (Babiloni *et al.*, 2006, 2009; Luckhaus *et al.*, 2008). Growing evidence shows that

Alzheimer's disease targets cortical neuronal networks related to cognitive functions, which is revealed by the impairment in functional connectivity in long range networks (Babiloni *et al.*, 2016). There are several types of measures of functional connectivity using EEG or magnetoencephalography (MEG) including spectral coherence, synchronization likelihood or information theory indexes. A decrease of alpha coherence, an increase of delta total coherence and an abnormal alpha fronto-parietal coupling have been described in Alzheimer's disease (Jelic *et al.*, 2000; Babiloni *et al.*, 2009). A reduction of alpha and beta synchronization likelihood was shown in MCI and Alzheimer's disease (Stam *et al.*, 2003). However, the usefulness of EEG characteristics as biomarkers for the evaluation of preclinical Alzheimer's disease is not yet fully established, as most studies have focused on EEG biomarkers at later stages of the disease, after the onset of symptoms. One recent study of the preclinical and prodromal stages of Alzheimer's disease using MEG demonstrated that the effects of amyloid- $\beta$  deposition were expressed as a prefrontal alpha power increment (Nakamura *et al.*, 2018). An EEG study in older people with subjective memory complaints found no association between cortical amyloid load and functional connectivity (Teipel *et al.*, 2018), whereas another study using MEG in cognitively normal individuals at risk for Alzheimer's disease showed altered functional connectivity in the default mode network (DMN) (Nakamura *et al.*, 2017). These results suggest that spectral power and functional connectivity, as measured by MEG or EEG, could potentially be sensitive biomarkers for the preclinical stage of Alzheimer's disease, but more studies are needed in this field. Moreover, very few studies of early stages of Alzheimer's disease consider neurodegeneration information when selecting subjects, whereas it has been suggested that studies combining an abnormal amyloid biomarker with an abnormal neurodegeneration biomarker provide much more powerful prediction of future cognitive decline and conversion to clinical Alzheimer's disease than studies focusing on an abnormal amyloid status alone (Knopman *et al.*, 2013; Vos *et al.*, 2013; Wirth *et al.*, 2013; Mormino *et al.*, 2014; Toledo *et al.*, 2014; Burnham *et al.*, 2016; Soldan *et al.*, 2016).

Our aim was to analyse EEG changes that take place in subjects at high risk of preclinical Alzheimer's disease and to assess the impact of amyloid load and Alzheimer's disease topography-specific neurodegeneration on EEG metrics. To evaluate if EEG metrics' changes were a consequence of neurodegeneration, amyloid burden, or a combination of the two, we divided the whole INSIGHT-preAD cohort into four groups of subjects depending on their amyloid status (evidenced by  $^{18}\text{F}$ -florbetapir PET) and neurodegeneration status (revealed by  $^{18}\text{F}$ -FDG PET). The first group was amyloid-positive and neurodegeneration-positive (A+N+), which corresponds to stage 2 of preclinical Alzheimer's disease according to Sperling *et al.* (2011). The second group was amyloid-positive and neurodegeneration-negative (A+N-), which corresponds to stage 1

of preclinical Alzheimer's disease according to Sperling *et al.* (2011). These first two groups belong to Alzheimer's disease continuum according to Jack *et al.* (2018). The third group was amyloid-negative and neurodegeneration-positive (A-N+), which corresponds to 'suspected non-Alzheimer's pathophysiology' (SNAP) (Jack *et al.*, 2012). The last group was the control group, defined by amyloid-negative and neurodegeneration-negative subjects (A-N-). We hypothesized that amyloid-positive and/or neurodegeneration-positive subjects would present specific EEG patterns and functional connectivity differences compared to control subjects. Moreover, we hypothesized that these EEG patterns would be modulated differently depending on the degree of severity of amyloid burden or hypometabolism.

To assess functional connectivity, we used weighted symbolic mutual information (wSMI), which is a novel measure to quantify global information sharing that was introduced to index consciousness in patients recovering from a coma (King *et al.*, 2013). The advantages of this information-theoretic measure are its robustness to common-source EEG artefacts and its ability to easily detect non-linear coupling. We decided to focus on wSMI in theta (4–8 Hz) and alpha (8–12 Hz) bands as the dominant resting state rhythms are typically observed at theta and alpha frequencies and these rhythms show maximum changes in Alzheimer's disease patients (Blinowska *et al.*, 2017); moreover, wSMI was shown to better discriminate between different states of consciousness in the theta band (King *et al.*, 2013; Sitt *et al.*, 2014).

The main objective of our research was to identify resting state EEG biomarkers of preclinical Alzheimer's disease and SNAP and to evaluate the impact of amyloid burden and neurodegeneration on EEG metrics. Electrophysiological biomarkers included spectral measures, algorithmic complexity and functional connectivity assessed with wSMI. The other aims were the exploration of cofactors involved in EEG metrics differences between the two groups, including apolipoprotein E (*APOE*) genotype, age, gender, educational level and hippocampal volume.

## Materials and methods

### INSIGHT-preAD study design and participants

Participants were recruited into the INSIGHT-preAD study cohort at Pitié-Salpêtrière University Hospital, Paris, France. The INSIGHT-preAD study has already been thoroughly described (Dubois *et al.*, 2018). This cohort currently includes baseline data of 318 cognitively normal individuals, between 70 and 85 years old, with subjective memory complaints and unimpaired cognition [Mini Mental State Examination (MMSE) score  $\geq 27$  and Clinical Dementia Rating score 0], no evidence of episodic memory deficit [Free and Cued Selective Reminding Test (FCSRT) total recall score  $\geq 41$ ].



Demographic, cognitive, functional, biological, genetic, genomic, imaging including brain structural and functional MRI,  $^{18}\text{F}$ -FDG PET and  $^{18}\text{F}$ -florbetapir PET, electrophysiological and other assessments were performed at baseline and regularly during follow-up. EEGs were performed every 12 months.

The ethics committee of the Pitié-Salpêtrière University Hospital approved the study protocol. Written informed consent according to the Declaration of Helsinki was provided by all participants.

## INSIGHT-EEG study participants

Of the 318 subjects of the INSIGHT-preAD cohort, we analysed baseline EEGs of 314 subjects; the EEG data of three subjects was rejected due to excessive EEG artefacts and one subject did not undergo  $^{18}\text{F}$ -FDG PET. Based on amyloid status (evidenced by  $^{18}\text{F}$ -florbetapir PET) and neurodegeneration status (evidenced by  $^{18}\text{F}$ -FDG PET brain metabolism in Alzheimer's disease signature regions), we classified the subjects into four groups: A+N+, A+N-, A-N+ and A-N- (control group).

## PET acquisition and processing

PET scans were acquired 50 min after injection of 370 MBq (10 mCi)  $^{18}\text{F}$ -florbetapir or 30 min after injection of 2 MBq/kg  $^{18}\text{F}$ -FDG. Reconstructed images were analysed with a pipeline developed by the Centre d'Acquisition et Traitement des Images (<http://cati-neuroimaging.com>) (Supplementary material). A  $^{18}\text{F}$ -florbetapir-PET standardized uptake value ratio (SUVR) threshold of 0.7918 was used to dichotomize subjects into amyloid-positive and -negative groups (Dubois *et al.*, 2018; Habert *et al.*, 2018).

The same image assessment pipeline was applied to measure brain glucose metabolism on  $^{18}\text{F}$ -FDG PET scans. Cortical metabolic indices were calculated in four bilateral regions of interest that are specifically affected by Alzheimer's disease (Jack *et al.*, 2012): posterior cingulate cortex, inferior parietal lobule, precuneus, and inferior temporal gyrus, and the pons was used as the reference region. Calculation of the neurodegeneration cut-off value is detailed in the Supplementary material. In the INSIGHT-preAD study, subjects were considered neurodegeneration-positive if the mean  $^{18}\text{F}$ -FDG PET SUVR of the four Alzheimer's disease signature regions was  $<2.27$ .

## EEG acquisition and processing

EEG data were acquired with a high-density 256-channel EGI system (Electrical Geodesics Inc.) with a sampling rate of 250 Hz and a vertex reference. During the recording, patients were instructed to keep awake and relaxed. The total length of the recording was 2 min, during which participants alternated 30-s segments of eyes closed and eyes open conditions. Sixty seconds of eyes closed resting state recording were selected for the analysis. For EEG data processing we used a pipeline that automates processing of EEG recordings with automated artefact removal and extraction of EEG measures (Sitt *et al.*, 2014; Engemann *et al.*, 2015, 2018). A band-pass filtering (from 0.5 to 45 Hz) and a notch filter at 50 Hz and 100 Hz were applied. Data were cut into 1-s epochs. Bad channels and bad epochs

were rejected with a procedure that is detailed in the Supplementary material.

## Calculation and analysis of EEG metrics

We analysed 314 high density 256-channel EEG recordings from INSIGHT-preAD baseline data. For the calculation of EEG metrics, we analysed the values of the first 224 electrodes, which were the scalp (non-facial) electrodes. For each recording, we extracted a set of measures organized according to a theory-driven taxonomy (Sitt *et al.*, 2014). Power spectral density (PSD), median spectral frequency (MSF) and spectral entropy measure dynamics of brain signal at a single electrode site and are based on spectral frequency content. Algorithmic complexity estimates the complexity of a signal based on its compressibility. It measures dynamics of brain signal at a single electrode site and is based on information theory. wSMI is also an information-theoretic metric and estimates functional connectivity between brain regions. For our main analysis, we calculated 10 EEG metrics: PSD in delta (1–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), beta (12–30 Hz), gamma (30–45 Hz), MSF, spectral entropy, algorithmic complexity, wSMI in theta and alpha band. The EEG metrics were averaged across all epochs (60 s recording). PSD was normalized as described in Sitt *et al.* (2014). In a supplementary analysis, we compared the results of functional connectivity measured by wSMI to two additional 'traditional' functional connectivity metrics, namely phase locking value (PLV) and weighted phase lag index (wPLI) (Supplementary material). All markers were computed using NICE (<https://github.com/nice-tools/nice>) and MNE-Python (<https://github.com/mne-tools/mne-python>). The collection of scripts used are publicly available (URL will be made available upon request).

## Statistical analysis

Statistical analyses were performed using R software, version 3.5.0. We compared baseline characteristics between the four groups using one-way ANOVA for continuous variables and  $\chi^2$  test for categorical variables. When global test was significant, *post hoc* Tukey test was performed for continuous variables and pairwise  $\chi^2$  test with Benjamini-Hochberg correction for categorical variables, to determine which groups differed from each other.

## Local regression of average EEG metrics in function of amyloid SUVR and FDG SUVR

First, we used local regression (LOESS) to study the relationship between average EEG metrics (mean value across all scalp electrodes), mean amyloid SUVR and mean  $^{18}\text{F}$ -FDG SUVR.

## EEG metrics analysis

To study the impact of amyloid load, brain metabolism, age, gender, educational level, *APOE*  $\epsilon 4$  and hippocampal volume on EEG metrics, we performed two types of analyses. The first analysis was on the mean value of each metric across all scalp (non-facial) electrodes. The second was on the value of each metric at each scalp electrode so there were 224 values for each metric per participant. For wSMI, connectivity measures

were summarized by calculating the median value from each electrode to all the other electrodes.

Multiple models were performed to evaluate the impact of main effects and interactions. Type II tests were performed. *P*-values were corrected for multiple testing on 10 measures with the Benjamini-Hochberg false discovery rate (BH-FDR) procedure.

For the analysis of average EEG metrics, multiple linear regressions were performed. Simple linear regressions were first performed to evaluate if amyloid load or brain metabolism should be included as categorical variables (A+, A-, N+, N-) or as continuous variables (amyloid SUVR, mean <sup>18</sup>F-FDG SUVR), by maximizing the coefficient of determination *R*<sup>2</sup>, depending on the EEG metrics. The effects of interest were included in multiple models as well as interaction between amyloid load and brain metabolism.

For the analysis of the value of each metric at each electrode, linear mixed models were carried out with the effects of interest as fixed effects as well as the electrode number, and the subject as random effect. Interactions between amyloid load, brain metabolism and electrode number were included in the models as well as all two-way interactions between these three effects. We performed a cluster-based permutation test with a threshold-free cluster enhancement (TFCE) method (Smith and Nichols, 2009) to correct for multiple comparisons on 224 electrodes and to see which electrodes showed statistically significant differences for pairwise comparisons between the following groups: A+N+ versus A-N-, A+N- versus A-N-, A-N+ versus A-N-, A+ versus A-, and N+ versus N-. The cluster-based permutation test is detailed in the [Supplementary material](#). We generated scalp topographical maps using MNE-Python (Gramfort *et al.*, 2013).

### Functional connectivity analysis at source level

To provide anatomically based interpretation of neural activity, we did a source level functional connectivity analysis on a representative sample of the four groups of participants ([Supplementary material](#)).

## Data availability

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

## Results

### Population baseline characteristics analysis

The mean age of all participants was 76.1 years [standard deviation (SD) 3.5] and 67.8% of the participants had a high educational level ([Table 1](#)). There were no differences between the four groups for age and educational level. There were more females in A-N- (66.3%) and A+N- (74.6%) groups compared to A+N+ group (36.0%). The proportion of *APOE* ε4 carriers was higher in A+N+ and A+N- groups than in A-N+ and A-N- groups (44.0% and 34.9% versus 5.9% and 14.3%, respectively). The four groups did not differ for cognitive scores except for the

FCSRT delayed free recall where A+N+ group had significantly lower scores than A+N- and A-N- groups [10.4 (SD 2.5) versus 11.8 (SD 2.3) and 12.0 (SD 2.1), respectively]. The mean <sup>18</sup>F-FDG PET SUVR was 2.2 (SD 0.1) in the A+N+ group, 2.2 (SD 0.1) in the A-N+ group, 2.5 (SD 0.2) in the A+N- group and 2.6 (SD 0.2) in the A-N- group. The mean amyloid SUVR was 1.1 (SD 0.2) in the A+N+ group, 1.0 (SD 0.2) in the A+N- group, 0.7 (SD 0.1) in the A-N+ group and 0.7 (SD 0.1) in the A-N- group. The total hippocampal volume measured on structural MRI was significantly lower in A+N+ subjects compared to A-N- subjects [2.6 (SD 0.2) versus 2.8 (SD 0.3), respectively].

### Local regression of average EEG metrics on amyloid SUVR and FDG SUVR

As a first exploratory step, we used local regression to study the relationship between average EEG metrics and mean amyloid SUVR ([Fig. 1](#)) and mean <sup>18</sup>F-FDG SUVR ([Fig. 3](#)).

The relationship between amyloid SUVR and PSD delta followed a U-shape curve whereas the relationship between amyloid SUVR and PSD beta, PSD gamma, MSF, spectral entropy and complexity followed an inverted U-shape curve. Amyloid SUVR inflection points values were between 0.96 and 0.98 for all the previous EEG measures. The relationship was less clear between amyloid burden, PSD alpha and PSD theta. The degree of severity of amyloid load did not seem to have an impact on wSMI theta and wSMI alpha. To better understand the relationship between amyloid load and EEG metrics we did local regression of average EEG metrics on amyloid SUVR first for N+ subjects only ([Fig. 2](#)) and second for N- subjects only ([Supplementary Fig. 1](#)). Interestingly, in N+ subjects, local regression of EEG metrics on amyloid SUVR showed much more obvious inverted U-shape curves for intermediate to very high amyloid load than the previous regression on the whole cohort, for PSD beta, PSD gamma, MSF, spectral entropy, complexity and also for wSMI theta. Moreover, in N+ subjects, the relationship between PSD delta and amyloid SUVR followed a more pronounced U-shape curve. After exceeding a certain level of amyloid load, complexity, spectral entropy, MSF, PSD beta, PSD gamma and wSMI theta decreased markedly and PSD delta increased noticeably. Amyloid burden did not show any noticeable effect on EEG measures in N- subjects ([Supplementary Fig. 1](#)). To summarize, the degree of severity of amyloid burden had a strong impact on EEG metrics in the presence of neurodegeneration, with increased high frequency oscillations for intermediate amyloid burden and a slowing of brain oscillations for high to very high amyloid load.

Local regression of average EEG metrics on mean <sup>18</sup>F-FDG SUVR ([Fig. 3](#)) showed a trend towards increased

**Table 1** Comparison of baseline characteristics between the four groups

	All participants	A–N– (control)	A–N+	A+N–	A+N+	P-value <sup>a</sup>
<b>Demographics</b>						
Number of subjects	314	175 (55.73%)	51 (16.24%)	63 (20.06%)	25 (7.96%)	..
Age, years	76.07 ± 3.47	75.62 ± 3.39	76.33 ± 3.64	76.81 ± 3.19	76.88 ± 4.01	0.057
Males	116 (36.94%)	59 (33.71%)	25 (49.02%)	16 (25.40%)	16 (64.00%)	..
Females	198 (63.06%)	116 (66.29%) <sup>e</sup>	26 (50.98%) <sup>f</sup>	47 (74.60%) <sup>e,g</sup>	9 (36.00%) <sup>f,h</sup>	0.001*
High educational level <sup>b</sup>	213 (67.83%)	124 (70.86%)	36 (70.59%)	35 (55.56%)	18 (72.00%)	0.141
APOE ε4 allele	61 (19.43%)	25 (14.29%) <sup>e,f</sup>	3 (5.88%) <sup>e,f</sup>	22 (34.92%) <sup>g,h</sup>	11 (44.00%) <sup>g,h</sup>	<0.001*
<b>Cognitive tests</b>						
Mini-Mental State Examination	28.66 ± 0.95	28.73 ± 0.98	28.71 ± 0.92	28.44 ± 0.92	28.60 ± 0.87	0.199
<b>Free and Cued Selective Reminding Test</b>						
Immediate Free Recall	29.96 ± 5.41	30.35 ± 5.36	30.10 ± 5.45	29.65 ± 5.37	27.68 ± 5.45	0.131
Immediate Total Recall	46.08 ± 1.98	46.18 ± 1.95	45.76 ± 2.21	46.19 ± 1.88	45.72 ± 1.95	0.427
Delayed Free Recall	11.83 ± 2.27	12.03 ± 2.11 <sup>e</sup>	11.84 ± 2.45	11.84 ± 2.32 <sup>e</sup>	10.44 ± 2.47 <sup>f,h</sup>	0.013*
Delayed Total Recall	15.67 ± 0.63	15.68 ± 0.63	15.63 ± 0.75	15.74 ± 0.48	15.56 ± 0.71	0.613
Frontal Assessment Battery	16.39 ± 1.69	16.51 ± 1.67	16.60 ± 1.70	16.02 ± 1.68	16.12 ± 1.72	0.160
<b><sup>18</sup>F-FDG PET imaging</b>						
Mean FDG SUVRs <sup>c</sup>	2.45 ± 0.25	2.56 ± 0.20 <sup>e,g</sup>	2.15 ± 0.11 <sup>f,h</sup>	2.52 ± 0.20 <sup>e,g</sup>	2.15 ± 0.12 <sup>f,h</sup>	< 0.001*
<b><sup>18</sup>F-florbetapir PET imaging</b>						
SUVRs	0.78 ± 0.19	0.68 ± 0.05 <sup>e,f</sup>	0.70 ± 0.06 <sup>e,f</sup>	1.00 ± 0.17 <sup>e,g,h</sup>	1.09 ± 0.24 <sup>f,g,h</sup>	< 0.001*
<b>Volumetric MRI, cm<sup>3</sup></b>						
Total hippocampal volume <sup>d</sup>	2.71 ± 0.31	2.76 ± 0.30 <sup>e</sup>	2.66 ± 0.33	2.65 ± 0.35	2.56 ± 0.21 <sup>h</sup>	0.004*

Data are mean ± SD or number (%).

<sup>a</sup>P-value for the comparison between the four groups. P-values were calculated by a one-way ANOVA for continuous data and a Chi<sup>2</sup> test for categorical data. \*P-value < 0.05.

<sup>b</sup>On a scale of 1–8, where 1 = primary education and 8 = higher education, high was defined as scores > 6.

<sup>c</sup><sup>18</sup>F-FDG PET indices partial-volume corrected.

<sup>d</sup>Normalized to the mean total intracranial volume.

Following indicate which groups significantly differ:

<sup>e</sup>Group differs from A+N+.

<sup>f</sup>Group differs from A+N–.

<sup>g</sup>Group differs from A–N+.

<sup>h</sup>Group differs from A–N–.

complexity, PSD beta, PSD gamma, spectral entropy, MSF and wSMI theta and decreased PSD delta when brain metabolism decreased. The relations between brain metabolism, PSD alpha and PSD theta were less clear. The level of brain metabolism did not seem to have an impact on wSMI alpha. Similar trends were found in local regression of EEG metrics on <sup>18</sup>F-FDG SUVR separately for A+ and A– subjects (Supplementary Figs 2 and 3). Thus, as a main effect, neurodegeneration in Alzheimer's disease signature regions seemed to increase high frequency oscillations, complexity, spectral entropy and functional connectivity measured by wSMI theta, except when neurodegeneration was associated with very high amyloid load, where the trend of EEG metrics reversed.

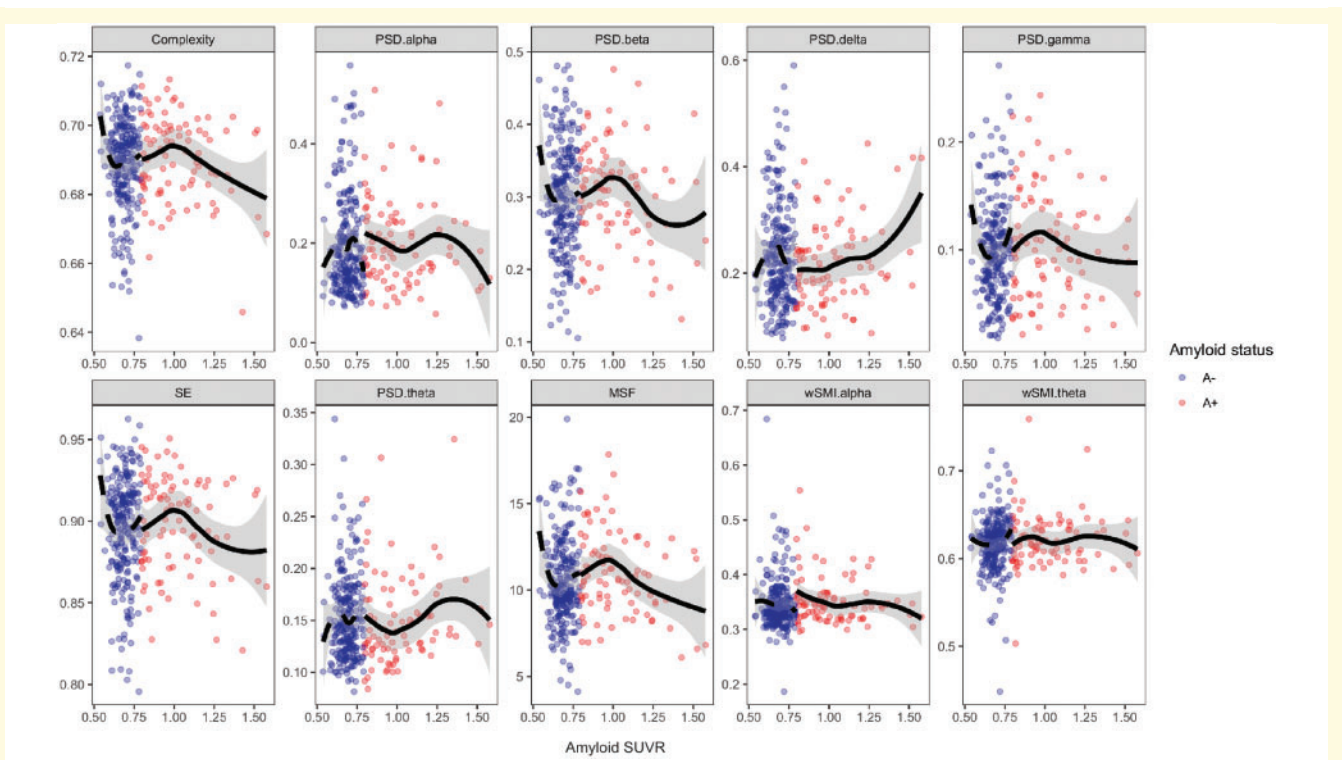
## Multiple linear regression of average EEG metrics in function of amyloid load and brain metabolism

We carried out multiple linear regression of average EEG metrics on all scalp electrodes to assess the impact of amyloid load and brain metabolism on EEG measures, adjusting on the following potential confounding variables: age,

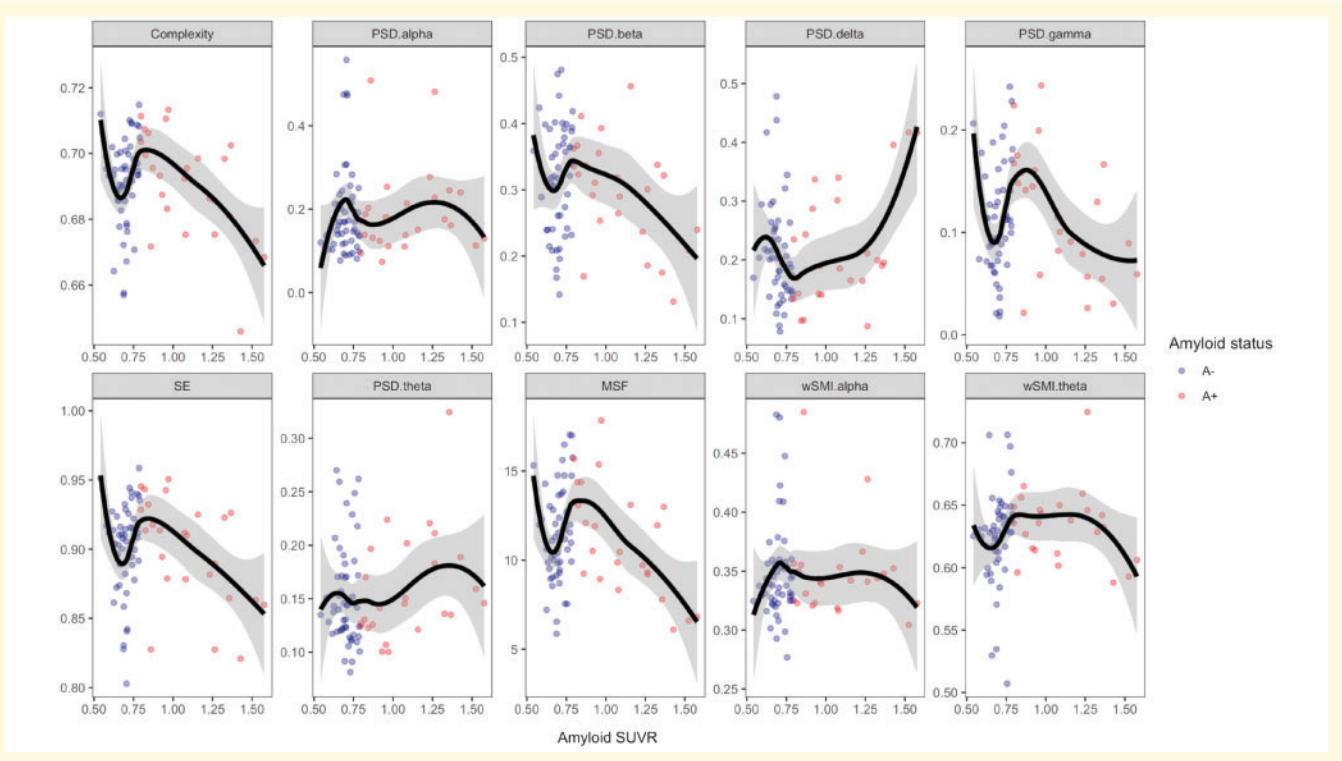
gender, education level, APOE ε4 status and hippocampal volume (Table 2).

We studied the impact of brain metabolism on EEG metrics (Table 2 and Fig. 4). N+ subjects had higher PSD gamma and higher MSF than N– subjects ( $P = 0.0157$  and  $P = 0.0064$ , respectively). A decrease in mean <sup>18</sup>F-FDG SUVR was associated with higher PSD theta and higher wSMI theta ( $P = 0.0203$  and  $P = 0.0452$ , respectively). N+ subjects showed a trend towards higher spectral entropy ( $P = 0.1665$ ) and lower PSD delta ( $P = 0.1067$ ). As previous local regression suggested that amyloid load had an impact on average EEG metrics only in N+ subjects and not in N– subjects, we analysed the interaction between amyloid load and brain metabolism (Table 2 and Fig. 5). There was a significant interaction between amyloid SUVR and neurodegeneration status for complexity ( $P = 0.0217$ ), PSD beta ( $P = 0.0348$ ) and MSF ( $P = 0.0136$ ) and a trend towards significance for spectral entropy ( $P = 0.0669$ ), PSD gamma ( $P = 0.0691$ ) and PSD delta ( $P = 0.1225$ ). With increasing amyloid load, N+ subjects showed decreased complexity, MSF and PSD beta and presented a trend towards decreased spectral entropy, decreased PSD gamma and increased PSD delta, meaning a slowing of brain

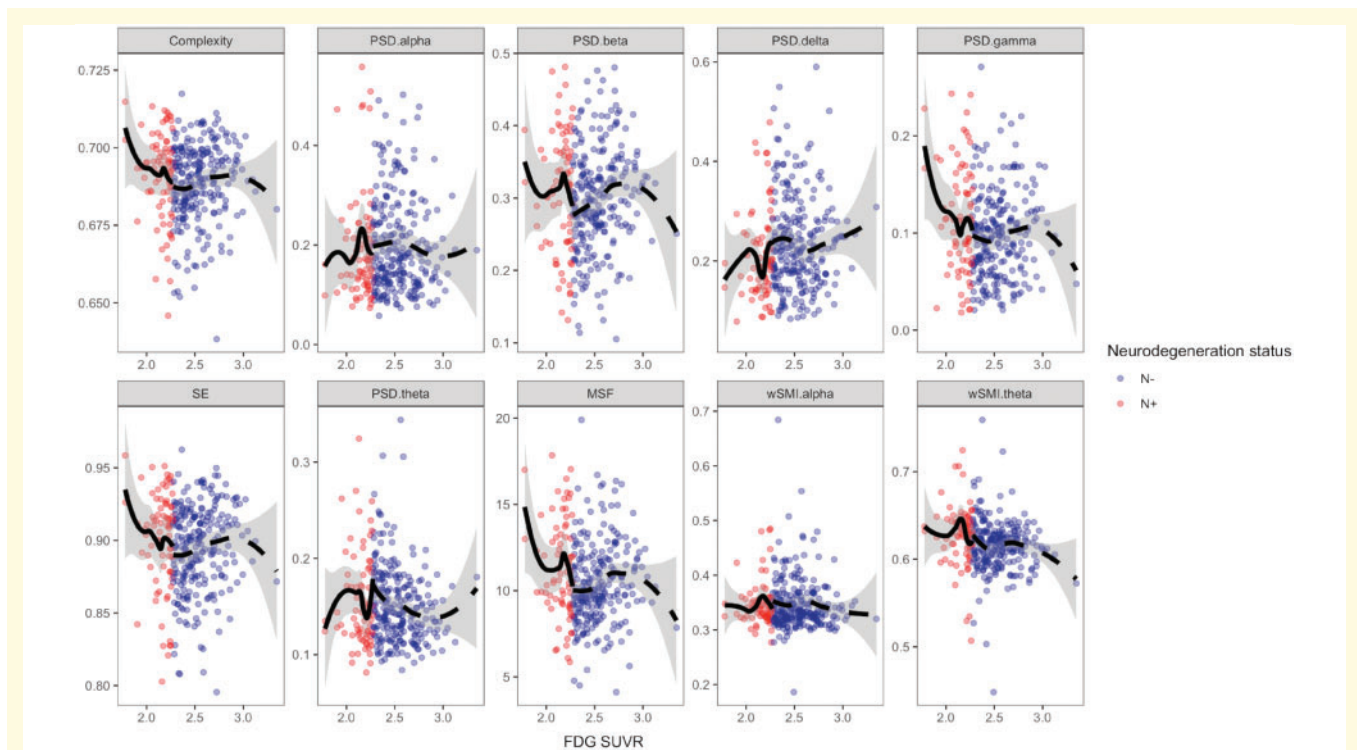




**Figure 1** Local regression of average EEG metrics across all scalp electrodes as a function of amyloid SUVR. SE = spectral entropy.



**Figure 2** Local regression of average EEG metrics across all scalp electrodes as a function of amyloid SUVR for neurodegeneration positive subjects only. SE = spectral entropy.



**Figure 3** Local regression of average EEG metrics across all scalp electrodes as a function of mean FDG SUVR. FDG = fluorodeoxyglucose; SE = spectral entropy.

oscillations. N+ subjects showed a trend towards higher PSD theta in the presence of amyloid positivity compared to N+A− subjects ( $P = 0.1064$ ). In N− subjects, amyloid load did not appear to have an impact on average EEG metrics. If not considering the interaction between amyloid load and neurodegeneration, amyloid load alone did not show a significant impact on average EEG metrics (Table 2 and Supplementary Fig. 4). This supports the fact that amyloid load has an impact on average EEG metrics only if associated with neurodegeneration. Results did not stay statistically significant after multiplicity correction on 10 EEG metrics.

### Relationship between average EEG metrics, age, gender, education, APOE $\epsilon 4$ and hippocampal volume

Males had higher average wSMI theta (FDR-corrected  $P < 0.0001$ ) and lower PSD delta (FDR-corrected  $P = 0.0256$ ) compared to females (Table 2). No significant relationship was found between gender and the other EEG metrics (Supplementary Fig. 5). There was no significant relationship between EEG metrics and educational level, age and hippocampal volume. wSMI theta was higher in the presence of APOE  $\epsilon 4$  genotype (Supplementary Fig. 6) than in the absence of APOE  $\epsilon 4$  genotype ( $P = 0.0493$ ). No significant relationship was found between APOE  $\epsilon 4$  and the other EEG metrics.

### 224 Electrodes analysis: topographical differences across EEG measures and groups

We evaluated topographical differences across EEG measures between the control group (A−N−) and the three other groups (A+N+, A+N− and A−N+) (Supplementary Table 1 and Fig. 6), then between N+ and N− subjects (Supplementary Fig. 7) and finally between A+ and A− subjects (Supplementary Fig. 8). The objectives were to assess the discrimination capacity of the different EEG metrics between groups and to better understand the impact of amyloid and neurodegeneration on EEG measures. All  $P$ -values were adjusted on APOE  $\epsilon 4$  status, gender, education level, age and hippocampal volume.

The A−N+ group showed maximum EEG changes compared to A−N− control group. A−N+ subjects had lower PSD delta in frontocentral regions and right temporal region, higher PSD beta, complexity, spectral entropy and wSMI theta in frontocentral regions and higher PSD gamma in frontocentral and temporal bilateral regions, compared to A−N− group. The A−N+ group presented a widespread increase of MSF in frontocentral and parieto-temporal regions. Thus, several EEG measures were efficient indices in discriminating A−N+ subjects from A−N− subjects. The A+N+ group showed only an increase in PSD gamma in left frontotemporal region and a



**Table 2 Results of multiple linear regression analysis of 10 average EEG metrics on all explanatory variables**

EEG metrics	Adjusted R <sup>2</sup>		Florbetapir		FDG		Gender		Educational level		Age at baseline		APOE ε4		Hippocampal volume		Interaction Florbetapir:FDG	
	P-value	corrected	P-value	corrected	P-value	corrected	P-value	corrected	P-value	corrected	P-value	corrected	P-value	corrected	P-value	corrected	P-value	corrected
Complexity <sup>c</sup>	0.025	0.2578	0.4876	0.2001	0.2859	0.0788	0.1716	0.1549	0.4894	0.4299	0.8403	0.2360	0.5507	0.7000	0.7028	0.0217 <sup>a</sup>	0.1085	
PSD.alpha <sup>c</sup>	-0.012	0.9376	0.9386	0.5815	0.5815	0.3075	0.3844	0.6780	0.8290	0.4566	0.8403	0.1915	0.5507	0.5324	0.7028	0.7544	0.7544	
PSD.beta <sup>c</sup>	0.012	0.3413	0.4876	0.2325	0.2906	0.1249	0.2082	0.1958	0.4894	0.5938	0.8403	0.9040	0.9293	0.2372	0.7028	0.0348 <sup>a</sup>	0.1161	
PSD.delta <sup>c</sup>	0.034	0.3108	0.4876	0.1067	0.2135	0.0051 <sup>a</sup>	0.0256 <sup>a</sup>	0.1347	0.4894	0.8596	0.8596	0.0548	0.2742	0.4439	0.7028	0.1225	0.1750	
PSD.gamma <sup>c</sup>	0.018	0.6529	0.8162	0.0157 <sup>a</sup>	0.0677	0.9583	0.9583	0.8290	0.8290	0.3602	0.8403	0.9293	0.9293	0.2529	0.7028	0.0691	0.1381	
SE <sup>c</sup>	0.009	0.3022	0.4876	0.1665	0.2775	0.3526	0.3918	0.1249	0.4894	0.5892	0.8403	0.8517	0.9293	0.5779	0.7028	0.0669	0.1381	
PSD.theta <sup>b</sup>	0.019	0.3411	0.4876	0.0203 <sup>a</sup>	0.0677	0.2140	0.3058	0.6211	0.8290	0.3552	0.8403	0.4182	0.6867	0.7028	0.7028	0.1064	0.1750	
MSF <sup>c</sup>	0.037	0.2677	0.4876	0.0064 <sup>a</sup>	0.0644	0.0858	0.1716	0.5198	0.8290	0.5305	0.8403	0.2754	0.5507	0.6792	0.7028	0.0136 <sup>a</sup>	0.1085	
wSMI.alpha <sup>b</sup>	0.001	0.2219	0.4876	0.4785	0.5317	0.0809	0.1716	0.7596	0.8290	0.7386	0.8403	0.4807	0.6867	0.0751	0.7028	0.2855	0.3568	
wSMI.theta <sup>b,c</sup>	0.177	0.9386	0.9386	0.0452 <sup>a</sup>	0.1129	<0.0001 <sup>a</sup>	<0.0001 <sup>a</sup>	0.8170	0.8290	0.7563	0.8403	0.0493 <sup>a</sup>	0.2742	0.3842	0.7028	0.5948	0.6609	

Adjusted coefficient of determination R-squared values (R<sup>2</sup>), P-values and Benjamini-Hochberg corrected P-values are shown.  
<sup>a</sup>p < 0.05. To maximize R<sup>2</sup> values, for each EEG metric, FDG and florbetapir were used either as continuous or binary measures.  
<sup>b</sup>FDG as continuous measure otherwise as binary measure.  
<sup>c</sup>Florbetapir as continuous measure otherwise as binary measure.  
 FDG = fluorodeoxyglucose; SE = spectral entropy.

discrete increase in MSF in left temporal region, compared to the A-N- group. The A+N+ group showed a trend towards increased wSMI theta in centro-parieto-temporal regions but did not reach statistical significance. The A+N- group showed significantly increased wSMI alpha in parieto-occipital regions compared to the A-N- group.

We compared the N+ group to the N- group (Supplementary Fig. 7) and found that N+ subjects presented similar EEG changes than the A-N+ group (as described earlier) although the EEG changes were less marked. N+ subjects presented increased MSF in fronto-central and parieto-temporal regions and increased PSD gamma in frontal and temporal bilateral regions. N+ subjects had a discrete diminution of PSD delta in frontocentral regions and a discrete increase in wSMI theta, spectral entropy and complexity in frontocentral regions. There was a trend toward increased PSD beta in frontocentral regions in N+ subjects but it did not reach statistical significance. MSF and PSD gamma were the most powerful metrics to discriminate between N+ and N- subjects (Supplementary Table 1; P = 0.0093 and P = 0.0182 for main effects of MSF and PSD gamma, respectively). Although there was a significant interaction between amyloid status and electrodes for wSMI alpha in a linear mixed model (P < 0.0001 and FDR-corrected P = 0.0003; Supplementary Table 1), the comparison of A+ versus A- group (Supplementary Fig. 8) showed only a trend towards increased wSMI alpha in parieto-occipital regions but did not reach cluster statistical significance.

### Comparison of wSMI with ‘traditional’ functional connectivity measures

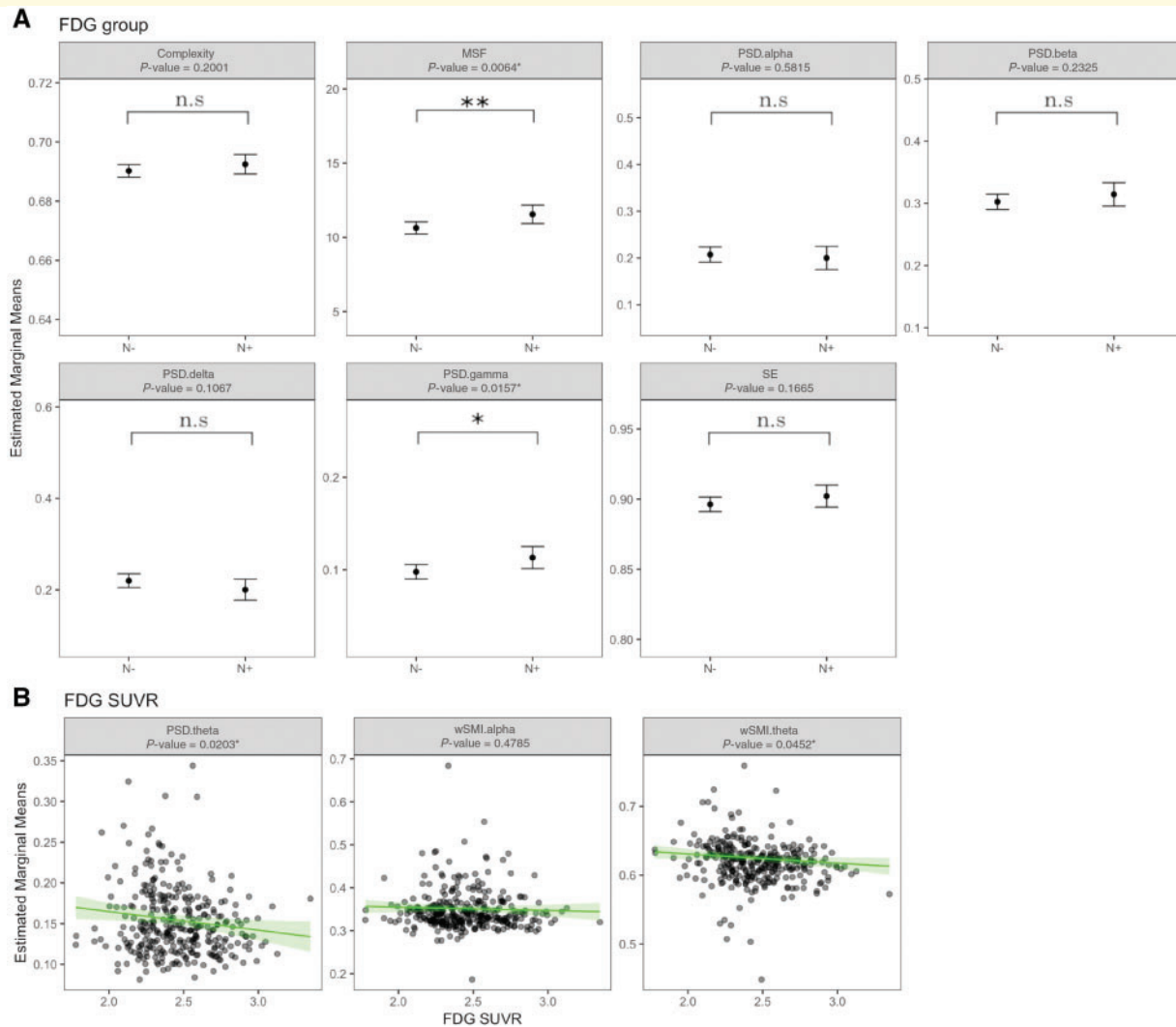
Results are detailed in the Supplementary material.

### Functional connectivity analysis at source level

Results of functional connectivity source analysis are described in the Supplementary material.

## Discussion

To our knowledge, this is the first study to demonstrate EEG changes in preclinical Alzheimer’s disease and SNAP. Moreover, we have explored the effects of Alzheimer’s disease topography-specific neurodegeneration and amyloid-β deposition on EEG metrics. The most prominent effects of neurodegeneration on EEG metrics were localized in frontocentral regions with an increase in high frequency oscillations (higher beta and gamma power) and a decrease in low frequency oscillations (lower delta power), higher spectral entropy, higher complexity and increased functional connectivity measured by wSMI in

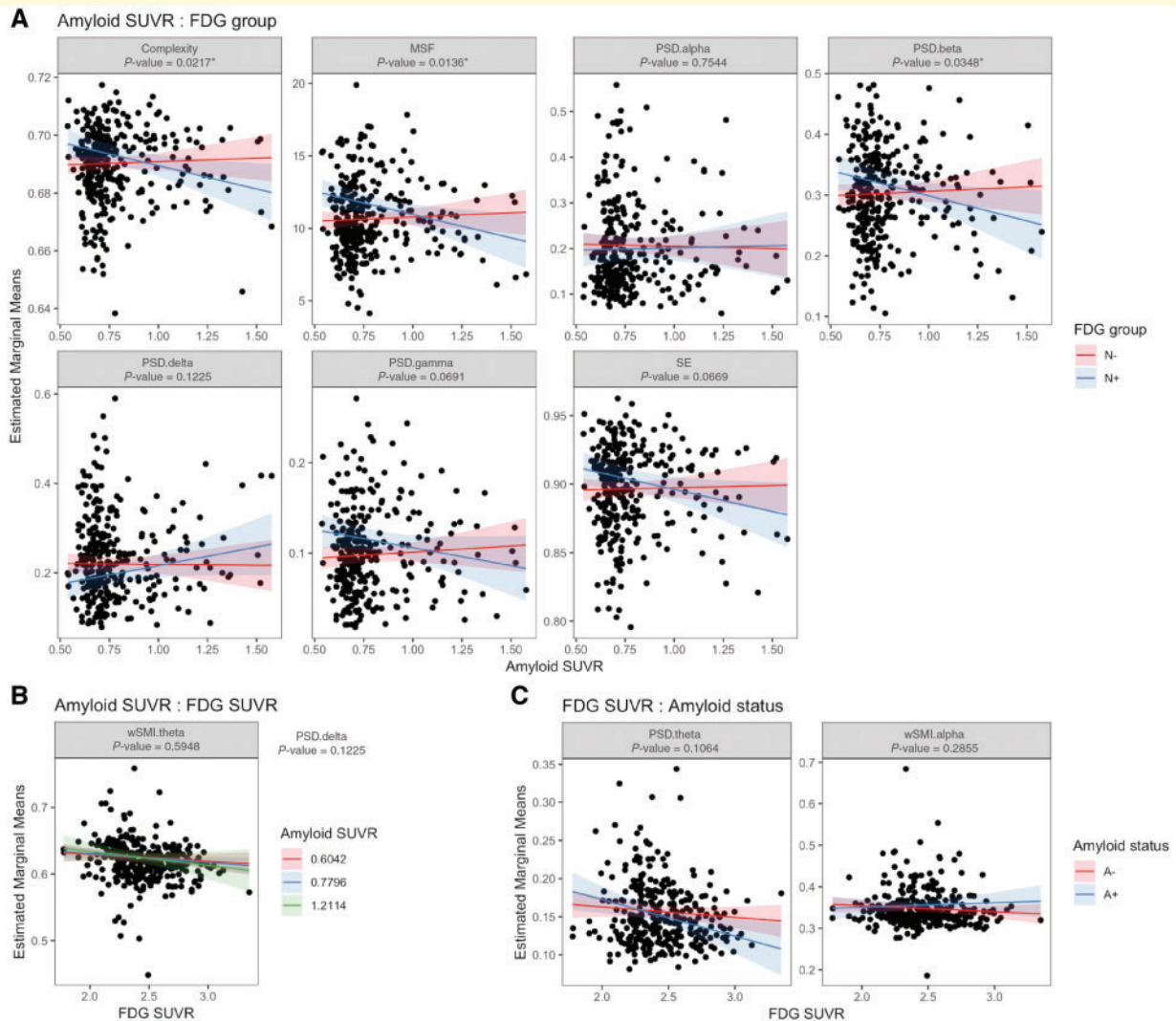


**Figure 4** Estimated marginal means from multiple linear regressions of average EEG metrics according to brain metabolism. Amyloid load and brain metabolism are used either as continuous or binary measures, depending on each EEG metric to maximize R-squared values. **(A)** Brain metabolism as binary measure (N+ versus N-). **(B)** Brain metabolism as continuous measure (mean FDG SUVR). Estimated marginal means and standard deviation are depicted; co-variables in the models were: age, education level, gender, APOE  $\epsilon$ 4 status, hippocampal volume and florbetapir (either binary or continuous). P-values are indicated with \* $P < 0.05$ ; \*\* $P < 0.01$ . n.s. = not significant; FDG = fluorodeoxyglucose; SE = spectral entropy.

theta band. Neurodegeneration was associated to a widespread increase of MSF. Interestingly, in the absence of neurodegeneration, at stage 1 of preclinical Alzheimer's disease according to Sperling *et al.* (2011), amyloid burden did not have any impact on average EEG metrics but had a local effect marked by an increased functional connectivity measured by wSMI alpha in parieto-occipital regions.

Importantly, in N+ subjects, we found a non-linear relationship between amyloid burden and EEG metrics, either following a U-shape curve for delta power or an inverted U-shape curve for PSD beta, PSD gamma, MSF, complexity, spectral entropy and wSMI theta. This means that in the presence of neurodegeneration, EEG patterns are modulated differently depending on the degree of severity of

amyloid burden. After N+ subjects exceed a certain threshold of amyloid load, the whole trend of EEG metrics reverses, meaning increased delta power and decreased beta and gamma power, MSF, spectral entropy, complexity and wSMI in theta band, with an EEG pattern getting close to the one observed in MCI and clinical Alzheimer's disease. The fact that N+ subjects have opposite EEG trends for intermediate amyloid load (i.e. increased high frequency oscillations) and high to very high amyloid load (i.e. slowing of brain oscillations) can explain why A+N+ subjects showed less EEG changes than A-N+ subjects, with only a discrete increase of PSD gamma and MSF. Indeed, in the A+N+ group, some subjects have intermediate amyloid load and others have very high amyloid load, so in the



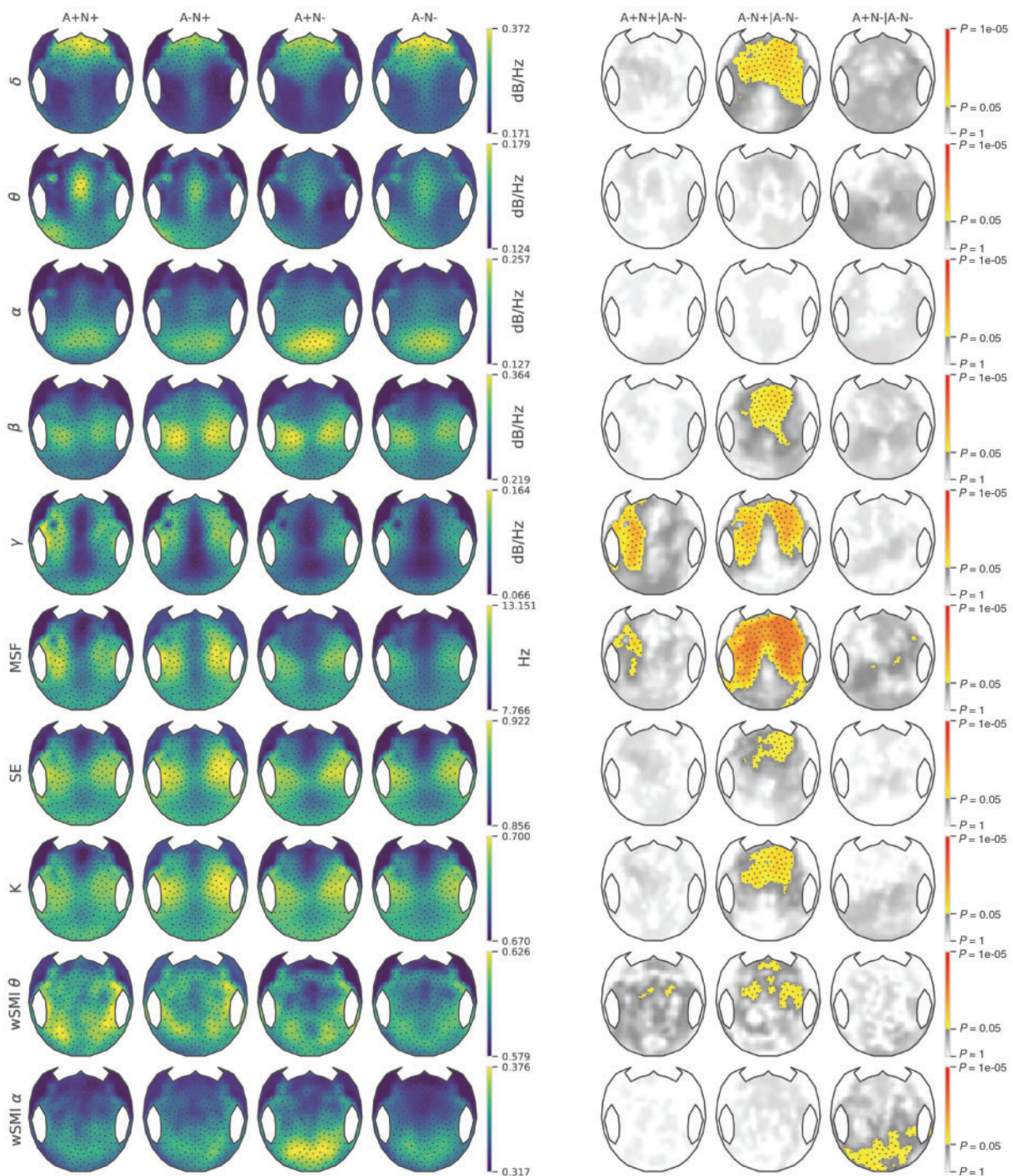
**Figure 5** Estimated marginal means from multiple linear regressions of average EEG metrics according to interactions between amyloid load and brain metabolism. Amyloid load and brain metabolism are used either as continuous or binary measures, depending on each EEG metric to maximize R-squared values. **(A)** Interaction between amyloid SUVR and FDG status. **(B)** Interaction between amyloid SUVR and mean FDG SUVR. **(C)** Interaction between mean FDG SUVR and amyloid status. Estimated marginal means and standard deviation are depicted; co-variables in the models were: age, education level, gender, APOE  $\epsilon$ 4 status, hippocampal volume and Flortbetapir (either binary or continuous). P-values are indicated with \* $P < 0.05$ . FDG = fluorodeoxyglucose; SE = spectral entropy.

A + N+ group some subjects have increased high frequency oscillations and others have a slowing of brain oscillations; these effects going in opposite directions, in the end at A + N+ group level very little EEG changes are visible, while EEG changes are actually present at individual level.

Therefore, it seems best to individualize two different EEG phases in N+ subjects, depending on the level of amyloid burden. We will first focus on the results for the first EEG phase in preclinical Alzheimer's disease subjects presenting subthreshold to intermediate amyloid burden, before amyloid load exceeds a critical threshold. Increasing high frequency spectral power in frontocentral regions is in line with a recent study, which showed a functional frontal upregulation revealed by an increased frontal

alpha power in preclinical Alzheimer's disease (Nakamura *et al.*, 2018). Compared to this previous study, we found a frontal upregulation in higher frequency bands that were beta (12–30 Hz) and gamma (30–45 Hz). Increased frontal functional upregulation has also been shown in other studies with an increased functional connectivity in frontal regions (Mormino *et al.*, 2011; Jones *et al.*, 2016). In an inverse way we found decreased frontal delta power in the presence of neurodegeneration, for subthreshold amyloid SUVR. A study by Nakamura *et al.* (2018) reported a negative correlation between regional metabolism in Alzheimer's disease signature regions and frontal delta power in an amyloid-positive group, which included MCI and cognitively normal subjects, MCI subjects showing higher frontal





**Figure 6** 224 electrodes topographical maps of EEG metrics. The topographical 2D projection (top = front) of each measure [normalized power spectral density in delta ( $\delta$ ), theta ( $\theta$ ), alpha ( $\alpha$ ), beta ( $\beta$ ), gamma ( $\gamma$ ), median spectral frequency (MSF), spectral entropy (SE), algorithmic complexity (K) and weighted symbolic mutual information in theta band and alpha band (wSMI  $\theta$  and wSMI  $\alpha$ )] is plotted for the A+N+ group, the A-N+ group, A+N- group and control group A-N- (columns). Statistics were done on 224 electrodes by non-parametric cluster permutation test. The three last columns indicate non-parametric cluster-based permutation test results for the pairwise comparisons: A+N+ versus A-N-, A-N+ versus A-N-, and A+N- versus A-N- for each EEG metric. The topographical maps in the three last columns are colour-coded according to the cluster permutation tests  $P$ -values (colour:  $P < 0.05$ , greyscale:  $P > 0.05$ ). Clusters of electrodes whose EEG metrics' values are significantly different from the control group (A-N-) are depicted.

delta power than cognitively normal subjects. At first sight these results could seem discrepant with our study but can be explained first by the fact that we studied cognitively normal subjects only and not MCI subjects; and second, we found increased delta power when neurodegeneration was associated to high amyloid burden, similarly to Nakamura *et al.* (2018), thus confirming that delta power increase is a marker of disease progression within the Alzheimer's disease continuum.

The first hypothesis to explain an increase in frontal high frequency oscillations concomitant with a decrease in low frequency oscillations in N+ subjects with subthreshold to intermediate amyloid load is a compensatory mechanism, which was also proposed in previous studies (Mormino *et al.*, 2011; Lim *et al.*, 2014; Jones *et al.*, 2016). A sufficient level of compensation is needed to maintain normal cognitive function despite amyloid burden and hypometabolism in preclinical Alzheimer's disease. Compensatory mechanisms would then fail once amyloid burden exceeds a certain level, explaining the reversal of EEG metrics trend, with a slowing of brain oscillations revealed by increased delta power and decreased beta and gamma power, with a spectral pattern getting close to the one typically found in MCI and Alzheimer's disease. Another explanation is that as participants in the INSIGHT-preAD study are selected on normal cognition, subjects with neurodegeneration may have a particularly high cognitive reserve, which is revealed by baseline higher spectral power in frontal regions, reduced low frequency oscillations and higher functional connectivity (Cohen *et al.*, 2009; Lim *et al.*, 2014); this cognitive reserve would be altered as amyloid load increases, which would explain why subjects with neurodegeneration and very high amyloid load show slowing of brain oscillations and lower functional connectivity.

We found a local increase of functional connectivity measured by wSMI alpha in parieto-occipital regions in subjects at stage 1 of preclinical Alzheimer's disease. This could be explained by abnormal transient neuronal hyperexcitability related to amyloid- $\beta$  deposition with a relative decrease in synaptic inhibition (Busche *et al.*, 2008; Palop and Mucke, 2010; Nakamura *et al.*, 2018). The 'acceleration' hypothesis suggests that once amyloid- $\beta$  deposition is initiated by independent events, a milieu of higher functional connectivity hastens this deposition, which eventually leads to the functional disconnection or metabolic deterioration in the subjects with amyloid burden (Cohen *et al.*, 2009; de Haan *et al.*, 2012; Johnson *et al.*, 2014; Lim *et al.*, 2014). The metabolic demands associated with high connectivity may be the detrimental phenomenon that triggers downstream cellular and molecular events associated with Alzheimer's disease (Jones *et al.*, 2016). Previous work in animal models has shown that intermediate levels of amyloid- $\beta$  enhance synaptic activity presynaptically (Abramov *et al.*, 2009), whereas abnormally high levels of amyloid- $\beta$  impair synaptic activity by inducing post-synaptic depression (Palop and Mucke, 2010). This is consistent with our

results showing basically two different EEG phases in preclinical Alzheimer's disease stage 2. In the early preclinical stage that is characterized by neurodegeneration combined with intermediate levels of amyloid- $\beta$ , there is an increase in brain oscillations and functional connectivity due to compensation and/or amyloid- $\beta$ -related excitotoxicity. Then, the increase in brain oscillations and functional connectivity would hasten amyloid- $\beta$  deposition. In a later preclinical stage characterized by neurodegeneration combined with high to very high levels of amyloid- $\beta$ , there is a slowing of brain oscillations and reduced functional connectivity due to compensatory mechanisms failure and/or post-synaptic depression, with an EEG pattern getting close to the one observed in MCI and Alzheimer's disease. The breakdown of initial functional compensation would facilitate accelerated tau-related neurodegenerative processes (Jones *et al.*, 2017).

In our study, we showed that a decrease in brain metabolism in Alzheimer's disease signature regions was associated with higher theta power. These results are in line with the study by Stomrud *et al.* (2010) on a small sample of cognitively normal subjects ( $n = 33$ ) showing that increased CSF total tau and phosphorylated tau as well as increased phosphorylated tau/amyloid- $\beta_{1-42}$  ratio in the CSF correlated with increased theta power, whereas amyloid- $\beta_{1-42}$  in itself was not correlated with theta power. It has been previously suggested that increased theta power could be linked to neuronal degeneration but may not be specific to Alzheimer's disease (Nakamura *et al.*, 2018).

To our knowledge, our work is the first to study complexity and spectral entropy in subjects with preclinical Alzheimer's disease, coupled with metabolic evidence of neurodegeneration and amyloid- $\beta$  biomarker information. The increased complexity and spectral entropy observed in frontal regions in the presence of neurodegeneration could also be explained by compensatory mechanisms. Compensation would then fail with increasing amyloid burden, with an EEG pattern becoming less complex and more regular, approximating the one observed in MCI/Alzheimer's disease (Hornero *et al.*, 2009; Staudinger and Polikar, 2011; Al-Nuaimi *et al.*, 2018).

One of the main strengths of our study was the use of a high-performing and practical EEG processing pipeline with automated artefact elimination and extraction of several validated EEG biomarkers. This tool avoids the need for the time-consuming manual removal of artefacts and the risk of possible human biases. Effective artefact removal is particularly important in a population of elderly subjects. Our results suggest that the EEG measures extracted with this pipeline can be successfully employed in a wide range of practical contexts whenever spectral or information-theory biomarkers are needed. wSMI has proved effective in assessing functional connectivity in previous studies (King *et al.*, 2013; Sitt *et al.*, 2014; Engemann *et al.*, 2015, 2018) because unlike several traditional synchrony measures it minimizes common-source artefacts and provides an efficient way to detect non-linear coupling.



Moreover, wSMI has already proven sensitive to detect aberrant networks in other neurodegenerative conditions, including Parkinson's disease (Melloni *et al.*, 2015) and behavioural variant frontotemporal dementia (Dottori *et al.*, 2017). Our study supports the idea that EEG being a non-invasive, cheap and widely available technique, could be used as a screening tool for identifying individuals at high risk of preclinical Alzheimer's disease and future cognitive decline. Moreover, EEG biomarkers seem to be useful tools to measure and monitor neurodegeneration.

Another novelty of our work is the division of our study population in four groups, based on amyloid and neurodegeneration criteria, in contrast to the more commonly used selection of individuals at risk for Alzheimer's disease based on amyloid biomarker alone with a dichotomous classification of subjects as amyloid-negative or positive. First, amyloid deposition alone does not necessarily represent progression to clinical Alzheimer's disease as both neuropathological and PET data show evidence of extensive amyloid- $\beta$  pathology in cognitively normal older people (Bennett *et al.*, 2006; Morris *et al.*, 2010; Jagust, 2016). Second, it has been shown that neurodegeneration, particularly synapse loss, is the aspect of Alzheimer's disease neuropathological change that correlates most closely with symptom onset and cognitive decline (Soldan *et al.*, 2016; Jack *et al.*, 2018) and several studies using  $^{18}\text{F}$ -FDG PET showed that cerebral metabolic rate of glucose reduction predicted cognitive decline from normal elderly cognition to MCI/Alzheimer's disease with a high accuracy, decliners showing greater reduction of  $^{18}\text{F}$ -FDG SUVR values (de Leon *et al.*, 2001; Jagust *et al.*, 2006; Mosconi *et al.*, 2009, 2010). A study by Teipel *et al.* (2018) found no association between cortical amyloid load and functional connectivity in the INSIGHT-preAD cohort, which is explainable first by the fact that authors only assessed the impact of amyloid load and not the effect of neurodegeneration on functional connectivity; and second, they used phase lag index to measure functional connectivity, which is affected by noise and volume conduction. The study of four groups of subjects depending on their amyloid and neurodegeneration status enabled us to explore EEG changes at different stages of preclinical Alzheimer's disease (stages 1 and 2) and to study SNAP subjects, who are also at risk of future cognitive decline (Caroli *et al.*, 2015). Moreover, we were able to assess independently the effects of neurodegeneration and amyloid burden on EEG metrics.

Our results showed increased wSMI theta in *APOE*  $\epsilon 4$  carriers. This is consistent with other studies showing increased functional connectivity in cognitively normal *APOE*  $\epsilon 4$  carriers (Filbey *et al.*, 2006; Kramer *et al.*, 2008), whereas other studies found reduced brain activity in *APOE*  $\epsilon 4$  carriers (Lind *et al.*, 2006) or no differences in functional connectivity according to *APOE* genotype (Bassett *et al.*, 2006; Nakamura *et al.*, 2017). We found that males had higher functional connectivity measured by wSMI theta; however, this result should be interpreted with caution as there was some gender imbalance between

groups. Some studies have found higher functional connectivity in males (Allen *et al.*, 2011; Filippi *et al.*, 2013), whereas others have reported that gender has a relatively small (Bluhm *et al.*, 2008) or lack of effect (Weissman-Fogel *et al.*, 2010) on resting state networks. Thus, further studies are needed to clarify the impact of gender and *APOE*  $\epsilon 4$  genotype on EEG metrics.

Our study presents some limitations. We divided the INSIGHT-preAD cohort into four groups of subjects based on  $^{18}\text{F}$ -florbetapir PET and  $^{18}\text{F}$ -FDG PET thresholds. However, principally for amyloid burden, this dichotomous distinction between A+ and A- categories is questionable as A- subjects are not necessarily completely free of amyloid, especially subjects that are slightly below the threshold. In the A-N+ (SNAP) group some subjects had subthreshold amyloid load so would be close to stage 2 of preclinical Alzheimer's disease. In the A+N+ group the population was heterogeneous, as some subjects had intermediate amyloid burden and others had high to very high amyloid burden, making it difficult to interpret the results at A+N+ group level, as EEG metrics went into opposite directions depending on the degree of severity of amyloid burden. For that reason, we decided it was best to analyse amyloid load as a continuous variable and to describe two EEG phases in stage 2 of preclinical Alzheimer's disease (for intermediate amyloid load and high to very high amyloid burden). Tau marker was not available, which is another limitation of this study, especially with regards to the recent NIA-AA research framework (Jack *et al.*, 2018), which stipulates that only individuals with both amyloid- $\beta$  and pathologic tau biomarkers would be considered to have Alzheimer's disease. However, it has been shown that there is a strong correlation between  $^{18}\text{F}$ -FDG PET hypometabolism in Alzheimer's disease-signature regions and tau pathology, and also between hippocampal atrophy and tau pathology (Gómez-Isla *et al.*, 1997; Nelson *et al.*, 2012). As in our study A+N+ subjects not only had a combination of high  $^{18}\text{F}$ -florbetapir retention and low  $^{18}\text{F}$ -FDG PET metabolism but also presented significant hippocampal volume reduction, it means that they have a high probability of pathologic tau deposits. We decided to do our principal analysis at scalp level and mainly use globally-averaged EEG measures so that the procedure would stay simple, keeping in mind that it could be applied as a possible routine screening tool in the future to identify individuals at high risk of preclinical Alzheimer's disease. To have a better interpretation in terms of cerebral regions we did functional connectivity analysis at source level on four samples of subjects (Supplementary material), but due to lack of power, we did not evidence any significant differences in functional connectivity at source level. Source analysis on a larger number of subjects will need to be done in future studies. Finally, the analysis of longitudinal EEG data in the INSIGHT-preAD cohort will be most interesting to monitor evolution of EEG metrics during follow-up, especially in patients who will cognitively decline and evolve to prodromal Alzheimer's disease.



To conclude, our work identified several EEG biomarkers that are effective indices of Alzheimer's disease topography-specific neurodegeneration. As these EEG biomarkers are modulated by the degree of severity of amyloid load, they will possibly help to distinguish between different stages of preclinical Alzheimer's disease. Our findings need to be replicated in further studies with a longitudinal analysis of EEG changes to finely assess the temporal evolution of these associations.

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## Competing interests

S.E. has received honoraria as a speaker or consultant for Eli Lilly, Biogen, Astellas Pharma, Roche and GE Healthcare. The other authors do not report any conflicts of interest.

## Supplementary material

Supplementary material is available at *Brain* online.

## Appendix

### INSIGHT-preAD study group

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A complete listing of MEMENTO study group members can be found at: [https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5576287/bin/13195\\_2017\\_288\\_MOESM3\\_ESM.docx](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5576287/bin/13195_2017_288_MOESM3_ESM.docx)

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