Neurobiology of Aging 57 (2017) 133–142

Contents lists available at ScienceDirect

Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging

EEG spectral analysis as a putative early prognostic biomarker in nondemented, amyloid positive subjects

Alida A. Gouw [a,b,*], Astrid M. Alsema [a,b], Betty M. Tijms [a], Andreas Borta [c], Philip Scheltens [a], Cornelis J. Stam [b], Wiesje M. van der Flier [a,d]

[a] Alzheimer Center and Department of Neurology, Neuroscience Campus Amsterdam, VU University Medical Center, Amsterdam, the Netherlands
[b] Department of Clinical Neurophysiology and MEG Center, Neuroscience Campus Amsterdam, VU University Medical Center, Amsterdam, the Netherlands
[c] Boehringer Ingelheim Pharma GmbH Co KG, Ingelheim am Rhein, Germany
[d] Department of Epidemiology and Biostatistics, Neuroscience Campus Amsterdam, VU University Medical Center, Amsterdam, the Netherlands

ARTICLE INFO

Article history:
Received 5 May 2016
Received in revised form 15 May 2017
Accepted 23 May 2017
Available online 1 June 2017

Keywords:
Electroencephalography
Prognostic biomarker
Clinical progression
Alzheimer's disease
Amyloid beta

ABSTRACT

We studied whether electroencephalography (EEG)-derived measures of brain oscillatory activity are related to clinical progression in nondemented, amyloid positive subjects. We included 205 nondemented amyloid positive subjects (63 subjective cognitive decline [SCD]; 142 mild cognitive impairment [MCI]) with a baseline resting-state EEG data and ≥1-year follow-up. Peak frequency and relative power of 4 frequency bands were calculated. Relationships between normalized EEG measures and time to clinical progression (conversion from SCD to MCI/dementia or from MCI to dementia) were analyzed using Cox proportional hazard models. One hundred eight (53%) subjects clinically progressed after 2.1 (IQR 1.3–3.0) years. In the total sample, none of the EEG spectral measures were significant predictors. Stratified for baseline diagnosis, we found that in SCD patients higher delta and theta power (HR [95% CI] = 1.7 [1.0–2.7] resp. 2.3 [1.2–4.4]), and lower alpha power and peak frequency (HR [95% CI] = 0.5 [0.3–1.0] resp. 0.6 [0.4–1.0]) were associated with clinical progression over time. In amyloid positive subjects with normal cognition, slowing of oscillatory brain activity is related to clinical progression.

1. Introduction

Alzheimer's disease (AD) develops gradually over the course of 15–20 years. One of the first pathological changes of the disease is the accumulation of amyloid beta in the brain, which starts many years before the appearance of first symptoms of cognitive decline (Jack et al., 2013). Identifying subjects in the earliest stages of the disease offers the opportunity to apply potential preventive measures, before neurodegeneration and synapse loss are irreversible. Recent research criteria have taken amyloid-β 1-42 concentration in CSF and amyloid PET imaging into account to support the diagnosis of AD in subjects with and without dementia (Albert et al., 2011; Dubois et al., 2014; McKhann et al., 2011; Sperling et al., 2011).

Synaptic dysfunction resulting from synaptic toxicity of amyloid beta supposedly occurs early in the cascade of events eventually leading to cognitive decline and dementia (Palop and Mucke, 2010; Selkoe, 2002; Sperling et al., 2013). The most clinically relevant method to capture in vivo synaptic functioning is electroencephalography (EEG) that directly measures postsynaptic dendritic currents of synchronized cortical neurons. Previous EEG studies in patients with dementia due to AD show a gradual diffuse slowing of brain electrical activity reflected by theta power increases and beta power decreases, followed in later stages by a decrease in alpha power and increase in delta power (de Haan et al., 2008; Jeong, 2004; van Straaten et al., 2014). At the mild cognitive impairment (MCI) stage, EEG abnormalities are intermediate between healthy controls and dementia patients (Kwak, 2006; van der Hiele et al., 2007). Several longitudinal studies in MCI have suggested that EEG measures are associated with incident clinical progression over 1–3 years (Huang et al., 2000; Jelic et al., 2000; Luckhaus et al., 2008). In subjects with subjective cognitive decline, only one study has been performed and reported prediction of decline to MCI by several spectral and covariance measures, predominantly in the theta band (Prichep et al., 2006). However, these studies did not take into account the underlying pathology, in particular amyloid status, in their study populations, so it remains unclear if these

* Corresponding author at: Alzheimer Center and Department of Neurology, VU University Medical Center, Department of Clinical Neurophysiology and MEG Center, VU University Medical Center, PO Box 7057, 1007 MB Amsterdam, the Netherlands. Tel.: +31 20 444 0722; fax: +31 20 444 4816.
E-mail address: AA.Gouw@vumc.nl (A.A. Gouw).

0197-4580/$ – see front matter © 2017 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.neurobiolaging.2017.05.017

subjects belonged to the AD pathophysiological continuum at all. To answer questions about prognosis in the nondementia phases of AD, it is therefore crucial to select subjects who have biomarker proof of underlying Alzheimer's pathology (Giannakopoulos et al., 2009; Sperling et al., 2011).

Although it has been demonstrated that subjects with positive amyloid markers in the preclinical and MCI stages have an increased risk to develop dementia compared with amyloid negative subjects (Van Harten et al., 2013), relationships with severity of impairment are modest and its prognostic value for predicting time to dementia is quite limited (Prestia et al., 2015; van Rossum et al., 2012b). Additional markers sensitive enough to predict cognitive decline are required. For the effective design of prevention trials in AD that are targeted against amyloid pathology, these prognostic markers and the selection of subjects with proven amyloid pathology are crucial (Hampel et al., 2011).

Here, we studied in nondemented subjects with an amyloid positive biomarker status, whether EEG-derived measures of brain oscillatory activity are associated with clinical progression. We hypothesized that diffuse slowing of oscillatory activity, reflected by increased relative power in the lower frequency bands (theta and delta) and decreased relative power in higher frequency bands (alpha and beta), is related to clinical progression.

2. Methods

2.1. Subjects

We included 205 nondemented, amyloid positive subjects from the Amsterdam Dementia Cohort (van der Flier et al., 2014). All subjects were referred to the Alzheimer Center between February 2001 and January 2014. They underwent a standardized screening including medical history, informant based history, physical and neurological examination, neuropsychological evaluation, EEG, magnetic resonance imaging, laboratory tests, and lumbar puncture. All diagnoses were made in a multidisciplinary consensus meeting and were based on the full standardized diagnostic work-up. Follow-up visits were generally performed annually. The large majority of these visits consisted of a standardized neuropsychological assessment and a neurological evaluation and diagnoses were re-evaluated in a multidisciplinary meeting. Inclusion criteria for the present study were: (1) amyloid positivity defined as CSF amyloid-β 1-42 $<$640 pg/mL (Zwan et al., 2014); (2) diagnosis of subjective cognitive decline (SCD) or mild cognitive impairment (MCI) using the standard diagnostic criteria (Albert et al., 2011; Jessen et al., 2014); (3) at least 1 year follow-up; and (4) availability of a 20-minute resting-state EEG at baseline. Exclusion criteria were: a medical history of other significant neurological disorders (e.g., current epilepsy, lobar infarcts/hemorrhages, and severe brain trauma) or psychiatric disorders (e.g., autism, schizophrenia), current use of acetylcholinesterase inhibitors, antipsychotic drugs, lithium, anti-epileptic drugs, or neuropathic pain medication. Primary end point was clinical progression, defined as a conversion from SCD at baseline to MCI or dementia at follow-up or conversion from MCI at baseline to dementia at follow-up. We also included a group of amyloid negative patients (CSF amyloid-β 1-42 $\geq$640 pg/mL) with similar inclusion and exclusion criteria. All subjects gave written informed consent for the storage of their examinations in a local database and for use of their data for research purposes. The ethical review board of the VU University Medical Center approved the study.

2.2. CSF analysis

CSF samples were collected by lumbar puncture between the L3/L4, L4/L5, or L5/S1 intervertebral space by a 25-gauge needle and syringe and collected in polypropylene tubes. CSF biomarker analyses were performed at the Neurochemistry laboratory of the department of Clinical Chemistry of the VUmc. Amyloid-β 1-42 (Aβ42), total tau, and tau phosphorylated at threonine 181 (p-tau) concentrations are measured with sandwich ELISAs (Innotest, beta-amyloid1-42, Innotest hTAU-Ag and Innotest PhosphoTAU-181p, Innogenetics, Belgium).

2.3. EEG

At baseline, a 20-minute resting-state EEG was recorded at 21 electrode positions of the 10–20 system. Three EEG-systems were used over the years: Nihon Kohden digital EEG equipment (EEG 2100; Nihon Kohden, Tokyo, Japan), and 2 versions of OSG digital equipment (BrainLab and BrainRT, OSG b.v., Rumst, Belgium). EEGs were recorded against an average reference including all electrodes, with the following order of channels: Fp2/Fp1, F8/F7, F4/F3, A2/A1, T4/T3, C4/C3, T6/T5, P4/P3, O2/O1, Fz, Cz, Pz. Sample frequency of these EEG recordings was 200 Hz (Nihon Kohden) or 500 Hz (BrainLab and BrainRT). Filter settings were: time constant 1 second (Nihon Kohden and BrainLab) or 0.6 seconds (BrainRT), low pass filter 70 Hz (Nihon Kohden and BrainLab) or 100 Hz (BrainRT) and no notch filter (all). Analog to digital conversion precision was 12 bit (Nihon Kohden and BrainLab) or 20 bit (BrainRT). Electrode impedance was kept below 5 kOhm. Patients were seated in a slightly reclined chair in a sound attenuated but fully lit room and were instructed to keep their eyes closed and stay awake. EEG technicians monitored the recording carefully and alerted the patients by sound stimuli at first signs of drowsiness. Based on the knowledge that at least 4 epochs per subject are needed to obtain stable values of quantitative EEG measures (Engels et al., 2015; Nuwer, 1988; van Diessen et al., 2015), we selected 5 epochs per subject (2048 samples; 10.2 seconds per epoch [Nihon Kohden] or 4096 samples; 8.2 seconds per epoch [BrainLab and BrainRT]). All epochs were selected by visual inspection by a trained EEG researcher (AA), based on the presence of a minimum of artifacts (e.g., excessive muscle activity, eye blinks) and drowsiness and were rated on quality: score 1 = no eye movement, muscle, signs of drowsiness or other artifacts; 2 = minimal presence of artifacts; 3 = moderate presence of artifacts; 4 = strong presence of artifacts. All epochs with a score 3 and 4 were evaluated by another rater (AG). If no consensus on sufficient quality was reached, the epochs were replaced by other epochs or the EEG was excluded from analyses. During this standard epoch selection procedure (Jobert et al., 2012; van Diessen et al., 2015), the investigator was blinded for baseline diagnosis and follow-up status.

2.4. EEG spectral analyses

EEG spectral analyses were performed with open-access software BrainWave (version 0.9.151.5, developed by CS; available at http://home.kpn.nl/stam7883/brainwave.html). Relative power in 5 standard frequency bands (delta: 0.5–4 Hz, theta: 4–8 Hz, alpha: 8–13 Hz, beta: 13–30 Hz, gamma: 30–48 Hz) and peak frequency (Hz; dominant frequency between 4–13 Hz) were calculated at each electrode using Fast Fourier Transformation. The gamma band was excluded for further analysis because EEG signal in this band is significantly contaminated with muscle artifacts (Whitham et al., 2007). EEG values of the 5 epochs per subject were averaged to obtain values at subject level. Global EEG measures were calculated by averaging values of all 21 electrodes. EEG measures at lobar level were obtained by averaging FP1, FP2, F3, F4, F7, F8, and Fz for the frontal lobes, C3, C4, and Cz for the central region, P3, P4, Pz for the parietal lobes, T3, T4, T5, T6, A1, and A2 for the temporal lobes, and O1 and O2 for the occipital lobes.