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EEG epochs with less alpha rhythm improve discrimination of mild Alzheimer's

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ABSTRACT

Background and objective: Eyes-closed-awake electroencephalogram (EEG) is a useful tool in the diagnosis of Alzheimer's. However, there is eyes-closed-awake EEG with dominant or rare alpha rhythm. In this paper, we show that random selection of EEG epochs disregarding the alpha rhythm will lead to bias concerning EEG-based Alzheimer's Disease diagnosis.
Methods: We compared EEG epochs with more than 30% and with less than 30% alpha rhythm of mild Alzheimer's Disease patients and healthy elderly. We classified epochs as dominant alpha scenario and rare alpha scenario according to alpha rhythm (8–13 Hz) percentage in O1, O2 and Oz channels. Accordingly, we divided the probands into four groups: 17 dominant alpha scenario controls, 15 mild Alzheimer's patients with dominant alpha scenario epochs, 12 rare alpha scenario healthy elderly and 15 mild Alzheimer's Disease patients with rare alpha scenario epochs. We looked for group differences using one-way ANOVA tests followed by post-hoc multiple comparisons ($p < 0.05$) over normalized energy values (%) on the other four well-known frequency bands (delta, theta, beta and gamma) using two different electrode configurations (parieto-occipital and central).
Results: After carrying out post-hoc multiple comparisons, for both electrode configurations we found significant differences between mild Alzheimer's patients and healthy elderly on beta- and theta-energy (%) only for the rare alpha scenario. No differences were found for the dominant alpha scenario in any of the five frequency bands.
Conclusions: This is the first study of Alzheimer's awake-EEG reporting the influence of alpha rhythm on epoch selection, where our results revealed that, contrarily to what was most likely expected, less synchronized EEG epochs (rare alpha scenario) better discriminated mild Alzheimer's than those presenting abundant alpha (dominant alpha scenario). In addition, we find out that epoch selection is a very sensitive issue in qEEG research. Consequently, for Alzheimer's studies dealing with resting state EEG, we propose that epoch selection strategies should always be cautiously designed and thoroughly explained.
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1. Introduction

1.1. *Dementia in modern life*

Dementia currently affects more than 25 million people in the world, most suffering from Alzheimer's disease (AD). In both developed and developing nations, Alzheimer's disease has had tremendous impact on affected individuals, caregivers, and society [1]. Moreover, AD has recently been ranked as the third most expensive disease and the sixth leading cause of death in the United States [2]. In 2012, the World Health Organization (WHO) stated that between 60% and 70% of dementia cases around the world were due to AD, making it the most common form of dementia. Notwithstanding, there is not an ideal biomarker to define AD, and definitive diagnosis can only be established on autopsy or biopsy [3]. As such, it called for improved and early diagnosis, as well as better care and support for patients, their families, and caregivers [4].

1.2. *EEG in the diagnosis of AD*

In this context, eyes-closed resting-state (task-free) electroencephalogram (EEG) has emerged as a reliable tool for diagnosis of cortical disorders such as AD [5–8]. EEG is relatively inexpensive [6], widely available, stable over time, and patient friendly [9]. Most common findings in EEG of AD patients are decrease in alpha and beta power [10], increase in slow rhythms [11] and increase in theta/alpha ratio [12]. Notwithstanding, EEG can show ambiguous results in early stages of AD [13,14]. Curiously, most controlled trials using EEG do not report enough details on epoch selection, trial design and execution to assess the risk of bias.

1.3. *Epoch selection in AD EEG studies*

Before performing a detailed EEG analysis at rest, it has to be specified how many seconds of recordings will be used later on, and a criterion has to be set down according to which data will be selected for further analysis [15]. Sadly, information on how EEG signal segments (called epochs) were selected is not fully detailed in most studies involving AD quantitative electroencephalography (qEEG), which means carrying out an in depth analysis of EEG signals using computer programs. In fact, despite the enormous volume of valuable information produced by the qEEG literature, there is neither an internationally accepted methodology to epoch selection nor standards of rhythm inclusion in epochs. Even well written papers do not explain EEG epoch selection properly. Some authors make reports concerning the rhythms and scalp locations they used, but tell nothing about epochs duration [16]; others simply said the procedures they used have been described elsewhere [17]. In other studies, statements are made regarding the absence of artifacts in the selected EEG data, confirmed by experts in the field, but no further details were given about the rhythms existent in the signals [18–20].

None of the above-mentioned studies provide detailed information concerning epoch selection criteria. Shockingly, sometimes epoch selection is not even cited [21–23]. Detailing of epoch selection methodology not only explains and clarifies the results, but also contributes to bias prevention. As a rule, we study Alzheimer's EEGs recordings obtained from subjects awake, eyes closed, resting comfortably in a semi-darkened, electrically shielded, sound attenuated room. Unfortunately, even when these ideal conditions are fulfilled in a patient completely awake, ordinary neurophysiologic issues can subject qEEG epoch selection to bias. Errors in epoch selection may occasionally occur due to biologic and non-biologic artifacts or intra- and inter-individual differences in generation of intrinsic cortical rhythmicity [24]. Other important sources of epoch selection error are cortical neuronal feedback loops from the thalamus [25,26] and the reticular activating system [27,28] that modulates fluctuations in consciousness.

1.4. *Epoch selection: the role of alpha rhythm and its intra- and inter-individual variability*

The International Federation of Societies for Electroencephalography and Clinical Neurophysiology (IFSECN) proposed that the term alpha rhythm must be restricted to rhythms from 8 to 13 Hz occurring during wakefulness, over posterior regions, generally showing higher voltage over occipital areas. Amplitude is variable but is mostly below 50 μV in adults. Alpha rhythm is best seen with eyes closed and under conditions of physical relaxation and relative mental inactivity. It is blocked or attenuated by attention due to visual, auditory, tactile, and other somatosensory stimuli or mental effort [29]. Also, according to Davis and Davis [30] there are four types of records regarding alpha activity: (a) dominant when alpha is present in more than 75% of the time record (found in 20% of healthy adults); (b) subdominant when alpha is present in <75% and >50% of the recording time (35% of healthy adults); (c) mixed when the alpha rhythm is present in <50% and >25% of the time record (20% of healthy adults); and (d) rare when alpha is present in less than 25% of the recording time (25% of healthy adults).

This classification accounts for the percent time of alpha appearance in occipital regions. Alpha rhythm also can be classified as M for minus or minimal, P for persistent, and R for responsive [31]. The P type shows no real persistence of alpha, but has a very short blocking response to eye opening. Another type of alpha rhythm is the "monotonous high voltage alpha," which shows little or no amplitude waxing and waning. Small differences in male and female EEG have also been reported [24]. Additionally, according to Palmore [32], the dominant posterior rhythm can also be classified as follows: (1) Alpha activity (A): between 8.5 and 12.5 cycles per second (c/s) and amplitude greater than 15 μV; (2) Low–voltage fast activity (LVF): observable activity predominantly fast and less than 15 μV in amplitude, with little or no alpha activity; (3) Diffuse fast activity (DF): between 13 and 30 c/s and greater than 20 μV in amplitude; and (4) Diffuse slow activity (DS): 8 c/s or slower and amplitude greater than 20 μV.

Consequently, the eyes-closed resting-awake EEG signal can characterize different neurophysiological conditions over time, and the alpha rhythm plays a key role in the differentiation between these situations. The aim of this study is to present a better methodology to EEG epoch selection. More specifically, herein we investigate whether the percentage of alpha

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