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A quantitative EEG and MRI analysis of intermittent temporal slowing in the elderly

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ABSTRACT

Objective: Whereas the correlation between diffuse slowing of EEG activity and neurodegenerative diseases such as Alzheimer’s disease is well established, intermittent slowing over the temporal regions, which is a frequent finding in the elderly, does not have a specific clinical correlate. In this study, we compared quantitative EEG parameters between patients with temporal slowing with no signs of neurological disease and controls to evaluate cortical function in the temporal lobes and other cerebral regions. We also compared the width of the temporal lobes on magnetic resonance imaging (MRI).

Methods: Mean dominant frequency and relative power in delta, theta, alpha, and beta frequency bands were examined in 20 patients older than 60 years with intermittent temporal slowing and 20 age-matched controls without significant lesions on MRI or medical conditions known to affect the EEG. Furthermore, the correlation between the frequency of temporal slowing and the mean dominant frequency and the width of the medial temporal lobes on MRI were examined.

Results: Mean dominant frequency and the relative power in the beta frequency band was lower in patients with temporal slowing than in controls in all of the cortical regions examined. No significant correlation was found between the frequency of slowing and the mean dominant frequency. There was no significant difference in the width of the medial temporal lobes.

Conclusions: Intermittent temporal slowing was correlated with diffusely reduced mean dominant frequency and a shift in relative power to lower frequency bands.

Significance: The results suggest that subclinical diffuse cerebral pathology may be present in subjects with intermittent temporal slowing, but prospective studies including tests of cognitive function, cerebral perfusion, metabolic status, and advanced neuroimaging should be conducted. © 2018 International Federation of Clinical Neurophysiology. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0).

1. Introduction

Intermittent slowing over the temporal regions is very frequently observed in the electroencephalograms (EEGs) of elderly subjects with neither cerebral structural lesions nor other signs of neurological disease. A prevalence of 43% in subjects aged 60–79 years (Hughes and Cayaffa, 1977) and 50% in healthy subjects older than 65 years (Oken and Kaye, 1992) has been reported. Little is known about the underlying mechanism, and it is not known whether this phenomenon is a benign trait related to normal aging or whether it may be a precursor for e.g. neurodegenerative diseases.

Quantitative EEG methods developed during the past decades have shown that increased theta and delta activity, especially in tempo-parietal and central regions, has been associated with impaired learning ability (Hartikainen et al., 1992), cognitive disability in general (Prichet al., 1994), and conversion to Alzheimer’s disease (AD) (Prichet al., 2007) in healthy elderly. Ageing itself is not correlated to changes in relative EEG power in delta or theta frequency bands (Koyama et al., 1997). In contrast, it is not clear whether or not intermittent slowing over the temporal regions identified visually in routine EEG has similar clinical correlates and this question has not specifically been addressed using quantitative EEG methods.

The main objective of this retrospective study was to compare the mean dominant frequency and relative power within defined frequency bands of the background activity over the occipital, parietal, temporal, and frontal regions in resting state EEG between patients with bilateral focal slowing in the delta range over the
temporal regions and age-matched controls. Patients with slowing in the delta range, and not in the theta range, which is more prevalent in healthy elderly, were examined, as this activity would more likely be correlated to cerebral pathology. We hypothesized that either focal pathology in the temporal lobes or diffuse cerebral pathology, such as preclinical AD or other amyloid related disease, would be reflected in changes in these parameters over the temporal regions or diffusely, respectively. As is the case for intermittent slowing over the temporal regions, cerebral amyloid positivity is highly prevalent in subjects with normal cognition, ranging from approximately 10% at age 50 to approximately 23% at age 70 and 44% at age 90 (Jansen et al., 2015). Second, we examined if there was a correlation between the degree (frequency) of focal slowing and the mean dominant frequency, which would support the hypothesis of an underlying pathology. Third, the width of the medial temporal lobes was compared to controls. A reduced width could suggest pathology in the temporal lobes and it has been shown that temporal lobe atrophy is related to amyloid pathology and AD (Dore et al., 2013).

2. Methods

2.1. Identification of patients and controls

The conclusions of standard 30 min outpatient EEGs recorded between January 2012 and December 2016 at Odense University Hospital in patients older than 60 years, for whom diagnostic work up showed no signs of neurological disease were examined with the aim of obtaining EEGs from 20 patients with temporal slowing and 20 age matched controls. EEGs had been recorded on a NicoletONe Neurodiagnostic system (Natus Neurology, Middleton, USA) according to the international 10–20 system using an average reference (all active electrodes) and a ground electrode on the forehead. Medical records including the results of cerebral MRI, medication and chronic medical conditions were reviewed. We excluded patients with cerebral, cerebellar or brain stem structural lesions including white matter lesions graded Fazekas 2 or Fazekas 3, use of medications known to affect the EEG, e.g. benzodiazepines, or chronic medical conditions known to affect the EEG, e.g. renal or hepatic failure or epilepsy. Next, the EEG was reviewed to verify the nature of the focal slowing (Fig. 1), which should occur exclusively over the temporal regions, asynchronously on both the left and the right side within the delta range and not be obviously related to drowsiness and exclude any other pathology such as diffuse slowing or epileptiform discharges. Patients with an EEG characterized by very low voltage or abundant artefacts were excluded. Twenty-three patients with slowing and 24 controls were identified and three patients with slowing and four controls were then excluded in order to adjust the age and sex of the two groups to comparable levels. Patient characteristics are presented in Table 1.

2.2. Estimation of the frequency of temporal slowing

In patients with temporal slowing, the frequency of focal slowing was quantified by calculating the number of potentials within the delta frequency range per minute after visual inspection of the EEGs.

Table 1

| Patient characteristics                   | Temporal slowing | Controls |
|------------------------------------------|------------------|----------|
| Sex (female/male)                        | 10/10            | 11/9     |
| Age (years, mean/median)                 | 70.5/71          | 70.5/69  |
| Any current medication (patients)        | 16               | 14       |
| Smoking (patients)                       |                  |          |
| - Current                                | 3                | 7        |
| - Previous                               | 4                | 3        |
| - Never                                  | 13               | 10       |
| Indication for EEG (patients)            |                  |          |
| - Syncope                                | 12               | 10       |
| - Transient sensory symptoms             | 4                | 4        |
| - Transient amnesia                      | 2                | 2        |
| - Other                                  | 2                | 4        |
| MRI                                      |                  |          |
| - Normal                                 | 5                | 6        |
| - White matter lesions (unspecifc)       | 15               | 14       |

Fig. 1. An example of intermittent slowing in the delta frequency range occurring independently over the left and right temporal regions included in the study.
entire standard EEG. Epochs with duration of approximately 15 s were inspected individually and the number of potentials in the delta frequency range over the temporal regions noted. The total number of potentials was then divided by the duration of the entire standard EEG, which was approximately 30 minutes. The lateralisation of the potentials was also noted.

2.3. Calculation of mean dominant frequency and relative power

The EEGs were analysed quantitatively using the NicoletOne nEEG v5.94.1.534 EEG reader. EEGs were reviewed visually to identify the first 100 seconds in which the patient had closed eyes and no focal slowing, major artefacts, or signs of drowsiness occurred, typically in the first part of the recording when the patient was instructed to close the eyes. This segment of the EEG was then used for analysis of mean dominant frequency and relative power of delta, theta, alpha, and beta frequency bands. The mean dominant frequency was calculated as

\[
\bar{f} = \frac{\sum_{i=1}^{n} f_i S_i}{\sum_{i=1}^{n} S_i}
\]

where \( f_i \) = frequency i; \( S_i \) = power of frequency i; \( n \) = the number of frequencies) using the frequency band 1-25.6 Hz, a frequency resolution of 0.25 Hz, based on fast fourier transformation following linear detrending. The relative power of delta (0.5–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), and beta (13–30 Hz) frequency bands was calculated as the percentage of absolute power in each of the frequency bands relative to the total absolute power. Mean dominant frequency and relative power was determined for each of the bipolar derivations P3-P4, O1-P3, O2-P4, O1-T3, O2-T4, T3-T5, T4-T6, F7-T3, F8-T4, F3-F2, and F4-Fz.

2.4. Measurement of the medial temporal lobe

MRIs were retrieved from the hospital digital radiology system (GE Centricity Enterprise) and coronal sections at the midbrain level were identified. To assess hippocampal atrophy, the linear minimal width of the medial temporal lobe (MTL) was determined using the software included in the radiology system (Fig. 2). This measure has previously been used to estimate atrophy of the MTL (Gao et al., 2003). Measurement was not technically feasible in 5 patients with temporal slowing and 3 controls because appropriately oriented coronal sections at the midbrain level were not available.

2.5. Statistical analysis

The Shapiro-Wilk normality test was applied to the mean dominant frequency, relative power and width of the medial temporal lobe in both patients with temporal slowing and controls to examine if the data were normally distributed and parametric statistical test could be used. The data for the width of the temporal lobe were normally distributed, but this was not the case for several derivations for mean dominant frequency and relative power. Comparison of mean dominant frequency and relative power between patients and controls was consequently performed using the non-parametric Wilcoxon rank-sum (Mann-Whitney) test whereas the width of the temporal lobe was compared using a one-sided unpaired t-test. As multiple comparisons were performed (11 for the mean dominant frequency and 36 for the relative power) the level of statistical significance was additionally corrected using the Bonferroni method dividing the desired level of p < 0.05 by the number of comparisons. The relation between the frequency of temporal slowing, calculated as the number of potentials in the delta range per minute as described in Section 2.3, and the mean dominant frequency was examined using linear regression. Statistical analyses were performed using Stata version 13.1 (StataCorp).

2.6. Approvals

The Danish Patient Safety Authority (case ref. 3-3013-1303/1) and the Danish Data Protection Agency approved the study.

3. Results

3.1. Frequency of temporal slowing

The mean frequency of temporal slowing (number of potentials per minute) was 1.5 (range 0.3 to 4.6). Slowing was more frequent on the left than the right side in 15 of 20 patients, and the overall ratio between the frequency on the left and the right sides was 1.7.

3.2. Mean dominant frequency analysis

Mean dominant frequency was lower in patients with temporal slowing than in controls in all (parietal, occipito-parietal, occipito-temporal, temporal, and frontal) regions (Fig. 3). However, the difference only reached statistical significance (P < 0.05) in the occipito-temporal, temporal, and fronto-temporal regions bilaterally. Considering a level of significance adjusted for multiple comparisons, a significant difference was only found in the left temporal region. The smallest absolute difference was found in the O2-P4-derivations (9.6 vs. 10.0 Hz) and the largest absolute difference in the F8-T4-derivation (8.6 vs. 10.2 Hz) and in general differences were larger in anterior than posterior regions. The lowest mean dominant frequency (8.0 Hz) was found in the F7-T3 derivation of patients with temporal slowing reflecting that all results were in the alpha frequency band.

3.3. Relative power analysis

The primary finding was a reduction in the relative power in the beta frequency band in patients with temporal slowing compared to controls in all regions. The difference between groups reached statistical significance in most regions (the occipito-temporal and temporal regions bilaterally, and the right occipito-parietal region) (Table 2). Considering a level of significance adjusted for multiple comparisons, no significant difference was found. Relative power in delta and theta frequencies were increased in patients with temporal slowing compared to controls in most regions (parietal, occipito-temporal, temporal, and frontal), while increased power in the theta and alpha frequency bands was found in the occipito-parietal region. The differences were not significant after adjusting for multiple comparisons.
3.4. Correlation between frequency of temporal slowing and mean dominant frequency

No significant correlation was found between the frequency of temporal slowing defined as the number of potentials per minute and the mean dominant frequency for any of the regions (data not shown). The distributions of the frequency of temporal slowing and mean dominant frequency for the derivation T3–T5, which was the one with the strongest correlation ($p = 0.07$), is presented in Fig. 4.
and Parkinson's disease (Soikkeli et al., 1991), but this finding is not specific as it is also seen in encephalopathies caused by e.g. hypoglycemia (Remvig et al., 2012). Reduced power in the beta frequency band reflecting a general shift to lower frequencies has been found to be a reliable marker for AD in several studies (Jeong, 2004). It is believed to be primarily related to cholinergic deficiency as acetylcholine is involved in desynchronization of the EEG and cholinergic drugs partly reverse EEG abnormalities in AD. The finding, however, is not specific to AD and is also seen in vascular dementia (Neto et al., 2015).

It is a limitation that we have sparse clinical information, especially regarding the cognitive performance of patients, including symptoms of mild cognitive impairment, and that we have no information regarding cerebral perfusion, e.g. the incidence of carotid stenosis or occlusion or the metabolic status including blood glucose. As a result we cannot exclude that temporal slowing and our findings of reduced dominant frequency reflect subclinical cerebral hypoperfusion or hypoglycaemia. In fact, previous studies (Hubbard et al., 1976; Inui et al., 2001) speculated that temporal slowing may be caused by atherosclerosis and cerebral hypoperfusion, but this hypothesis has not been tested in prospective studies. A higher prevalence of stenosis of the internal carotid artery on the left side could explain the findings of a higher prevalence of temporal slowing on this side, also found by Torres et al. (1983), which was replicated in the present study.

Neuropsychological function was examined in previous studies, but the results were conflicting as one study (Visser et al., 1987) found that verbal fluency was reduced, whereas other studies (Busse et al., 1956; Oken and Kaye, 1992) found no psychological dysfunction. A small, controlled follow-up study of patients with intermittent slowing (Shigeta et al., 1995) found no correlation with MRI changes or neuropsychological decline, but slowing occurred rather infrequently and almost exclusively in the fast theta range.

In conclusion, the results of this retrospective study suggest that temporal slowing may be related to mild, diffuse cerebral dysfunction, which is most pronounced over the temporal regions.

Prospective studies in healthy elderly subjects including repeated extensive testing of cognitive functions, cerebral perfusion, metabolic status, recording of cognitive event related potentials, which are considered sensitive markers for cognitive impairment (Howe, 2014), and MRI measurements of cortical and frontal and ventricular cerebrospinal fluid volumes (Wahlund et al., 1996) are needed to further clarify mechanisms behind and possible neurodegenerative pathophysiological correlations to this phenomenon.

Conflict of interest
None.

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