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Research paper

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.

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 ageing 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 temporo-parietal and central regions, has been associated with impaired learning ability (Hartikainen et al., 1992), cognitive disability in general (Prichep et al., 1994), and conversion to Alzheimer's disease (AD) (Prichep, 2007) in healthy elderly. Ageing in 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

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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

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 (unspecific)	15	14

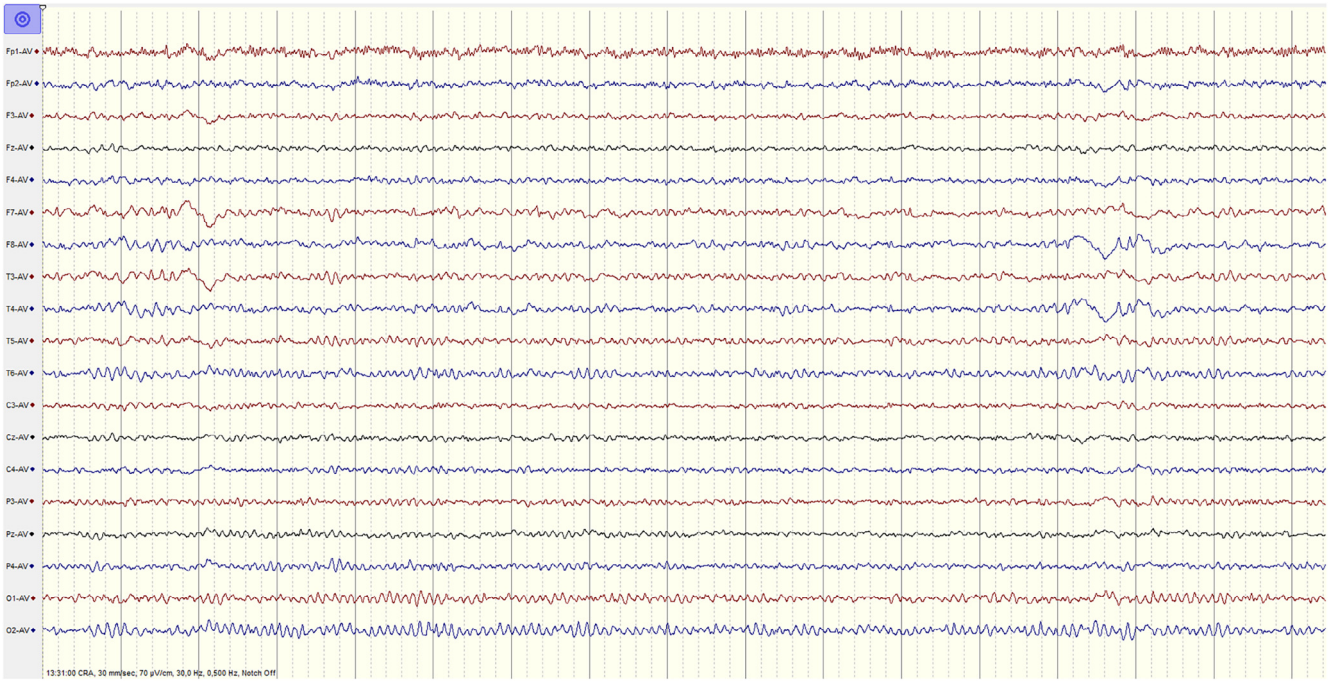

Fig. 1. An example of intermittent slowing in the delta frequency range occurring independently over the left and right temporal regions included in the study.

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 $\sum_{i=1}^{n} fi\ Si / \sum_{i=1}^{n} Si$ (fi = frequency i; Si = 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-Fz, 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).

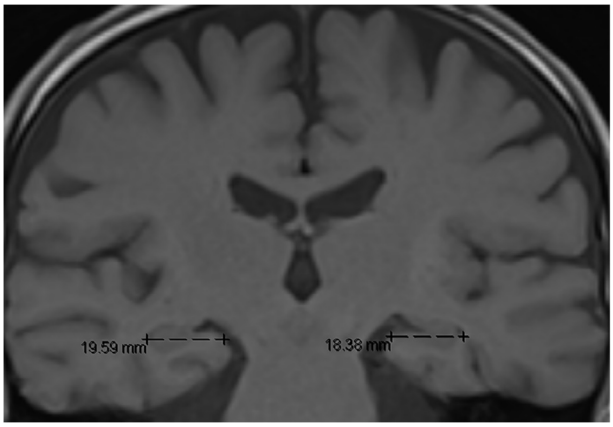

Fig. 2. Measurement of the linear minimal width of the medial temporal lobe at the midbrain level.

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.

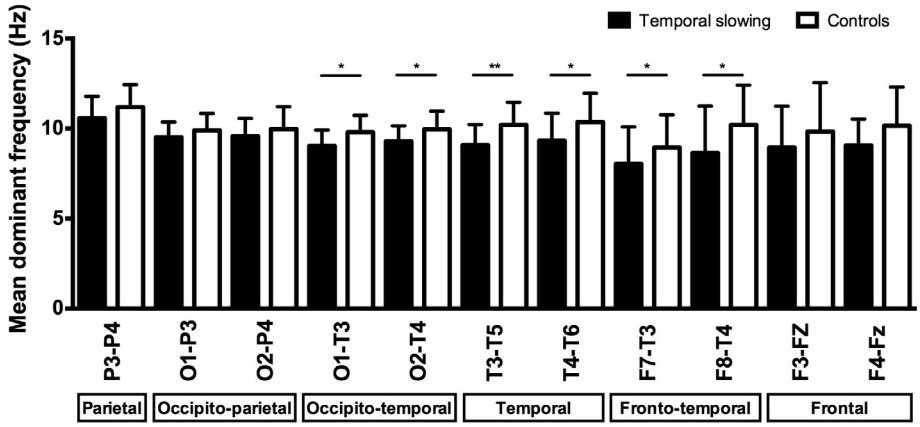

Fig. 3. Mean dominant frequency in cortical regions. Error bars: Standard deviation. $^{*}P < 0.05$; $^{**}P < 0.01$.

Table 2
Relative EEG power in delta, theta, alpha and beta frequency ranges in the parietal, occipito-parietal, occipito-temporal, temporal, and frontal regions.

	Frequency range	Temporal slowing, % (SD)	Controls, % (SD)	P
Parietal region				
P3-P4	Delta	13.6 (5.8)	10.8 (6.5)	0.079
	Theta	14.4 (6.9)	11.3 (6.1)	0.130
	Alpha	45.3 (13.5)	47.6 (14.6)	0.482
	Beta	26.6 (11.7)	30.3 (13.1)	0.372
Occipito-parietal region				
O1-P3	Delta	15.2 (10.5)	15.5 (10.0)	0.725
	Theta	14.5 (8.5)	12.3 (8.2)	0.358
	Alpha	54.9 (18.6)	51.8 (16.8)	0.358
	Beta	15.4 (8.2)	20.4 (10.4)	0.096
O2-P4	Delta	13.7 (6.8)	14.6 (11.5)	0.482
	Theta	13.7 (10.1)	11.9 (7.5)	0.646
	Alpha	58.3 (18.8)	53.5 (17.8)	0.358
	Beta	14.3 (10.0)	20.0 (10.7)	0.037
Occipito-temporal region				
T3-O1	Delta	19.3 (10.2)	16.1 (11.2)	0.234
	Theta	14.8 (8.1)	11.1 (6.9)	0.123
	Alpha	53.3 (19.4)	54.3 (18.0)	0.850
	Beta	12.6 (8.0)	18.4 (8.9)	0.014
T4-O2	Delta	17.8 (8.9)	16.0 (9.6)	0.433
	Theta	13.2 (8.1)	11.0 (6.3)	0.482
	Alpha	56.1 (18.5)	52.9 (16.3)	0.534
	Beta	13.0 (7.6)	20.1 (8.8)	0.011
Temporal region				
T3-T5	Delta	21.3 (9.2)	16.6 (11.5)	0.083
	Theta	17.6 (8.9)	12.3 (7.2)	0.058
	Alpha	45.2 (15.5)	47.3 (18.2)	0.766
	Beta	15.9 (9.6)	23.8 (12.2)	0.028
T4-T6	Delta	19.3 (11.0)	16.4 (11.0)	0.224
	Theta	16.4 (11.3)	11.1 (6.8)	0.137
	Alpha	48.8 (18.1)	47.8 (17.3)	0.746
	Beta	15.5 (11.1)	24.7 (13.7)	0.023
Frontal region				
F3-Fz	Delta	38.9 (15.3)	36.2 (17.4)	0.482
	Theta	16.7 (6.4)	13.1 (5.7)	0.079
	Alpha	20.3 (9.2)	20.8 (11.1)	0.935
	Beta	24.1 (14.4)	29.9 (17.1)	0.344
F4-Fz	Delta	37.6 (13.1)	35.1 (13.5)	0.725
	Theta	16.8 (6.6)	13.1 (6.3)	0.048
	Alpha	20.7 (8.2)	20.1 (8.0)	0.978
	Beta	24.9 (9.3)	31.7 (13.4)	0.144

P: Wilcoxon rank-sum test.

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.

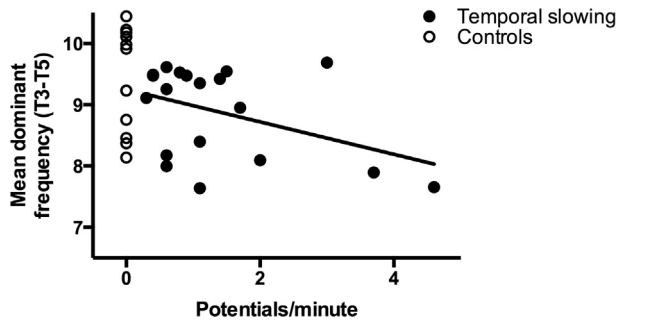

Fig. 4. Relationship between mean dominant frequency and the frequency of intermittent temporal slowing calculated as the number of potentials per minute over the left temporal region (T3–T5), which is the region with the strongest correlation ($p = 0.07$). Mean dominant frequency for controls is presented for comparison.

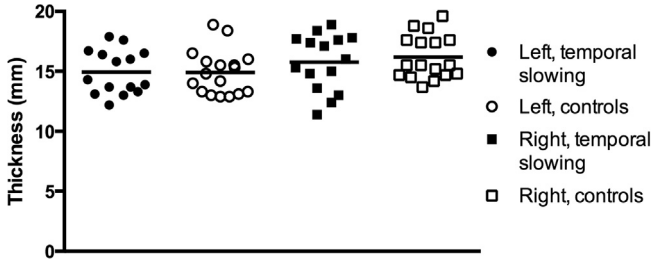

Fig. 5. Linear minimal width of the medial temporal lobe on the left and the right side in patients with intermittent temporal slowing and controls. Horizontal lines indicate mean width.

3.5. Measurement of the medial temporal lobes.

There was no statistically significant difference in mean linear minimal width of the medial temporal lobe between patients with temporal slowing and controls on both the left and the right side (Fig. 5).

4. Discussion

Increased theta and delta activity in the temporal region has previously been correlated to cognitive dysfunction (Hartikainen et al., 1992; Prichep et al., 1994; Prichep, 2007). To our knowledge, this is the first quantitative EEG analysis specifically comparing elderly patients with intermittent slowing in the delta frequency range in the temporal region, identified by visual inspection of standard EEGs, to subjects without slowing. We found that 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. There was a non-significant trend towards a lower mean dominant frequency in patients with a high frequency of temporal slowing. This correlation may have been statistically significant with inclusion of more patients. Comparison of the width of the temporal lobe between patients with and without slowing did not indicate selective atrophy of the temporal lobe. Taken together the results indicate a diffuse, rather than a focal disturbance in patients with temporal slowing.

The major strength of this study is that we were able to identify patients without focal cerebral lesions on MRI or medical conditions, which are known to affect the EEG with intermittent temporal slowing and controls who were highly comparable regarding the reasons for referral to EEG as well as other characteristics.

It is well established that dominant frequency is reduced in neurodegenerative disorders such as AD (Brenner et al, 1988) 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.

References

Brenner, R.P., Reynolds, C.F., Ulrich, R.F., 1988. Diagnostic efficacy of computerized spectral versus visual EEG analysis in elderly normal, demented and depressed subjects. Electroencephalogr. Clin. Neurophysiol. 69, 110–117.

Busse, E.W., Barnes, R.H., Friedman, E.L., Kelty, E.J., 1956. Psychological functioning of aged individuals with normal and abnormal electroencephalograms. J. Nerv. Ment. Dis. 124, 135–141.

Dore, V., Villemagne, V.L., Bourgeat, P., Fripp, J., Acosta, O., Chetelat, G., et al., 2013. Cross-sectional and longitudinal analysis of the relationship be- tween Abeta deposition, cortical thickness, and memory in cognitively unimpaired individuals and in Alzheimer disease. JAMA Neurol. 70, 903–911.

Gao, F.Q., Black, S.E., Leibovitch, F.S., Callen, D.J., Lobaugh, N.J., Szalai, J.P., 2003. A reliable MR measurement of temporal lobe width from the Sunnybrook Dementia Study. Neurobiol. Aging 24, 49–56.

Hartikainen, P., Soininen, H., Partanen, J., Helkala, E.L., Riekkinen, P., 1992. Aging and spectral analysis of EEG in normal subjects: a link to memory and CSF AchE. Acta Neurol. Scand., 148–155

Howe, A.S., 2014. Meta-analysis of the endogenous N200 latency event-related potential subcomponent in patients with Alzheimer's disease and mild cognitive impairment. Clin. Neurophysiol. 125, 1145–1151.
Hubbard, O., Sunde, D., Goldensohn, E.S., 1976. The EEG in centenarians. Electroencephalogr. Clin. Neurophysiol. 40, 407–417.
Hughes, J.R., Cayaffa, J.J., 1977. The EEG in patients at different ages without organic cerebral disease. Electroencephalogr. Clin. Neurophysiol. 42, 776–784.
Inui, K., Motomura, E., Kaige, H., Nomura, S., 2001. Temporal slow waves and cerebrovascular diseases. Psychiat. Clin. Neurosci. 55, 525–531.
Jansen, W.J., Ossenkoppele, R., Knol, D.L., Tijms, B.M., Scheltens, P., Verhey, F.R., et al., 2015. Prevalence of cerebral amyloid pathology in persons without dementia: a meta-analysis. JAMA 313, 1924–1938.
Jeong, J., 2004. EEG dynamics in patients with Alzheimer's disease. Clin. Neurophys. 115, 1490–1505.
Koyama, K., Hirasawa, H., Okubo, Y., Karasawa, A., 1997. Quantitative EEG Correlates of Normal Aging in the Elderly. Clin. Electroencephalogr. 28, 160–165.
Neto, E., Allen, E.A., Aurlien, H., Nordby, H., Eichele, T., 2015. EEG spectral features discriminate between Alzheimer's and vascular dementia. Front. Neurol. 6, 25.
Oken, B.S., Kaye, J.A., 1992. Electrophysiologic function in the healthy, extremely old. Neurology 42, 510–526.
Prichep, L.S., John, E.R., Ferris, S.H., Reisberg, B., Almas, M., Alper, K., et al., 1994. Quantitative EEG Correlates of Cognitive Deterioration in the Elderly. Neurobiol. Aging. 15, 85–90.
Prichep, L.S., 2007. Quantitative EEG and electromagnetic brain imaging in aging and in the evolution of dementia. Ann. NY Acad. Sci. 1097, 156–167.
Remvig, L.S., Elsborg, R., Sejling, A.S., Sørensen, J.A., Sønder Snogdal, L., Folkestad, L., et al., 2012. Hypoglycemia-related electroencephalogram changes are independent of gender, age, duration of diabetes, and awareness status in type 1 diabetes. J. Diabet. Sci. Technol. 6, 1337–1344.
Shigeta, M., Julin, P., Almkvist, O., Basun, H., Rudberg, U., Wahlund, L.-O., 1995. EEG in successful ageing; a 5 year follow-up study from the eighth to ninth decade of life. Electroencephalogr. Clin. Neurophysiol. 95, 77–83.
Soikkeli, R., Partanen, J., Soininen, H., Pääkkönen, A., Riekkinen Sr., P., 1991. Slowing of EEG in Parkinson's disease. Electroencephalogr. Clin. Neurophysiol. 79, 159–165.
Torres, F., Faoro, A., Loewenson, R., Johnson, E., 1983. The electroencephalogram of elderly subjects revisited. Electroencephalogr. Clin. Neurophysiol. 56, 391–398.
Wahlund, L.O., Almkvist, O., Basun, H., Julin, P., 1996. MRI in successful aging, a 5-year follow-up study from the eighth to ninth decade of life. Magn. Reson. Imaging. 14, 601–608.
Visser, S.L., Hooijer, C., Jonker, C., Van Tilburg, W., De Rijke, W., 1987. Anterior temporal focal abnormalities in EEG in normal aged subjects; correlations with psychopathological and CT brain scan findings. Electroencephalogr. Clin. Neurophysiol. 66, 1–7.