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## Left Temporal Neuronal Hyperexcitability as a Predictor of Mild Cognitive Impairment: Clinical and Neurophysiological Study

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### Abstract

**Introduction:** Mild cognitive impairment (MCI) usually is the early stage of dementia which is defined as decreasing in mental abilities such cognition, memory, and speech not too severe to interfere daily activities. MCI diagnosis is rather hard and usually assumed as normal consequences of aging. Diagnosis is usually performed through a combination of extensive testing and eliminations of other possible causes. "Seizures" or neuronal hyperexcitability in the temporal lobe, transiently impair cognition and steadily damage hippocampal circuitry, leading to progressive memory loss.

**Objective:** The objective of this study was demonstrated that EEG pattern abnormalities in the left temporal in healthy subjects, are an early sign of progressive cognitive impairment.

**Material and methods:** This was an clinical and neurophysiology observational study in healthy adults patients with EEG pattern characterized by slow activity in left temporal region. This study lasted three years in total, being divided into two phases: recruitment (for an entire year) and follow-up after 1 year. Admission criteria were checked. The follow-up consisted of neuropsychological assessment with Mini Mental State Examination (MMSE) and MRI scan. Our analysis was based on pooled of patients from neurophysiology department in Italy from February 2010 to July 2013. The EEG activity was recorded continuously from 19 electrodes positioned according to the 10–20 International system.

**Results:** One hundred forty patients were recruited and one hundred thirty completed the 24-month study. Of the ten patients who did not complete the study. In case group we had 60 subjects, 15 males and 45 females with

sharp slow-wave in left temporal region on EEG. In control group we had 70 subjects, 30 males and 40 females with normal EEG. 57 patients (Case) and 33 patients (Controls) showed a mild cognitive impairment (MMSE  $\geq$  23 adjusted for age and education). 49 patients (Case) and 21 patients (Controls) with deep lacunar infarcts or subcortical white matter alterations on MRI scan. Analysis performed according to methods proposed by Koch showed that pattern EEG of slow waves significantly correlated with both variables MCI ( $P < 0.0001$ ) and vascular alterations ( $P < 0.0001$ ).

**Discussion:** In our sample, pattern EEG was predictive for vascular abnormalities and MCI more than 50% after a few years.

**Conclusion:** In summary, typical geographic alterations in left temporal region are "indicators" or "markers" of early cognitive impairment and may be used as prevention strategies. EEG may be considered a useful tool for early diagnosis of MCI. Further translational exploration of these issues in animals and/or humans studies over the coming years will determine new therapeutic approaches directed at selectively suppressing aberrant network excitability in the temporal lobe.

**Keywords:** Mild cognitive impairment; Hippocampal hyper-excitability; Electroencephalogram; Slow waves

### Introduction

The temporal lobe is a structure anatomically connected to the memory, cognitive processes and affectivity and frequently implicated in epilepsy [1]. Temporal lobe epilepsy and mild cognitive impairment are both subject to intensive memory research. Memory problems are a core characteristic of both

conditions and we wonder if there are analogies which would enrich the two distinct research communities [2].

Dementia is a definition for decline in various mental abilities such as memory, speech and cognition severe enough to interfere with daily life [3]. Mild cognitive impairment (MCI) usually is the early stage of dementia which is defined as decreasing in mental abilities such as cognition, memory, and speech not too severe to interfere with daily activities. MCI diagnosis is rather hard and usually assumed as normal consequences of aging [4].

Diagnosis is usually performed through a combination of extensive testing (psychological tests, neurological examination, and magnetic resonance) and eliminations of other possible causes [5].

“Seizures” or neuronal hyper-excitability in the temporal lobe, transiently impair cognition and steadily damage hippocampal circuitry, leading to progressive memory loss, but the mechanisms for hyper-excitability in AD brain are largely unknown.

In the recent years, several research groups have applied different analyzing methods to find some relations between EEG signal and MCI. In patients with sporadic dementia, scalp-recorded EEG patterns typically show abnormalities predominantly composed for slowed background rhythms [6].

Monitoring the mental state contributes both to prevention and monitoring initial symptoms of cognitive impairment will decrease considerably memory complaints and prevent the onset of neurodegenerative diseases. We also state early detection of cognitive impairment will delay dementia and associated illness [7].

## Objective

The objective of this study was evaluated the correlation between EEG pattern abnormalities in the left temporal region and a progressive cognitive impairment.

## Material and Methods

### Study design

This was a clinical and neurophysiology case-control study in healthy adult's patients with EEG pattern characterized by slow activity in left temporal region.

The investigator did not intervene and rather simply “observed” and assessed the strength of the relationship between a risk factor and disease variables [8]. In fact, case-control study usually identifies subjects by outcome status at the outset of the investigation. Once outcome status is identified and subjects are categorized as cases, controls (subjects without the outcome but from the same source population) are selected.

This study lasted three years in total, being divided into two phases: recruitment (for an entire year) and follow-up after 1 year. Admission criteria were checked. The follow-up consisted

of neuropsychological assessment with Mini Mental State Examination (MMSE) and MRI scan.

### Patient population

Our analysis was based on pooled of patients from Neurophysiology Department in Italy from February 2010 to July 2013. These subjects aged between 40 and 60 years and referred to our out-patient department for episodes of loss of consciousness, headache, dizziness.

Inclusion criteria were: 1) adult patients (aged 40-60 years), 2) pattern EEG with slow waves in left temporal; 3) written informed consent.

Exclusion criteria were: 1) brain trauma; 2) brain cancer; 3) severe psychiatric diseases; 4) degenerative neurological disease; 5) brain malformations; 6) history of childhood epilepsy; 6) abnormal values of laboratory screen considered to be of clinical significance; 7) chronic medications; 8) pathological perinatal events; 9) alcohol and substance abuse.

Withdrawal criteria were: withdrawal of informed consent; deterioration in seizure control sufficient to cause clinical concern; other severe illness.

Each subject underwent a pre-inclusion study evaluation that included history, physical examination, EEG and MRI.

**Case group:** Subjects with typical alterations on EEG as sharp slow-wave in the left temporal.

**Control group:** Subjects without specific alterations on EEG.

### Electroencephalogram recording

All EEG signals were recorded in the morning times while subjects resting comfortably in a quiet room with closed eyes. The EEG activity was recorded continuously from 19 electrodes positioned according to the 10–20 International system. Data were recorded using 32 channel digital EEG device with 256 Hz sampling rate (Galileo NT, EBneuro, Italy). Electrodes-skin impedance was set below 5 kΩ.

The recording duration was 30 min because longer recordings would reduce the variability of the data and suppress noise and artifacts, but also possibly increase the slowing of EEG oscillations due to reduced vigilance. Hence, during recording procedure, subjects were been checked out continuously to keep them conscious and avoid drowsiness.

### Statistical analysis

The average was expressed as means  $\pm$  SD. The investigated variables were the number of patients with cognitive impairment and that one with MRI abnormalities among those who were with and without left temporal lesion EEG pattern (LTEP). We dichotomized those as “absent” or “present”. So we examined the univariate odds ratios (ORs) that provided an estimate of the strength of association between LTEP and explored variables.

The odd ratio was calculated with a 95% confidence interval (CI) for both, according to [9] while P-value is calculated according to Sheskin [10].

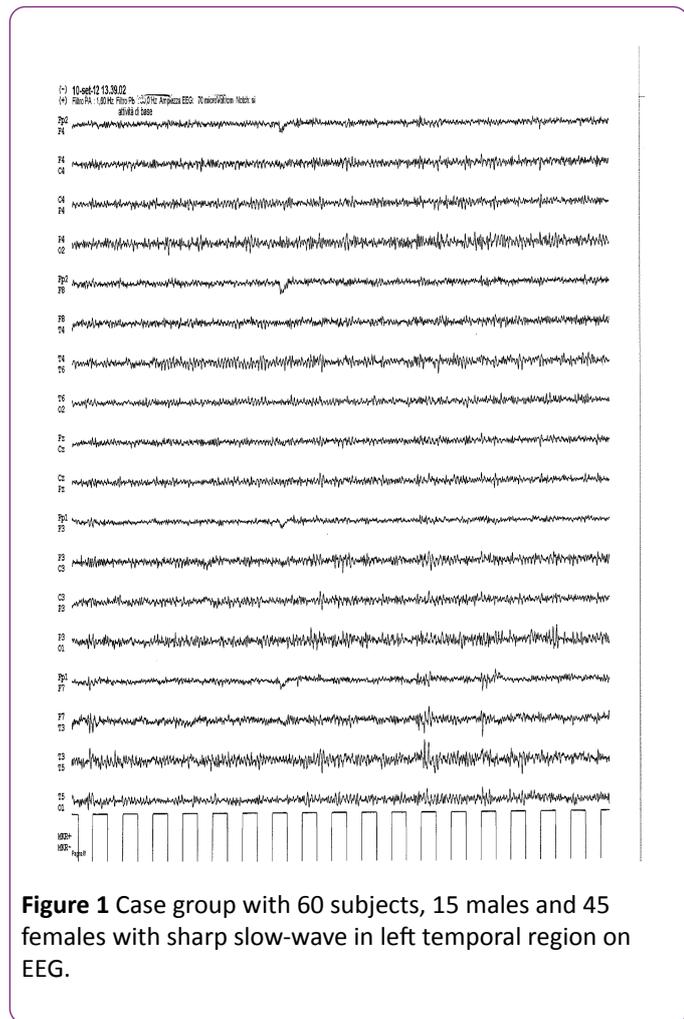
## Results

### Demographic and clinical data

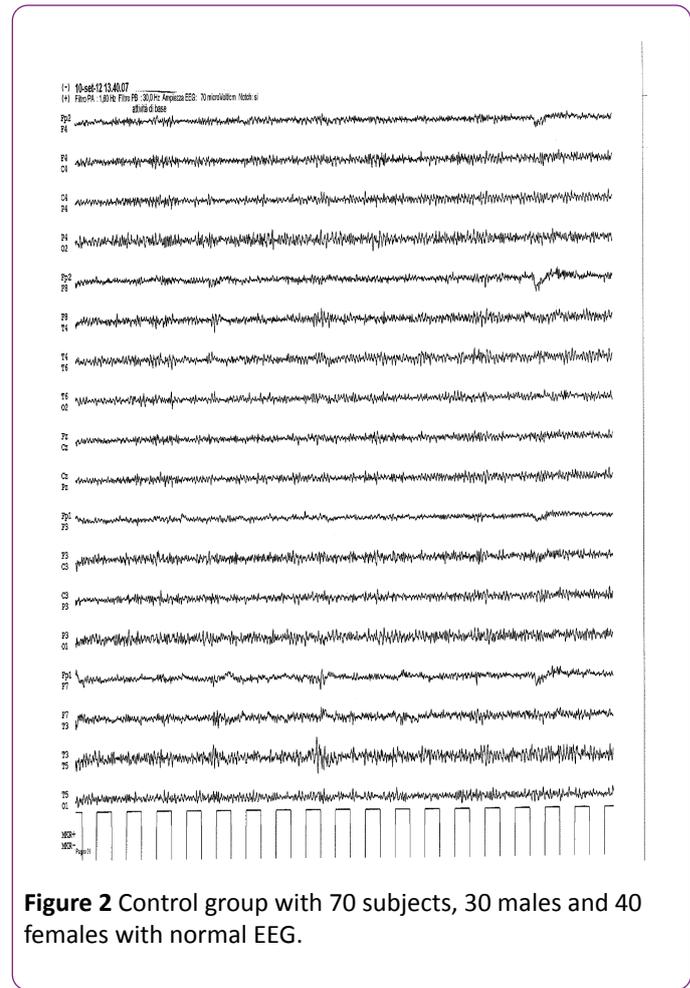
One hundred forty patients were recruited and one hundred thirty completed the 24-month study.

Of the ten patients who did not complete the study, five patients in experimental group and three patients in control group did not have follow-up and were excluded from outcome analyses. The reasons for withdrawal were intercurrent illness (8 patients) and death (2 patients).

Population included 85 females and 45 males. In case group we had 60 subjects, 15 males and 45 females with sharp slow-wave in left temporal region on EEG (**Figure 1**) Mean age was  $58.2 \pm 7.1$  years. In control group we had 70 subjects, 30 males and 40 females with normal EEG (**Figure 2**). Mean age was  $54.1 \pm 8.2$  years.



**Figure 1** Case group with 60 subjects, 15 males and 45 females with sharp slow-wave in left temporal region on EEG.



**Figure 2** Control group with 70 subjects, 30 males and 40 females with normal EEG.

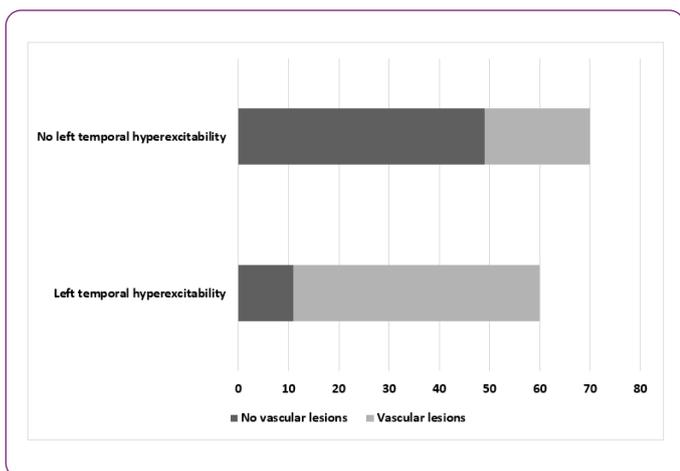
Demographic characteristics and clinical data for 130 patients are summarized in **Table 1**.

**Table 1** Summary of demographic data.

	Sex	Age (mean)	Episodes of loss of consciousness	Headache	Dizziness
Case (n=60)	15 males 45 females	58.2 ± 7.1	32	19	9
Control (n=70)	30 males 40 females	54.1 ± 8.2	35	25	10

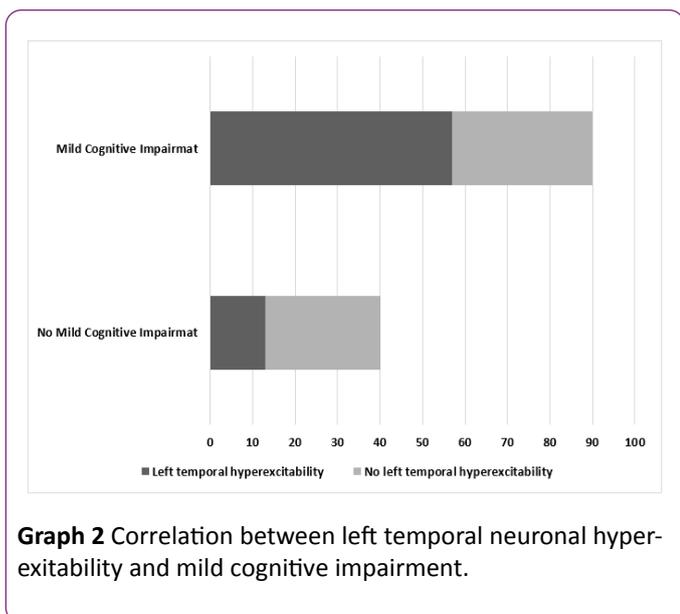
### Outcome analysis

57 patients (Case) and 33 patients (Controls) showed a mild cognitive impairment (MMSE  $\geq 23$  adjusted for age and education) (**Graph 1**).



**Graph 1** Correlation between left temporal neuronal hyperexcitability and vascular lesions.

49 patients (Case) and 21 patients (Controls) with deep lacunar infarcts or subcortical white matter alterations on MRI scan (**Graph 2**).



**Graph 2** Correlation between left temporal neuronal hyperexcitability and mild cognitive impairment.

Overall, 95% had development neurocognitive impairment in case group vs 47% in control group.

Nearly 8% of patients were unavailable for follow-up and this was a study limitation.

Analysis performed according to methods proposed by Koch showed that pattern EEG of slow waves significantly correlated with both variables MCI ( $P < 0.0001$ ) and vascular alterations ( $P < 0.0001$ ). The outcome analysis is summarized in **Table 2**.

**Table 2** Outcome analysis – Odd ratio and 95% confidence interval estimates by EEG patterns, predicting in vascular lesions and MCI.

	OR	95% CI	Z statistic	p-value
Patients with MCI	21.30	6.30 to 74.52	4.79	$P < 0.0001$

(n= 57/60)				
Patients with vascular lesions (n=49/60)	10.39	4.53 to 28.84	5.53	$P < 0.0001$

## Discussion

Diagnosis of MCI is hard, and symptoms are often dismissed as normal consequences of aging. In this study, we proposed a reliable and accurate method to discriminate MCI versus normal cases using neurophysiological features.

In fact, in our sample, pattern EEG was predictive for vascular abnormalities and MCI more than 50% after a few years. As described in the literature, well-designed observational study have been shown to provide results similar to randomized controlled trials [11].

Neurons, glial cells, endothelial cells of the blood-brain barrier produce pro-inflammatory elements such as IL-1 beta as answer at injuries: this process precedes the neuronal hyperexcitability condition. The hypothesis suggested that injuries in some regions in the patient’s brain with dementia are caused by inflammatory process. Thus, neuro-excitability and cognitive impairment have the same cause. Furthermore, a lot of studies show that the cerebrovascular disease can stimulate plaques and neurofibrillary tangles, typical elements in brain’s dementia.

## Conclusion

The proposed feature selection and classification procedure shows very promising and interesting results.

In summary, typical geographic alterations in left temporal region are “indicators” or “markers” of early cognitive impairment and may be used as a prevention strategy. EEG is non-invasive and inexpensive; therefore it would be very efficient and effective screening tool to detect MCI patients for early diagnosis of MCI.

Further studies should focus to determine new therapeutic approaches directed to selectively suppressing aberrant network excitability in the temporal lobe.

## Conflicts of Interest

There are no conflicts of interests.

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