

## Functional Connectivity as a Neurophysiological Biomarker of Alzheimer's Disease

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A.V. Medvedeva\*, N.N.Yahno

Neurological Department of First Moscow Medical University, Russia

### Abstract

Alzheimer's disease (AD) is one of the most frequent neurodegenerative disorder. AD selectively involves cerebral neuronal networks facilitating higher cognitive functions. The increasing disruption of cortical connectivity during the course of the disease could be a functional correlate of the cognitive decline. EEG-coherence is a sensitive marker of functional connectivity in the human brain, whereas fMRI allows the detection of activation patterns in various brain regions which could be functionally coupled.

The aim of this study was to correlate fMRI activation patterns and EEG-coherence in patients with Alzheimer's disease (AD) of and age-matched healthy control subjects, thus investigating differences of functional connectivity between the groups.

**Methods:** 131 patients with AD (mild, moderate degree) were included in the investigation according to the diagnostic criteria of DSM -5 and AD-MKB 10. 45 AD patients were on galantamine, 43 -memantine and 43 -combined therapy. 45 patients with Mild cognitive impairment (MCI) were included in the investigation. Patients were recruited via the memory clinic at the First Moscow Medical University; control group was recruited at the First Moscow Medical University. The degree of dementia was evaluated by clinical dementia rating scale (Clinical Dementia Rating Scale-Sum of Boxes (CDR-SB)). The age of patients in the main AD group was 60-80 years, mean age 73 years. There were 25 women and 20 men. The control group includes 45 patients which were similar by age and gender characteristics with the other groups. Standard neuropsychological investigation was performed in AD and control group. Patients were included in the study undergoing fMRI and resting EEG-recordings.

**Results:** There were found interhemispheric temporal disconnections as well as inferior parietal disconnections with the hippocampus, medial temporal regions, medial frontal regions, and the ACC (the anterior cingulate gyrus). Temporal connections in delta band correlated with global function, as well. These findings suggest that disruption of global neural networks is related to AD pathophysiology. Furthermore, our results indicate that functional connectivity, assessed by fMRI and EEG-coherence may potentially represent a neurophysiological biomarker of AD, and help in early detection of the neurodegenerative disease.

**Conclusion:** EEG coherence measurements based on eLORETA analyses seem to be a useful approach to investigate connectivity between regions of interest as defined by fMRI and resting EEG activation patterns. Functional connectivity, assessed by fMRI and EEG-coherence may potentially represent a neurophysiological biomarker of AD. The combination of fMRI and EEG data with neurophysiological investigation of cognitive impairment gives more diagnostic possibilities for detection the early stage of cognitive decline.

**Key words:** Functional connectivity, Alzheimer's disease, EEG-coherence, LORETA, FMRI

### Introduction

Alzheimer's disease (AD) is one of the most frequent neurodegenerative disorder. More than 50 % of population suffers of cognitive decline of Alzheimer's type. At the age 60-64 years the dementia of Alzheimer type is about 1 % of population, after 85 the prevalence is 40% [1-9]. Dementia is result of longterm progression of mild cognitive impairment (MCI) of amnesic type. MCI is a predementia stage of the disease reflecting current evidence that measureable biomarker changes in the brain may occur years before symptoms affecting memory, thinking or behavior can be

\*Corresponding Author: A.V. Medvedeva,  
Neurological Department of First Moscow Medical  
University, Russia, Email: [anastasia\\_medved@mail.ru](mailto:anastasia_medved@mail.ru)

detected by affected individuals or their physicians. People with MCI, especially MCI involving memory problems, are more likely to develop Alzheimer's disease or other dementias than people without MCI. That's why it's important that people experiencing cognitive impairment seek help as soon as possible for diagnosis and possible treatment. Mild cognitive impairment is a "clinical" diagnosis representing a doctor's best professional judgment about the reason for a person's symptoms. If a physician has difficulty confirming a diagnosis of MCI or the cause of MCI, biomarker tests such as brain imaging and cerebrospinal fluid tests may be performed to determine if the individual has MCI due to Alzheimer's [10-21]. Still there is no definite treatment of AD, the therapy on the early stage may delay the onset of the neurodegenerative disorder. Biomarkers of AD including beta-amyloid, tau protein in CSF, genetic mutations and Apoprotein E, brain amyloid deposition revealed by PET imaging may potentially increase the diagnostic accuracy. The low cost EEG which is widely spread might detect brain functional abnormalities at the early stage.

AD is thought to be the disconnection syndrome. In these context the study question is to find whether in AD the main neurodegenerative process is mostly associated with functional loss of the neural networks. EEG has recently been used to evaluate the functional connectivity of brain regions in AD. EEG coherence seems to be the indicator of the connectivity (brain network analysis) probably could be useful in evaluating the risk of conversion from MCI to AD and could serve as neurophysiological biomarker of AD.

AD is thought to represent a disconnection syndrome [22]. EEG has recently been used to evaluate the functional connectivity of brain regions in AD. In these studies, the clinical stage of AD was closely correlated with the functional connectivity assessed by EEG analysis. Analyses of coherence, a measure of linear functional connectivity, were useful in evaluating the risk of conversion from mild cognitive impairment (MCI) to AD. This suggests that brain network analysis (i.e., functional connectivity) of AD patients may aid in diagnosing early stage of AD.

Recent neuroimaging and neurophysiological findings suggest that disintegrated functional connectivity denotes the core of the pathophysiological mechanism underlying AD pathology. In this way we could interpret AD as a structural and functional network disorder.

Great interest was put to the functional networks in the brain resting state of patients with dementia. The brain resting state is considered to be a condition, with neural activity and interneuronal connections in particular circuits (e.g., the default mode network; DMN) that are interrupted during sensorimotor or cognitive tasks. This intrinsic function in the resting state allows the brain to be ready for changes or stimuli of internal and external surroundings. Thus, exploring functional connectivity in the resting state rather than during performance of a specific task might elucidate an intrinsic functional disintegration of brain regions in AD patients.

To evaluate resting-state synchronization in the functional networks, various methods of connectivity assessment have been applied to EEG data. Most AD studies of functional connectivity have used coherence, a linear connectivity measure that is based on the amplitude or power of the EEG signals, showing decreased

connections in various brain networks. Exact Low Resolution Electromagnetic Tomography (eLORETA) [23,24] is a three-dimensional, discrete, linear, and weighted minimal norm inverse solution method. It is uniquely endowed with the property of exact localization to a test point source at any location, albeit with low spatial resolution. The method produces a low resolution estimate of any distribution of electric neuronal activity. In a detailed and exhaustive comparison to other competing linear inverse solution, it was shown that eLORETA has improved localization properties in the presence of noise, and in multiple source situations [24]. A recently developed method of nonlinear functional connectivity called "lagged phase synchronization" [24], implemented in the eLORETA statistical package, is resistant to non-physiological artifacts, particularly low spatial resolution and volume conduction. It was proved that imaginary coherence, as well as for the imaginary phase coherence related to phase synchronization [14] are biased and strongly affected by volume conduction and low spatial resolution. This lagged connectivity method is considered to be accurately corrected because it depicts the connectivity of two signals after the artifactual instantaneous (zero-lag) components have been excluded. The connectivity patterns of the classic phase synchronization which contains the instantaneous (zero-lag) artifact are not often associated with the true physiological interactions [24]. The lagged connectivity measure is relatively robust to the strength of the instantaneous components. Thus it can detect physiological "non-zero" lagged connectivity even when a large instantaneous artifact exists, while the conventional coherence indices fail to identify a lagged connection in the presence of the large instantaneous component [24]. Due to a proper modeling of the two components of a functional connection (i.e., instantaneous and lagged), the eLORETA algorithm is considered to identify true physiological connectivity. Furthermore, it can be utilized to filtered data, therefore providing a frequency decomposition of the functional brain connectivity [24].

In the present study, we aimed to identify the abnormal EEG patterns or functional connectivity of AD patients with eLORETA. The combination of fMRI and EEG and standard neurophysiological investigation gives more possibilities for diagnosis the early stage of cognitive decline [25,16,26].

## Patients and methods

All investigated patients were due to diagnostic criteria of AD- MKB10 [27] and DSM-5 [28]. 131 patients with AD (mild, moderate degree) were included in the investigation. The groups consisted of  $n = 131$  individuals each, matched for age and gender. Initially,  $n = 131$  patients with mild and moderate AD and  $n = 46$  elderly healthy control (HC) subjects participated in the study, of which one patient aborted the scan session. Patients were recruited via the memory clinic at the First Moscow Medical University; control group was recruited at the First Moscow Medical University. The degree of dementia was evaluated by clinical dementia rating scale (Clinical Dementia Rating Scale-Sum of Boxes (CDR-SB)).

45 AD patients were on galantamine, 43-memantine and 43-combined therapy. The age of patients in the main group 60-80 years, mean age 73 years. There were 25 women and 20 men. The control group includes 45 patients which were similar by age and gender characteristics with the other groups.

45 MCI patients had same characteristics (age, gender) as the AD group. In our investigation in the main group of AD patients the duration of the disease was from 6 months to 4.3 years, on average 3,3 years. In control group of AD patients the cognitive disorders lasted from 2.5- 6.7 years, on average 4.5 years.

The duration of cognitive disorders was from the moment of diagnosis and beginning of symptomatic "antidementia" therapy with memantine, galantamine or their combination. Light degree of dementia was in the 68 % of patients, moderate in 32%. The same situation with the degree of cognitive disorders was in the group of AD patients on long term treatment-in prevalence were patients with light degree of dementia. So, the main group of AD and the group on long term treatment had same characteristics (age, gender, part of patients with light and severe degree of dementia) (Figure 1).

The group of AD patients on long term treatment differed from the AD main group with longer duration of treatment and longer duration of the disease. AD patients more frequently have complains on memory loss (85,5%), brain activity (78,8%), difficulties in finding the proper word (17.9%). There were complaints on social and daily disadaptation. Subjects exhibited no neurological or radiological abnormalities (e.g., normal pressure hydrocephalus or extensive microinfarcts, no vascular lesions), and no psychiatric diseases. AD patients showed no signs

of dementia not due to AD (e.g., vascular dementia).Patients with AD had no significant vascular risk factors, no vascular lesions on MRI. The main group did not significantly differed from the group on long term treatment. The patients with AD did not have arterial hypertension with unstable duration, hyperlipedemia, there were no major atherosclerosis in arteries by ultrasound investigation, no diabetes mellitus. Standard neuropsychological investigation was performed in AD,MCI and control groups which included the following tests- MMSE- Mini Mental State Examination [Folstein M.F et al. [29],FAB- Frontal Assessment Battery) [Dubois B.] [30], clock drawing test-[Lezak M.D., 27], 12 world list immediate and delayed recall (subscore, total) [ Grober E., Bushke H.] [31,32].

Electrophysiological investigation was performed in resting state and with specific cognitive tasks. There was used 10-20 system with investigation of spectral power and intra/interhemispheric coherence.

CT, MRI scans were performed in 99%. There was found atrophy of parieto- temporal regions.

None of the patients had vascular risk factors and lesions, so vascular dementia or combined dementias were excluded. Patients with AD had no significant vascular risk factors, no vascular lesions on MRI. Vascular or combined type of dementia was excluded. Statistical analyses was performed by SPSS v.

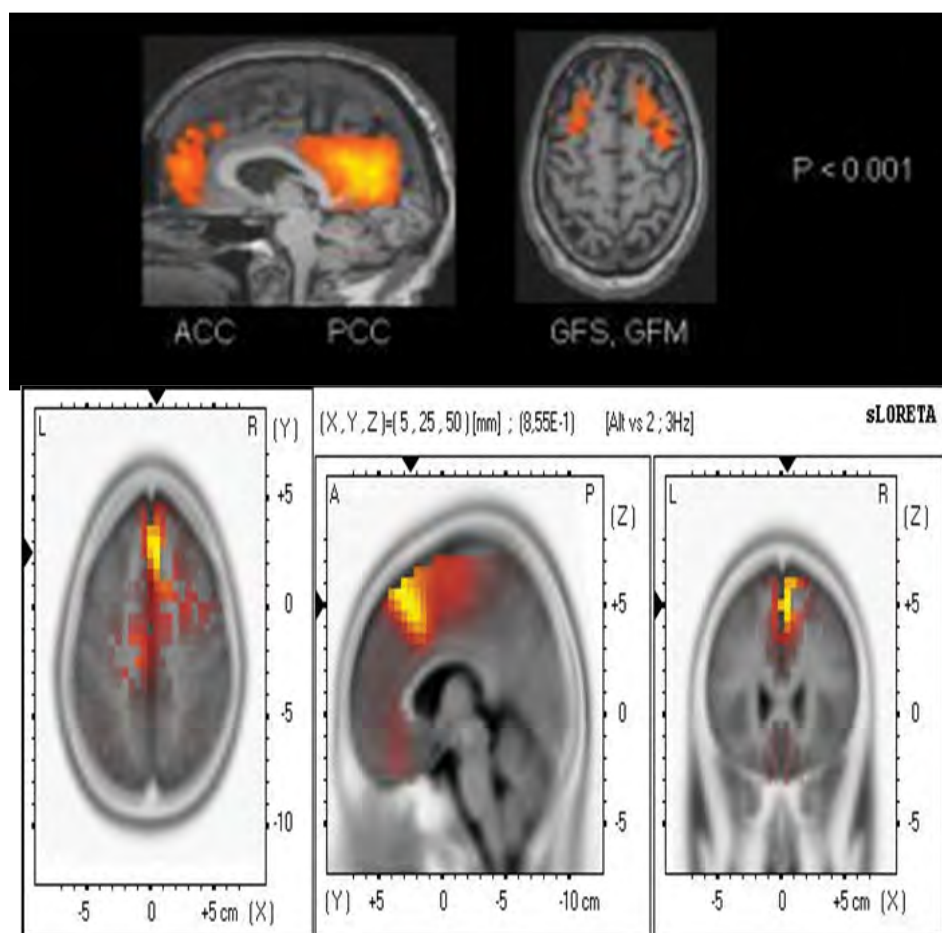


Figure 1: Comparison of healthy elderly subjects vs. MCI patients. fMRI activations ( $p < 0.001$ ) and EEG- LORETA current source density activations. Correspondence in frontal, but not in posterior regions.

16.0. It was used Student criteria (t- test), Mann-Witney (U-test), Spearman coefficient, ANOVA analyses. The study was approved by the local ethics committee of the First Moscow Medical University. All participants gave written informed consent, and all procedures were carried out in accordance with the Helsinki declaration (Figures 2 and 3).

### Data Preprocessing EEG Data

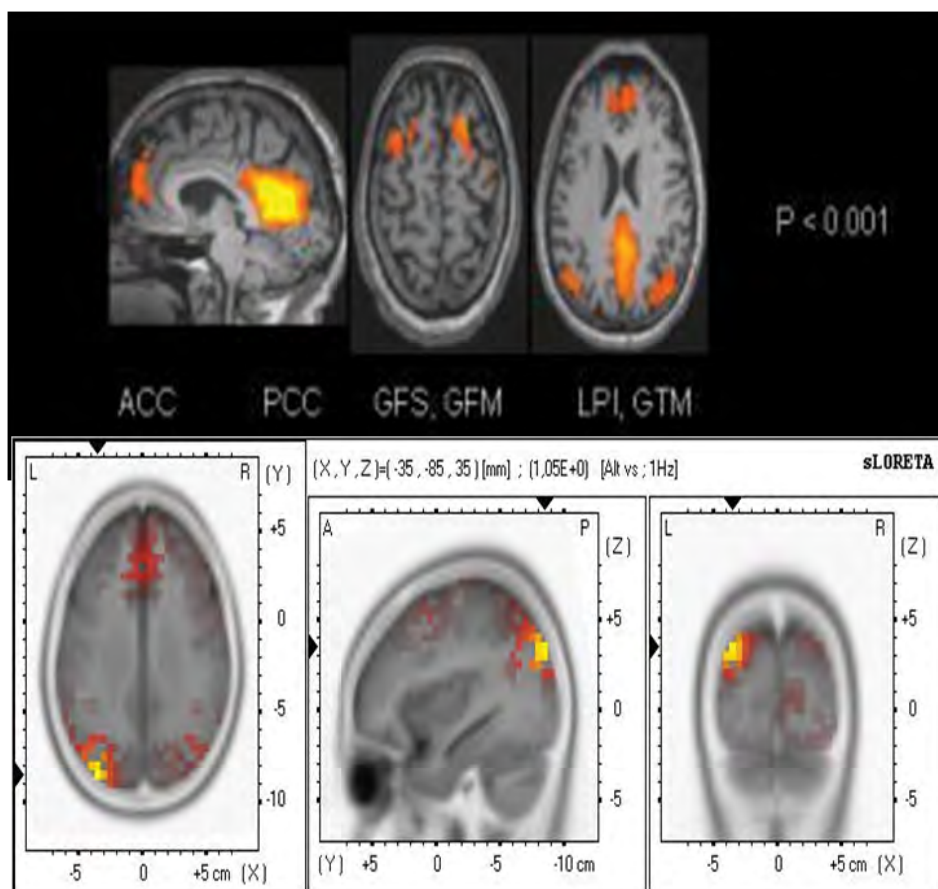
#### EEG recordings and data acquisition

The subject's EEG were recorded with a digital 19-channel scalp EEG device, using the International 10-20 system (i.e., Fp1, Fp2, F7, F3, Fz, F4, F8, T7, C3, Cz, C4, T8, P7, P3, Pz, P4, P8, O1, O2). The EEG data were acquired with a linked ears reference, sampled at 500 Hz, and filtered offline between 0.53 Hz and 30 Hz. Electrode impedance was kept below 5 kΩ. EEG recording included eyes open and closed states with vigilance control. For all subjects, we selected 40 s of artifact-free EEG data and fragmented them into 2-s segments off-line. EEG artifacts were manually excluded by visual inspection of skilled and certified electroencephalographers. Segments including blink artifact, muscle artifact, electrocardiograph (ECG) artifact, and signs of drowsiness were rejected, and only reliable, awake EEG data were selected, so that we could adequately estimate brain function during the resting-state. EEG data were analyzed with the eLORETA-KEY software package.

At least 2-s data of continuous artifact-free EEG recordings as one epoch are required for eLORETA analyses. Thus, we excluded EEG data with continual artifact which did not include merely 2 s of artifact-free interval. In order to avoid behavioral and EEG drowsiness, the skilled experimenter monitored the participants and eventual appearance of EEG drowsiness, if any, verbally gave them instructions and warnings. Such EEG drowsiness was additionally rejected in data processing. Furthermore, EEG data with low-amplitude (less than 10 μV) basic rhythms were excluded, avoiding the relative overestimation of non-physiological signals. Ocular and muscular artifacts were also rejected. These activities usually exhibited more than 100 μV amplitude. However, we also excluded ocular and muscular artifacts less than 100 μV if some suspicious activities could be considered these kinds of artifacts from its wave form and distribution. The epochs, including sporadic slow waves, were excluded for exploring the steady resting-state.

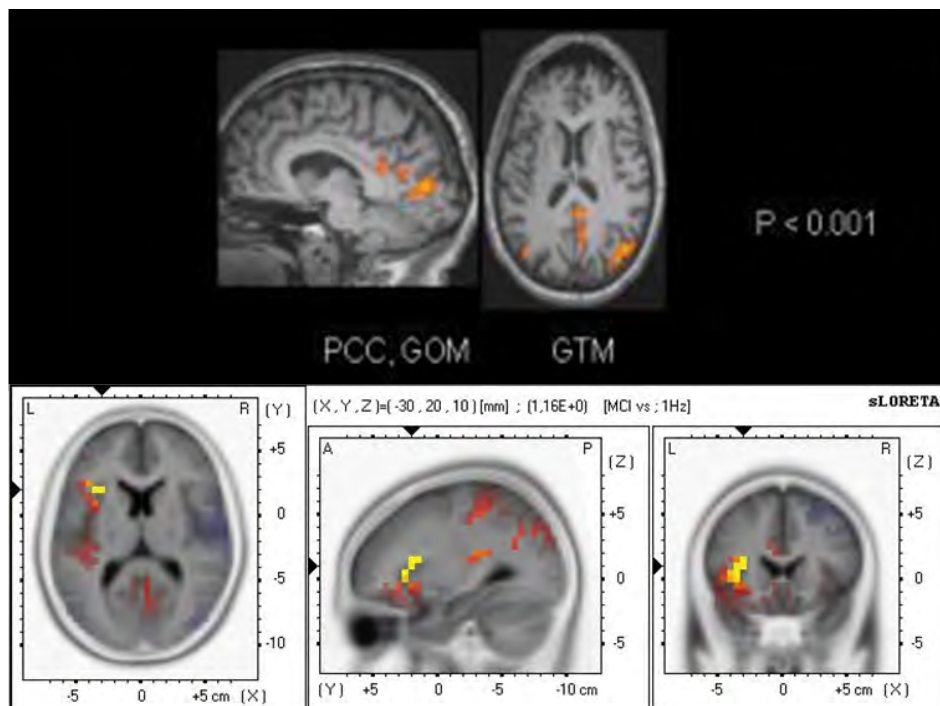
### EEG source localisation

We analyzed the cortical distribution of current source density, using eLORETA. The head model of eLORETA and the electrode coordinates are based on the Montreal Neurological Institute average MRI brain map (MNI152) [33-35]. The solution space was limited to the cortical gray matter, including 6239 voxels of 5 cubic mm spatial resolution. The eLORETA tomography has been



**Figure 2:** Comparison of healthy elderly subjects vs. AD patients. fMRI activations ( $p < 0.001$ ) and EEG-LORETA current source density activations. Correspondence in frontal, but not in posterior regions.





**Figure 3:** Comparison of MCI and AD patients. fMRI activations ( $p < 0.001$ ) and EEG-LORETA current source density activations. Correspondence in posterior regions.

validated in several studies using fMRI [36,37], structural MRI [38] and intracranial EEG.

Selected artifact-free EEG fragments were analyzed to calculate the eLORETA cortical current source density from 0.53 Hz to 30 Hz. The current source density of the eLORETA cortical functioning image was calculated for six frequency bands: delta (2-4 Hz), theta (4-8 Hz), alpha1 (8-10 Hz), alpha2 (10-13 Hz), beta1 (13-20 Hz), beta2 (20-30 Hz).

### Functional connectivity analysis

To analyze the functional connectivity we adopted a voxel-wise approach to determine cortical regions of interest (ROI). To create the ROIs, eLORETA defined the MNI coordinates of the cortical voxels underlying the electrode sites. Although detailed information on eLORETA connectivity algorithm has been published recently elsewhere [39-42,23,24], we briefly summarize about this method. Cortical ROIs were determined. Based upon different researches of functional connectivity [43], 21 ROIs were selected. Three additional ROIs (Aud, auditory fields; Vis, Visual fields) as they have investigated in studies on brain functional networks [44].

To analyze functional connectivity between all pairs of ROIs, we used lagged phase synchronization. Lagged phase synchronization is a method for evaluating the similarity between signals in the frequency domain, based on normalized Fourier transforms. Thus, lagged phase synchronization is associated with nonlinear functional connectivity. This lagged connectivity measure is considered to be accurately corrected as it represents the connectivity of two signals after excluding the instantaneous zero-lag component (i.e., a lot of artifact elements). Such a correction is necessary because scalp EEG signals or estimated

intracranial signals (EEG tomography) often include non-physiological components or physical artifacts, such as volume conduction that usually affect other connectivity indices. Thus, the lagged phase synchronization is considered to include only physiological connectivity information.

### Statistical analysis

For statistical analysis of current source density, eLORETA applies a statistical nonparametric mapping method (SnPM) [45]. We assessed the difference of cortical source localization between groups in each frequency band with voxel-by-voxel independent  $F$ -ratio-tests, based upon eLORETA log-transformed current source density power. In the resulting three-dimensional statistical mapping, cortical voxels with significant differences were identified by means of a nonparametric permutation/randomization procedure (i.e., based on the Fisher's permutation method, with the threshold set at the 5% probability level), comparing the mean source power in each voxel and the distribution in the permuted values. By evaluating the empirical probability distribution of the "maximal-statistics" in the null hypothesis, permutation and randomization tests have demonstrated to be effective in controlling the Type I error in neuroimaging studies [45]. eLORETA used 5000 data randomizations to determine the critical probability threshold values for the actually observed log  $F$ -ratio values with correction for multiple comparisons across all voxels and all frequencies, without the need to rely on Gaussianity. The use of SnPM for eLORETA images has been confirmed in several studies [23,24].

### Results

The data of cognitive tests are presented in (table1 and table 2). There was significant difference between the groups

**Table 1:** Results of the data of cognitive functions in AD patients on different types of therapy and their combination.

Group Test	Main group		Combined therapy (n 43)	Control group (n 45)
	Monotherapy Galantamin (n 45)	Monotherapy Memantine (n 43)		
MMSE	20±2.1*	22±1.2*+	22.3±1.5*#	29±1.4
Clock drawing test	6.8±2.1*	7±1.2*+	7±1.2*#	9,6±1.1
FAB	13±1.4*	14±1.5*+	14.2±1.6*#	17±1

NOTES: There are only significant data presented in the table MMSE- Mini-Mental State Examination  
FAB- Frontal assessment battery

\*-significant data between groups and controls,  
+- significant data between the group of AD on memantin and galantamin  
#- significant data between the group of AD on galantamin and combined

**Table 2:** Results of the data of 12 word learning tests in AD patients on different types of therapy and their combination.

Group Test	Main group		Combined (n 43)	Control (n 45)
	Monotherapy galantamin (n 45)	Monotherapy memantine (n 43)		
12 word learning test total	7,3±1.2*	7,7±1.3*	7.3±1.4*	11,7±1.1
12 word list immediate recall	6.3±1.2*	6.7±1.3*	6.3±1.4*	8.6±1.1
12 word list immediate recall with help	1±1.1*	1±1.1*	1±1.1*	3.1±1.1
12 word list delayed recall total	6,2*±1	6,1±1.1*	6.8±1.3*	11,3±1.1
12 word list delayed recall	5.2±1.1*	5.1±1.1*	5.8±1.1*	7.9±1.1
12 word list delayed recall with help	1±1.1*	1±1.1*	1±1.1*	3.4±1.1

NOTES:\* There are only significant data presented in the table between the groups and controls

on therapy and controls in MMSE, FAB, Clock drawing test. We did not find difference between the AD groups on acatinol memantin and galantamin in 12 world learning test (immediate recall, immediate recall with help, delayed recall, delayed recall with help). There was found difference only between AD groups and controls in 12 world learning test. There were statistically significant differences between AD and MCI patients for theta band coherences (6,5-8 Hz) between anterior cingulate gyrus and left temporal gyrus (AD < MCI, p < 0,05); between AD and control subjects for theta band coherence between anterior cingulate gyrus and right temporal gyrus (AD < controls, p < 0,01), between anterior cingulate gyrus and left hippocampus (AD < controls, p < 0,01), and between anterior cingulate gyrus and right parietal gyrus (AD <,controls, p,<,0,01).

Furthermore, MCI-subjects showed reduced coherence compared with healthy controls between anterior cingulate gyrus and left frontal superior gyrus within delta, theta and alpha1-bands (p < 0,05). Theta coherence was statistically significantly lower in patients with MCI compared with controls between anterior and posterior cingulate gyrus, anterior cingulate gyrus and left/right temporal gyrus, posterior cingulate gyrus and superior frontal gyrus (MCI < controls, p < 0,01), and between right and left temporal gyri (MCI < controls, p<0,05). Activation patterns (fMRI, eLORETA) were different between groups with less activation in the groups of patients, especially within the anterior cingulate gyrus.

## Discussion

There were statistically significant differences between AD and MCI patients for theta band coherences (6,5-8 Hz) between anterior cingulate gyrus and left temporal gyrus (AD < MCI, p < 0,05); between AD and control subjects for theta band coherence between anterior cingulate gyrus and right temporal gyrus (AD < controls, p < 0,01), between anterior cingulate gyrus and left hippocampus (AD < controls, p < 0,01), and between anterior cingulate gyrus and right parietal gyrus (AD <,controls, p,<,0,01). Furthermore, MCI-subjects showed reduced coherence compared

with healthy controls between anterior cingulate gyrus and left frontal superior gyrus within delta, theta and alpha1-bands (p < 0,05). Theta coherence was statistically significantly lower in patients with MCI compared with controls between anterior and posterior cingulate gyrus, anterior cingulate gyrus and left/right temporal gyrus, posterior cingulate gyrus and superior frontal gyrus (MCI < controls, p < 0,01), and between right and left temporal gyri (MCI < controls, p<0,05). Activation patterns (fMRI, eLORETA) were different between groups with less activation in the groups of patients, especially within the anterior cingulate gyrus.

Coherence as a measure of functional connectivity is an important research tool in neurology and psychiatry. By using *exact low resolution brain electromagnetic tomography* (eLORETA, Pascual-Marqui 2007) distributed cortical networks can be localized and investigated. The cortical networks in AD and MCI as identified in this study are in agreement with the literature. The assessment of voxel-based connectivity between cortical regions may help identifying local and network abnormalities in neurodegenerative disorders. The disruption of functional connectivity is considered to be associated with functional deficits, and most likely indicate a loss of structures involved in the neural networks. The characterization of connectivity loss could prove useful in the differential diagnosis of neurodegenerative diseases [46,14,47,48]. The patterns of aberrant lagged phase synchronization identified in our study could be helpful for the diagnosis of AD. Application of a new theoretical scheme to the research of neural network alterations may provide insights into the underlying pathophysiological mechanisms of this disease [49-58].

## Conclusion

Coherence as a measure of functional connectivity is an important research tool. This involved specifically interhemispheric temporal connections as well as inferior parietal connectivity with the hippocampus, medial temporal regions, medial frontal regions, and the ACC (the anterior cingulate

gyrus). Temporal connections in delta band correlated with global function, as well. These findings suggest that disruption of global neural networks is related to AD pathophysiology. Furthermore, our results indicate that abnormalities in lagged phase synchronization, as a non-linear connectivity measure, may potentially represent a neurophysiological biomarker of AD, and help in the early detection of the neurodegenerative disease.

The combination of fMRI and EEG data with neurophysiological investigation of cognitive impairment gives more diagnostic possibilities for detection the early stage of cognitive decline.

## Summary

Alzheimer's disease (AD) is one of the most frequent neurodegenerative disorder. More than 50 % of population suffers of cognitive decline of Alzheimer's type. Coherence as a measure of functional connectivity is an important research tool in psychiatry. By using *exact low resolution brain electromagnetic tomography* (eLORETA, Pascual-Marqui 2007) distributed cortical networks can be localized and investigated. The cortical networks in AD and MCI as identified in this study are in agreement with the literature. The assessment of voxel-based connectivity between cortical regions may help identifying local and network abnormalities in neurodegenerative disorders.

The aim was to find functional connectivity between ROI's in AD, MCI groups and healthy controls.

131 patients with AD were investigated. There were several groups -group of monotherapy with memantin, monotherapy with galantamin, combined therapy with memantin and galantamin and control group.

The findings of the investigation suggest that disruption of global neural networks is related to AD pathophysiology. Furthermore, our results indicate that abnormalities in lagged phase synchronization, as a non-linear connectivity measure, may potentially represent a neurophysiological biomarker of AD, and help in the early detection of the neurodegenerative disease.

The combination of fMRI and EEG data with neurophysiological investigation of cognitive impairment gives more diagnostic possibilities for detection the early stage of cognitive decline.

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