Research Article

Direction of Information Flow in Alzheimer's Disease and MCI Patients

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Is directionality of electroencephalographic (EEG) synchronization abnormal in amnesic mild cognitive impairment (MCI) and Alzheimer's disease (AD)? And, do cerebrovascular and AD lesions represent additive factors in the development of MCI as a putative preclinical stage of AD? Here we reported two studies that tested these hypotheses. EEG data were recorded in normal elderly (Nold), amnesic MCI, and mild AD subjects at rest condition (closed eyes). Direction of information flow within EEG electrode pairs was performed by directed transfer function (DTF) at δ (2–4 Hz), θ (4–8 Hz), α1 (8–10 Hz), α2 (10–12 Hz), β1 (13–20 Hz), β2 (20–30 Hz), and γ (30–40 Hz). Parieto-to-frontal direction was stronger in Nold than in MCI and/or AD subjects for α and β rhythms. In contrast, the directional flow within interhemispheric EEG functional coupling did not discriminate among the groups. More interestingly, this coupling was higher at θ, α1, α2, and β1 in MCI with higher than in MCI with lower vascular load. These results suggest that directionality of parieto-to-frontal EEG synchronization is abnormal not only in AD but also in amnesic MCI, supporting the additive model according to which MCI state would result from the combination of cerebrovascular and neurodegenerative lesions.

1. Introduction

It has been shown that modifications of resting electroencephalographic (EEG) rhythms can be observed during pathological aging. When compared to healthy elderly (Nold) subjects, Alzheimer's disease (AD) patients have been characterized by high power of δ (0–4 Hz) and θ (4–7 Hz) rhythms, and low power of posterior α (8–12 Hz) and/or β (13–30 Hz) rhythms [1–7]. These EEG abnormalities have been associated with altered regional cerebral blood flow/metabolism and with impaired global cognitive function, as evaluated by mini mental state examination (MMSE; [5, 8–11]. Furthermore, posterior α rhythms have shown a power decrement even in subjects with amnesic mild cognitive impairment (MCI), a clinical state between elderly normal cognition and dementia, which is characterized by the objective evidence of memory deficit either isolated or combined with other cognitive impairment [3, 7, 12–15].

More recently, the hypothesis that the amplitude of EEG rhythms, which are affected by AD processes, is relatively preserved in amnesic MCI subjects in whom the cognitive decline is mainly explained by white-matter vascular load has been tested.

Despite the converging evidence of abnormal cortical EEG rhythms in MCI and AD, EEG power alone does not reliably predict conversion from MCI to dementia. A reasonable hypothesis is that the amplitude of EEG rhythms per se does not capture one of the main features of AD, namely the impairment of functional neural connectivity. In this vein, it has been reported that AD patients present an abnormal linear coupling of EEG rhythms between cortical regions, as revealed by spectral EEG coherence [16–22]. Such a coherence denotes linear temporal synchronicity of coupled EEG rhythms, as a reflection of neural sources whose firing is oscillating with a nearly identical timing and phase. It has been proposed that functional coupling

of cortical rhythms is related to brain processes involving the coupled sources and is modulated by cholinergic systems [23]; AD is characterized by a disruption of basal forebrain cholinergic inputs to cortex and hippocampus [24]. This is why a decrease of cortical EEG coherence might be a sensible and reliable marker of AD.

Both linear and nonlinear connectivity have an important limitation: they do not reflect the direction of the information flux within the functional coupling of brain rhythms at paired brain sites. One can overcome this limitation by the computation of the directed transfer function (DTF; [25]). DTF has been proven to be reliable for the modeling of directional information flux within linear EEG functional coupling, as an intrinsic feature of cerebral functional connectivity [26–28]. Concerning the functional role of intrinsic directional connectivity in cognition, a dominant parietal-to-frontal directional flux within EEG coupling has been reported in healthy awake subjects during visuospatial information processing [15, 29]. Across pathological aging, a reduction of parietal-to-frontal directional information flow within EEG functional coupling in both MCI and mild AD subjects compared to Nold subjects it has been shown, in line with the idea of a common pathophysiological background linking these conditions.

In the present study, we summarized the results of two previous studies [30, 31] testing the hypothesis that directionality of frontoparietal functional coupling of EEG rhythms are affected by AD processes but relatively preserved in amnesic MCI subjects in whom the cognitive decline is mainly explained by white-matter vascular load (as revealed by MRI). Resting EEG was recorded in Nold, Alzheimer, and amnesic MCI subjects, while the directionality of frontoparietal functional coupling of EEG rhythms was estimated by DTF.

2. Methods

2.1. Subjects. In the first multicentric EEG study, 73 AD patients, 69 amnesic MCI patients, and 64 Nold subjects were recruited. In the second study, 80 amnesic MCI subjects were enrolled. Furthermore, 40 cognitively normal elderly (Nold) subjects were recruited to form control group. These individual data sets were mostly overlapped in the two studies.

Local institutional ethics committees approved the studies. All experiments were performed with the informed and overt consent of each participant or caregiver, in line with the Code of Ethics of the World Medical Association (Declaration of Helsinki) and the standards established by the Author's Institutional Review Board.

2.2. Diagnostic Criteria. Probable AD was diagnosed according to NINCDS-ADRDA [32] and DSM IV criteria. All recruited AD patients underwent general medical, neurological, and psychiatric assessments. Patients were also rated with a number of standardized diagnostic and severity instruments that included the Mini Mental State Examination (MMSE, [33]), the Clinical Dementia Rating Scale (CDR, [28]), the 15-item version of the Geriatric Depression

Scale (GDS, [34]), the Hachinski Ischemic Scale (HIS, [35]), and the Instrumental Activities of Daily Living scale (IADL, [36]). Neuroimaging diagnostic procedures (CT or MRI) and complete laboratory analyses were carried out to exclude other causes of progressive or reversible dementias, in order to have a homogeneous AD patient sample. Exclusion criteria included, in particular, evidence of (i) frontotemporal dementia, (ii) vascular dementia based on clinical and radiological grounds, (iii) extrapyramidal syndromes, (iv) reversible dementias, and (v) fluctuations in cognitive performance and visual hallucinations (suggestive of a possible Lewy body dementia). Inclusion and exclusion criteria for amnesic MCI diagnosis aimed at selecting elderly persons with objective cognitive deficits, especially in the memory domain, who did not meet the criteria for dementia or AD [37, 38]. Inclusion criteria for amnesic MCI subjects were (i) objective memory impairment on neuropsychological evaluation, as defined by performances ≥1.5 standard deviation below the mean value of age- and education-matched controls for a test battery including Busckhe-Fuld and memory Rey tests, (ii) normal instrumental activities of daily living as documented by history and evidence of independent living as assessed by a formal questionnaire (IADL, see above), and (iii) a clinical dementia rating score of 0.5. Exclusion criteria for amnesic MCI were (i) MCI subjects without objective memory deficits, (ii) AD, as diagnosed by the procedures described above, (iii) evidence of concomitant dementia such as frontotemporal, vascular dementia, reversible dementias (including dementia of depression), fluctuations in cognitive performance, and/or features of mixed dementias, (iv) evidence of concomitant extrapyramidal symptoms, (v) clinical and indirect evidence of depression as revealed by GDS scores greater than 14, (vi) other psychiatric diseases, epilepsy, drug addiction, alcohol dependence, and use of psychoactive drugs or drugs interfering with brain cognitive functions including acetylcholinesterase inhibitors, and (vii) current or previous uncontrolled systemic diseases or traumatic brain injuries.

The Nold subjects were recruited mostly among nonconsanguineous patients' relatives. All Nold subjects underwent physical and neurological examinations as well as cognitive screening. Subjects affected by chronic systemic illnesses, subjects receiving psychoactive drugs, and subjects with a history of present or previous neurological or psychiatric disease were excluded. All Nold subjects had a geriatric depression scale score lower than 14 (no depression).

2.3. Magnetic Resonance Imaging. High-resolution sagittal T1-weighted volumetric magnetic resonance images (MRIs) were acquired in 80 MCI subjects of the second study using a 1.0 T Magnetom scanner (Siemens, Erlangen, Germany), with a gradient echo 3D technique: TR = 10 ms, TE = 4 ms, TI = 300 ms, flip angle = 10°, field of view = 250 mm, acquisition matrix 160 × 256, and a slice thickness of 1.3 mm.

In order to rate the subcortical vascular lesions (SVLs), a single operator visually assessed digital MRI images of MCI subjects [39]. Interrater reliability calculated with weighted k value was 0.67, indicative of moderate agreement (as indicated by the Wahlund scale). The SVLs were scored separately

for the right and left hemispheres with the following scores: 0 (no lesion), 1 (focal lesions), 2 (beginning confluence of lesions), or 3 (diffuse involvement of the entire region). The MRI data of an MCI subject could not be used for technical problems. Another MCI subject was not further considered due to an abnormal EEG spectrum. In total, 78 MCI subjects were considered for the DTF analysis.

2.4. Composition of the Experimental Groups of MCI Subjects. Based on the Wahlund scale score, the MCI subjects were subdivided in two subgroups: 36 with low degree of white-matter lesion (MCI V−, score of Wahlund scale <3) and 42 with higher degree of white-matter lesion (MCI V+, score of Wahlund scale ≥3). The two subgroups of MCI subjects were comparable for demographic and clinical features.

Table 1 summarizes the relevant demographic and clinical data of MCI, AD, and Nold of the first study (part a) and the MCI V−, MCI V+, and Nold of the second study (part b). Of note, age, education, gender, and IAF were used as covariates in all the statistical evaluations of the cortical sources of EEG rhythms to remove possible confounding effects.

2.5. EEG Recordings. EEG data were recorded in resting subjects (eyes-closed) by specialized clinical units. All EEG recordings were performed (0.3–70 Hz bandpass) from 19 electrodes positioned according to the International 10–20 System (i.e., Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, O2). To monitor eye movements, the electrooculogram (0.3–70 Hz bandpass) was also collected. All data were digitized in continuous recording mode (5 min of EEG; up to 256 Hz sampling rate). In all subjects, EEG recordings were performed in the late morning. State of vigilance was controlled by visual inspection of EEG traces during recording session and subjects' drowsiness was avoided by verbal warnings. At the time of EEG recording, no patient received medications that could influence EEG rhythms such as benzodiazepines.

2.6. DTF Analysis: "Direction" of the Functional Connectivity Estimated by the Mvar Model. Before computing the DTF, the EEG data were preliminarily normalized by subtracting the mean value and dividing by the variance, according to standardized rules by Kaminski and Blinowska [25]. An important step of the DTF method was the computation of the so-called Mvar model [25–27]. EEG data at 9 electrodes (F3, Fz, F4, C3, Cz, C4, P3, Pz, P4) were simultaneously given as an input to the Mvar model towards the computation of the directional information flux among all the pair combinations of these electrodes. This model was used to estimate the "direction" of the information flow within the EEG rhythms between the frontal and parietal regions (F3-P3, Fz-Pz, F4-P4). In nonmathematical terms, coefficients of the Mvar model fitted to the data can be interpreted as causal influence of signal recorded from electrode A on signal recorded from electrode B, or information flow between electrodes A and B. A direction of information flow from A to B is stated when that case is statistically more probable

Table 1: Mean values (± standard error) of the demographic and clinical characteristics of the investigated cohorts.

(a)

Study 1	AD	aMCI	Nold
Subject	73	69	64
MMSE	20.9 ± 0.5	26.6 ± 0.2	28.6 ± 0.2
Age	74.1 ± 1.0	74.1 ± 0.8	73.7 ± 0.9
Education	9.8 ± 0.6	9.8 ± 0.5	9.7 ± 0.6
IAF	8.6 ± 0.2	9.2 ± 0.2	9.2 ± 0.1
Female/Male	35F/39M	38F/31M	32F/32M

(b)

Study 2	MCI V−	MCI V+	Nold
Subject	36	42	40
MMSE	26.7 ± 0.3	26.0 ± 0.3	28.4 ± 0.2
Age	68.5 ± 1.3	72.6 ± 1.0	69.1 ± 1.1
Education	7.7 ± 0.7	7.1 ± 0.5	7.6 ± 0.5
IAF	9.4 ± 0.2	9.3 ± 0.2	9.4 ± 0.1
Female/Male	23F/13M	23F/19M	22F/18M

than a directionality from B to A. This Mvar model has already been used successfully to estimate the "direction" of the corticocortical and corticomuscular information flow [40–42].

The mathematical core of the Mvar algorithm used in this work is based on the ARfit programs running on the platform Matlab 6.5. The model order was 7, as estimated by the Akaike criterion suggested in previous DTF studies; that order has been demonstrated to be valid for the evaluation of EEG rhythms at both low- and high-frequencies along wakefulness and sleep [25–27]. The goodness of fit was evaluated by visual inspection of the values of noise matrix V of the Mvar model.

The Mvar model is defined as

$$\sum_{j=0}^{p} A_j X_{t-j} = E_t, \tag{1}$$

where X_t is the L-dimensional vector representing the L-channel signal at time t; E_t is white noise; A_j is the $L * L$ matrix of the model coefficients, and p is the number of time points considered in the model. From the identified coefficients of the model A_j, spectral properties of the signals can be obtained by the following z-transformation of the above equation:

$$X(z) = H(z)E(z), \tag{2}$$

where $H(z)$ is a transfer function of the system

$$H(z) = \left(\sum_{j=0}^{p} A_j z^{-j} \right)^{-1},$$

$$z^{(-j)} = \exp(-2\pi i j f \, dt), \tag{3}$$

where f is frequency and dt is the time step.

Since the transfer function $H(f)$ is not a symmetric matrix, the information transmission from the jth to the ith channel is different from that from the ith to the jth channel. The DTF from the jth channel to the ith channel is defined as the square of the element of $H(f)$ divided by the squared sum of all elements of the relevant row,

$$\text{DTF}_{ij}(f) = \frac{\left|H_{ij}\right|^2}{\sum_{m=1}^{L}\left|H_{im}(f)\right|^2}. \tag{4}$$

A substantial difference between $\text{DTF}(f)_{ij}$ and $\text{DTF}(f)_{ji}$ may suggest an asymmetric information flow from electrode i to electrode j. When $\text{DTF}(f)_{ij}$ is greater in magnitude than $\text{DTF}(f)_{ji}$, the "direction" of the information flow is from electrode j to electrode i. On the other hand, the "direction" of the information flow is from electrode i to electrode j, when $\text{DTF}(f)_{ji}$ is greater in magnitude than $\text{DTF}(f)_{ij}$. Of note, the normalization of the DTF depends on the denominator of the previous formula.

To simplify the visualization and statistical analysis of the DTF results, the anterior-posterior directional flow of information of EEG functional coupling was indexed as "parietal-to-frontal" minus "frontal-to-parietal" DTF values, namely anterior-posterior DTFdiff values. Positive anterior-to-posterior DTFdiff values indicated a prevalence of parietal-to-frontal over frontal-to-parietal direction of the information flux.

The fact that the DTF analysis was done on the difference between the two reciprocal DTF directions should require a careful interpretation of the results. A zero value of such a difference meant equivalence of the two opposite DTF directions within the period of EEG data acquisition; namely, that the DTF directions were equally strong or equally weak or both equal to zero in the EEG period taken into account. It should be emphasized that this equivalence is true for the whole EEG period, but not necessarily for subperiods. At this preliminary stage of the study, we preferred to evaluate the DTF values for the entire EEG period, since the DTF values for shorter periods are supposedly less reliable from the statistical point of view [6, 43].

2.7. Statistical Analysis of DTFdiff Values. Statistical comparisons were performed by repeated measure ANOVAs. The Mauchley test evaluated the sphericity assumption and correction of the degrees of freedom was carried out using the Greenhouse-Geisser procedure. Subjects' age, gender education, and IAF were used as covariates in the statistical design. The Duncan test was used for post hoc comparisons ($P < .05$).

Statistical analysis of the anterior-to-posterior DTFdiff values ("direction" of the information flow between frontal and parietal regions) was performed using a three-way ANOVA including the factors Group (AD, amnesic MCI, and Nold; independent variable), Band (δ, θ, $\alpha1$, $\alpha2$, $\beta1$, $\beta2$, γ), and Electrode pair (F3-P3, Fz-Pz, and F4-P4) for the first study, and Group (MCI V−, MCI V+, and Nold; independent variable), Band (δ, θ, $\alpha1$, $\alpha2$, $\beta1$, $\beta2$, γ), and Electrode pair (F3-P3, Fz-Pz, and F4-P4) for the

second study. The working hypothesis was a statistical effect indicating a progressive reduction of anterior-to-posterior DTFdiff values across Nold, MCI V−, and MCI V+ subjects.

3. Results

The Nold subjects showed wide positive anterior-posterior DTFdiff values (parietal-to-frontal DTF values prevailing over frontal-to-parietal values), which were maximum in magnitude at $\alpha1$ for all electrode pairs of interest (F3-P3, Fz-Pz, F4-P4). Compared to Nold subjects, AD patients were characterized by a decrease of these DTFdiff values. MCI subjects presented a DTF trend similar to that of the AD, except for $\alpha1$, $\alpha2$, and $\beta1$ in which they showed intermediate values of anterior-to-posterior DTFdiff values, when compared to those of Nold and AD. In contrast to the anterior-to-posterior, inter-hemispheric DTFdiff values had similar magnitude values in the three groups, for all electrode pairs of interest (F3-F4, C3-C4, P3-P4).

Statistical ANOVA of the anterior-to-posterior DTFdiff values showed a two-way ANOVA interaction ($F(12,1218) = 3.49$; $P < .00001$) between the factors group (AD, amnesic MCI, Nold) and Band (δ, θ, $\alpha1$, $\alpha2$, $\beta1$, $\beta2$, γ). Duncan post hoc testing showed that the anterior-posterior DTFdiff values matched the patterns Nold > MCI > AD ($\beta1$: $P < .05$ to $P < .000001$), Nold > AD (θ: $P < .01$; $\alpha1$: $P < .000005$; $\alpha2$: $P < .000005$; $\beta2$: $P < .05$), and Nold > MCI (θ: $P < .01$; $\alpha1$: $P < .00001$; $\alpha2$: $P < .00001$). The upper part of Figure 1 shows the mean anterior-to-posterior DTFdiff values computed in the Nold, amnesic MCI, and AD subjects, for all frequency bands of interest (δ, θ, $\alpha1$, $\alpha2$, $\beta1$, $\beta2$, γ), obtained by averaging the anterior-to-posterior DTFdiff values of the three electrode pairs (F3-P3, Fz-Pz, F4-P4). These values represent the above-mentioned two-way ANOVA interaction.

Statistical ANOVA of the inter-hemispheric DTFdiff values showed no statistically significant effect including the factor group (AD, amnesic MCI, Nold). The bottom part of Figure 1 reports the mean inter-hemispheric DTFdiff values computed in the Nold, amnesic MCI, and AD subjects at all frequency bands of interest (δ, θ, $\alpha1$, $\alpha2$, $\beta1$, $\beta2$, γ), obtained by averaging the inter-hemispheric DTFdiff values of the three electrode pairs (F3-F4, C3-C4, P3-P4).

Compared to Nold subjects, MCI V− patients were characterized by a decrease of these DTFdiff values. MCI V+ subjects showed intermediate values of anterior-to-posterior DTFdiff values, when compared to those of Nold and MCI V−.

Statistical ANOVA of the anterior-to-posterior DTFdiff values showed a two-way ANOVA interaction ($F(12,690) = 3.65$; $P < .000001$) between the factors Group (MCI V−, MCI V+, Nold) and Band (δ, θ, $\alpha1$, $\alpha2$, $\beta1$, $\beta2$, γ). Duncan post hoc testing showed that the anterior-posterior DTFdiff values matched the patterns Nold > MCI V+ > MCI V− (θ: $P < .019$ to $P < .000002$; $\alpha1$: $P < .0016$ to $P < .000001$; $\alpha2$: $P < .0015$ to $P < .000001$; $\beta1$: $P < .015$ to $P < .000002$).

Figure 2 shows the mean anterior-to-posterior DTFdiff values computed in the Nold, MCI V+, and MCI V−

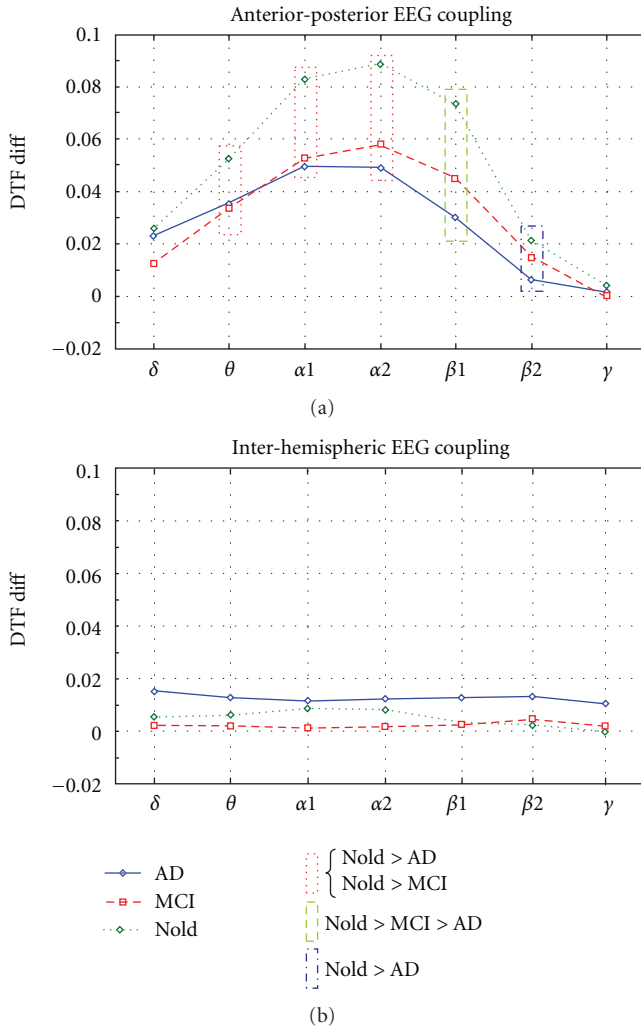FIGURE 2: Means of anterior-posterior DTFdiff values computed in the Nold, MCI V−, and MCI V+ subjects for all frequency bands of interest (δ, θ, $\alpha1$, $\alpha2$, $\beta1$, $\beta2$, γ). These means were obtained averaging the anterior-posterior DTFdiff values of the three electrode pairs (F3-P3, Fz-Pz, F4-P4), in order to represent a two-way ANOVA interaction ($F(12,690) = 3.65$; $P < .000001$) between the factors group (MCI V−, MCI V+, Nold) and Frequency band.

FIGURE 1: (a) Means of anterior-posterior DTFdiff values computed in the Nold, amnesic MCI, and AD for all frequency bands of interest (δ, θ, $\alpha1$, $\alpha2$, $\beta1$, $\beta2$, γ) averaging the anterior-posterior DTFdiff values of the three electrode pairs (F3-P3, Fz-Pz, F4-P4), in order to represent a two-way ANOVA interaction ($F(12,1218) = 3.49$; $P < .00001$) between the factors group (AD, amnesic MCI, Nold) and Frequency band (δ, θ, $\alpha1$, $\alpha2$, $\beta1$, $\beta2$, γ). (b) Means of inter-hemispheric DTFdiff values computed in the same subjects and frequency bands of interest. Means were obtained averaging the inter-hemispheric DTFdiff values of the electrode pairs (F3-F4, C3-C4, P3-P4).

subjects, for all frequency bands of interest (δ, θ, $\alpha1$, $\alpha2$, $\beta1$, $\beta2$, γ), obtained by averaging the anterior-to-posterior DTFdiff values of the three electrode pairs (F3-P3, Fz-Pz, F4-P4). These values represent the above-mentioned two-way ANOVA interaction.

4. Discussion

It has been shown previously that frontal-to-parietal direction of information flux within EEG functional coupling is an intrinsic feature of cerebral connectivity [6, 15, 29, 43, 4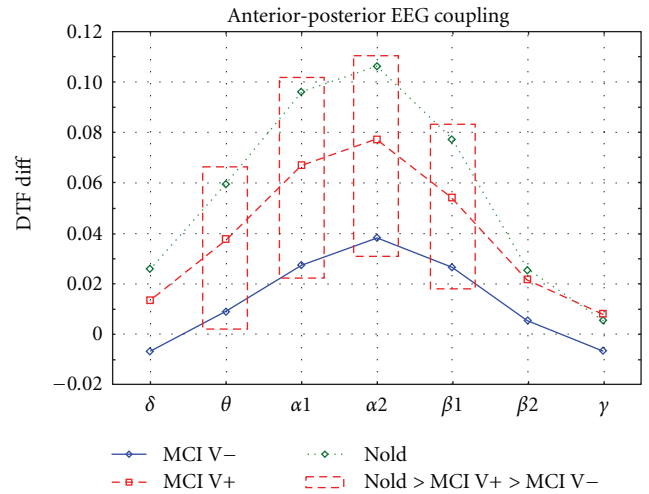4]. In the first study, we tested whether that direction of information flux is abnormal in pathological aging conditions such as amnesic MCI and AD, in line with the hypothesis that amnesic MCI is a preclinical stage of AD at the group level. Results showed that parietal-to-frontal direction of the information flux within EEG functional coupling was stronger in Nold than in amnesic MCI and/or AD subjects, principally at α and β rhythms. In contrast, the directional flow within inter-hemispheric EEG functional coupling did not discriminate among the three groups. These results suggest that directional information flux within EEG frontal-to-parietal coupling is quite sensitive to the preclinical stage of the AD at the group level. In the second study, we tested the hypothesis that dominant parietal-to-frontal EEG coupling, which is affected by AD processes as revealed in the first study, is relatively preserved in amnesic MCI subjects in whom the cognitive decline is mainly explained by white-matter vascular load. As main results, the dominant parietal-to-frontal EEG coupling at θ, α, and β rhythms was maximum in Nold, intermediate in MCI V+, and low in MCI V− subjects. These results are in line with the additive model of cognitive impairment, postulating that the cognitive impairment arises as the sum of neurodegenerative and cerebrovascular lesions. EEG might be especially sensitive to aging neurodegenerative processes and would be relatively spared in elderly subjects in whom the cognitive impairment is mainly explained by cerebrovascular lesions. The results of the present studies motivate future investigations aimed at evaluating the functional coupling of frontal and parietal sources of EEG activity as revealed by high-resolution techniques including linear or nonlinear inverse estimation and realistic modeling of the head as a volume conductor [5, 45].

References

[1] T. Dierks, R. Ihl, L. Frolich, and K. Maurer, "Dementia of the Alzheimer type: effects on the spontaneous EEG described by dipole sources," *Psychiatry Research*, vol. 50, no. 3, pp. 151–162, 1993.

[2] T. Dierks, V. Jelic, R. D. Pascual-Marqui et al., "Spatial pattern of cerebral glucose metabolism (PET) correlates with localization of intracerebral EEG-generators in Alzheimer's disease," *Clinical Neurophysiology*, vol. 111, no. 10, pp. 1817–1824, 2000.

[3] C. Huang, L. O. Wahlund, T. Dierks, P. Julin, B. Winblad, and V. Jelic, "Discrimination of Alzheimer's disease and mild cognitive impairment by equivalent EEG sources: a cross-sectional and longitudinal study," *Clinical Neurophysiology*, vol. 111, no. 11, pp. 1961–1967, 2000.

[4] N. V. Ponomareva, N. D. Selesneva, and G. A. Jarikov, "EEG alterations in subjects at high familial risk for Alzheimer's disease," *Neuropsychobiology*, vol. 48, no. 3, pp. 152–159, 2003.

[5] J. Jeong, "EEG dynamics in patients with Alzheimer's disease," *Clinical Neurophysiology*, vol. 115, no. 7, pp. 1490–1505, 2004.

[6] C. Babiloni, G. Binetti, E. Cassetta et al., "Mapping distributed sources of cortical rhythms in mild Alzheimer's disease. A multicentric EEG study," *NeuroImage*, vol. 22, no. 1, pp. 57–67, 2004.

[7] T. Koenig, L. Prichep, T. Dierks et al., "Decreased EEG synchronization in Alzheimer's disease and mild cognitive impairment," *Neurobiology of Aging*, vol. 26, no. 2, pp. 165–171, 2005.

[8] E. P. Sloan, G. W. Fenton, N. S. J. Kennedy, and J. M. MacLennan, "Electroencephalography and single photon emission computed tomography in dementia: a comparative study," *Psychological Medicine*, vol. 25, no. 3, pp. 631–638, 1995.

[9] G. Rodriguez, F. Nobili, G. Rocca, F. De Carli, M. V. Gianelli, and G. Rosadini, "Quantitative electroencephalography and regional cerebral blood flow: discriminant analysis between Alzheimer's patients and healthy controls," *Dementia and Geriatric Cognitive Disorders*, vol. 9, no. 5, pp. 274–283, 1998.

[10] G. Rodriguez, F. Copello, P. Vitali, G. Perego, and F. Nobili, "EEG spectral profile to stage Alzheimer's disease," *Clinical Neurophysiology*, vol. 110, no. 10, pp. 1831–1837, 1999.

[11] G. Rodriguez, F. Nobili, F. Copello et al., "^{99m}Tc-HMPAO regional cerebral blood flow and quantitative electroencephalography in Alzheimer's disease: a correlative study," *The Journal of Nuclear Medicine*, vol. 40, no. 4, pp. 522–529, 1999.

[12] R. Zappoli, A. Versari, M. Paganini et al., "Brain electrical activity (quantitative EEG and bit-mapping neurocognitive CNV components), psychometrics and clinical findings in presenile subjects with initial mild cognitive decline or probable Alzheimer-type dementia," *Italian Journal of Neurological Sciences*, vol. 16, no. 6, pp. 341–376, 1995.

[13] S. Elmståhl, "Postural hypotension and EEG variables predict cognitive decline: results from a 5-year follow-up of healthy elderly women," *Dementia and Geriatric Cognitive Disorders*, vol. 8, no. 3, pp. 180–187, 1997.

[14] V. Jelic, S. E. Johansson, O. Almkvist et al., "Quantitative electroencephalography in mild cognitive impairment: longitudinal changes and possible prediction of Alzheimer's disease," *Neurobiology of Aging*, vol. 21, no. 4, pp. 533–540, 2000.

[15] C. Babiloni, G. Binetti, E. Cassetta et al., "Sources of cortical rhythms change as a function of cognitive impairment in pathological aging: a multicenter study," *Clinical Neurophysiology*, vol. 117, no. 2, pp. 252–268, 2006.

[16] K. P. O'Connor, J. C. Shaw, and C. O. Ongley, "The EEG and differential diagnosis in psychogeriatrics," *British Journal of Psychiatry*, vol. 135, no. 2, pp. 156–162, 1979.

[17] V. Jelic, P. Julin, M. Shigeta et al., "Apolipoprotein E $\varepsilon4$ allele decreases functional connectivity in Alzheimer's disease as measured by EEG coherence," *Journal of Neurology Neurosurgery and Psychiatry*, vol. 63, no. 1, pp. 59–65, 1997.

[18] T. Locatelli, M. Cursi, D. Liberati, M. Franceschi, and G. Comi, "EEG coherence in Alzheimer's disease," *Electroencephalography and Clinical Neurophysiology*, vol. 106, no. 3, pp. 229–237, 1998.

[19] Y. Wada, Y. Nanbu, M. Kikuchi, Y. Koshino, T. Hashimoto, and N. Yamaguchi, "Abnormal functional connectivity in Alzheimer's disease: intrahemispheric EEG coherence during rest and photic stimulation," *European Archives of Psychiatry and Clinical Neuroscience*, vol. 248, no. 4, pp. 203–208, 1998.

[20] Y. Wada, Y. Nanbu, Y. Koshino, N. Yamaguchi, and T. Hashimoto, "Reduced interhemispheric EEG coherence in Alzheimer disease: analysis during rest and photic stimulation," *Alzheimer Disease and Associated Disorders*, vol. 12, no. 3, pp. 175–181, 1998.

[21] V. Knott, E. Mohr, C. Mahoney, and V. Ilivitsky, "Electroencephalographic coherence in Alzheimer's disease: comparisons with a control group and population norms," *Journal of Geriatric Psychiatry and Neurology*, vol. 13, no. 1, pp. 1–8, 2000.

[22] G. Adler, S. Brassen, and A. Jajcevic, "EEG coherence in Alzheimer's dementia," *Journal of Neural Transmission*, vol. 110, no. 9, pp. 1051–1058, 2003.

[23] Z. Xiang, J. R. Huguenard, and D. A. Prince, "Cholinergic switching within neocortical inhibitory networks," *Science*, vol. 281, no. 5379, pp. 985–988, 1998.

[24] M. Mesulam, "The cholinergic lesion of Alzheimer's disease: pivotal factor or side show?" *Learning and Memory*, vol. 11, no. 1, pp. 43–49, 2004.

[25] M. J. Kaminski and K. J. Blinowska, "A new method of the description of the information flow in the brain structures," *Biological Cybernetics*, vol. 65, no. 3, pp. 203–210, 1991.

[26] A. Korzeniewska, S. Kasicki, M. Kamiński, and K. J. Blinowska, "Information flow between hippocampus and related structures during various types of rat's behavior," *Journal of Neuroscience Methods*, vol. 73, no. 1, pp. 49–60, 1997.

[27] M. Kamiński, K. Blinowska, and W. Szelenberger, "Topographic analysis of coherence and propagation of EEG activity during sleep and wakefulness," *Electroencephalography and Clinical Neurophysiology*, vol. 102, no. 3, pp. 216–227, 1997.

[28] T. Mima, T. Matsuoka, and M. Hallett, "Functional coupling of human right and left cortical motor areas demonstrated with partial coherence analysis," *Neuroscience Letters*, vol. 287, no. 2, pp. 93–96, 2000.

[29] C. Babiloni, F. Babiloni, F. Carducci et al., "Human cortical rhythms during visual delayed choice reaction time tasks: a high-resolution EEG study on normal aging," *Behavioural Brain Research*, vol. 153, no. 1, pp. 261–271, 2004.

[30] C. Babiloni, G. B. Frisoni, M. Pievani et al., "White matter vascular lesions are related to parietal-to-frontal coupling of EEG rhythms in mild cognitive impairment," *Human Brain Mapping*, vol. 29, no. 12, pp. 1355–1367, 2008.

[31] C. Babiloni, R. Ferri, G. Binetti et al., "Directionality of EEG synchronization in Alzheimer's disease subjects," *Neurobiology of Aging*, vol. 30, no. 1, pp. 93–102, 2009.

[32] G. McKhann, D. Drachman, and M. Folstein, "Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA

work group under the auspices of Department of Health and Human Services Task Force on Alzheimer's disease," *Neurology*, vol. 34, no. 7, pp. 939–944, 1984.

[33] M. F. Folstein, S. E. Folstein, and P. R. McHugh, "'Mini mental state'. A practical method for grading the cognitive state of patients for the clinician," *Journal of Psychiatric Research*, vol. 12, no. 3, pp. 189–198, 1975.

[34] J. A. Yesavage, T. L. Brink, and T. L. Rose, "Development and validation of a geriatric depression screening scale: a preliminary report," *Journal of Psychiatric Research*, vol. 17, no. 1, pp. 37–49, 1982.

[35] W. G. Rosen, R. D. Terry, P. A. Fuld, R. Katzman, and A. Peck, "Pathological verification of ischemic score in differentiation of dementias," *Annals of Neurology*, vol. 7, no. 5, pp. 486–488, 1980.

[36] M. P. Lawton and E. M. Brody, "Assessment of older people: self-maintaining and instrumental activities of daily living," *The Gerontologist*, vol. 9, no. 3, pp. 179–186, 1969.

[37] R. C. Petersen, R. Doody, A. Kurz et al., "Current concepts in mild cognitive impairment," *Archives of Neurology*, vol. 58, no. 12, pp. 1985–1992, 2001.

[38] F. Portet, P. J. Ousset, P. J. Visser et al., "Mild cognitive impairment (MCI) in medical practice: a critical review of the concept and new diagnostic procedure. Report of the MCI Working Group of the European Consortium on Alzheimer's Disease," *Journal of Neurology, Neurosurgery and Psychiatry*, vol. 77, no. 6, pp. 714–718, 2006.

[39] C. Geroldi, R. Rossi, C. Calvagna et al., "Medial temporal atrophy but not memory deficit predicts progression to dementia in patients with mild cognitive impairment," *Journal of Neurology, Neurosurgery and Psychiatry*, vol. 77, no. 11, pp. 1219–1222, 2006.

[40] T. Mima, T. Matsuoka, and M. Hallett, "Information flow from the sensorimotor cortex to muscle in humans," *Clinical Neurophysiology*, vol. 112, no. 1, pp. 122–126, 2001.

[41] C. Babiloni, F. Babiloni, F. Carducci et al., "Coupling between "hand" primary sensorimotor cortex and lower limb muscles after ulnar nerve surgical transfer in paraplegia," *Behavioral Neuroscience*, vol. 118, no. 1, pp. 214–222, 2004.

[42] C. Babiloni, F. Carducci, F. Vecchio et al., "Functional fron-toparietal connectivity during short-term memory as revealed by high-resolution EEG coherence analysis," *Behavioral Neuroscience*, vol. 118, no. 4, pp. 687–697, 2004.

[43] C. Babiloni, F. Babiloni, F. Carducci et al., "Human alpha rhythms during visual delayed choice reaction time tasks: a magnetoencephalography study," *Human Brain Mapping*, vol. 24, no. 3, pp. 184–192, 2005.

[44] C. Babiloni, L. Benussi, G. Binetti et al., "Apolipoprotein E and alpha brain rhythms in mild cognitive impairment: a multicentric electroencephalogram study," *Annals of Neurology*, vol. 59, no. 2, pp. 323–334, 2006.

[45] C. Babiloni, G. Binetti, A. Cassarino et al., "Sources of cortical rhythms in adults during physiological aging: a multicentric EEG study," *Human Brain Mapping*, vol. 27, no. 2, pp. 162–172, 2006.