Neuroscience 316 (2016) 143–150

CORTICAL CONNECTIVITY AND MEMORY PERFORMANCE IN COGNITIVE DECLINE: A STUDY VIA GRAPH THEORY FROM EEG DATA

F. VECCHIO,[a]* F. MIRAGLIA,[a] D. QUARANTA,[b,c] G. GRANATA,[a] R. ROMANELLO,[a] C. MARRA,[b,c] P. BRAMANTI[d] AND P. M. ROSSINI[a,b]

[a] *Brain Connectivity Laboratory, IRCCS San Raffaele Pisana, Rome, Italy*

[b] *Institute of Neurology, Department of Geriatrics, Neuroscience & Orthopedics, Catholic University, Policlinic A. Gemelli, Rome, Italy*

[c] *Neuropsychological Center, Catholic University, Rome, Italy*

[d] *IRCCS Centro Neurolesi Bonino-Pulejo, Messina, Italy*

Abstract—Functional brain abnormalities including memory loss are found to be associated with pathological changes in connectivity and network neural structures. Alzheimer's disease (AD) interferes with memory formation from the molecular level, to synaptic functions and neural networks organization. Here, we determined whether brain connectivity of resting-state networks correlate with memory in patients affected by AD and in subjects with mild cognitive impairment (MCI). One hundred and forty-four subjects were recruited: 70 AD (MMSE Mini Mental State Evaluation 21.4), 50 MCI (MMSE 25.2) and 24 healthy subjects (MMSE 29.8). Undirected and weighted cortical brain network was built to evaluate graph core measures to obtain Small World parameters. eLORETA lagged linear connectivity as extracted by electroencephalogram (EEG) signals was used to weight the network. A high statistical correlation between Small World and memory performance was found. Namely, higher Small World characteristic in EEG gamma frequency band during the resting state, better performance in short-term memory as evaluated by the digit span tests. Such Small World pattern might represent a biomarker of working memory impairment in older people both in physiological and pathological conditions.

Key words: graph theory, Alzheimer and MCI, functional connectivity, EEG and alpha band, eLORETA, memory.

INTRODUCTION

Memory is the ability to encode, store, retain and retrieve information and past experiences. What we have stored in our memory archives gives us the capability to learn and adapt new information and to build relationships with previous experiences. ''Semantic Memory" is the store of encyclopedic memories, referring to people, words and general concepts, learned and retained from education, daily activity, and emotional experiences (Binder and Desai, 2011). Therefore, all memory systems are central to our ability to perform daily life activities and to correctly function as individuals contributing to societal life; it is therefore conceivable that age-related memory impairments represent significant sources of morbidity and disability (Khan et al., 2014). Episodic memory loss is also featuring neurodegenerative diseases such as Alzheimer's disease (AD). Episodic memory loss is among the initial AD symptoms (Jahn, 2013); both working or short-term memory and long-term memory are affected during the disease. AD pathology interferes with memory formation from molecular level, to synaptic functions and neural networks organization (Aisen et al., 2010).

On the one hand, clinical and neuropsychological analysis of memory deficits triggers the definition of AD subtypes, disease staging and prognosis. Despite new AD criteria that allow the earlier diagnosis of the disease by inclusion of biomarkers derived from cerebrospinal fluid or hippocampal volume analysis (Dubois et al., 2010, 2014), neuropsychological testing remains the main pillar of AD diagnosis and staging.

On the other hand, to perform the variety of human cognitive tasks, brain regions do not work separately, but interact through complex and dynamic neural networks with time- and task-varying architecture. A recent challenge is to understand how the functionally specialized brain areas interact within the frame of dynamic networks during cognitive performances including memory (Basar and Schurmann, 2001; Miller and Wilson, 2008). This is particularly challenging when dealing with dynamic interactions among neural assemblies which change in a time frame in the order of few tens of milliseconds.

Watts and Strogatz introduced the concept of 'Small-World' network organization, focusing on an optimal balance between local specialization and global integration (Watts and Strogatz, 1998). This approach, combined with graph theory concepts, is a promising way to characterize brain functional organization (Bassett and Bullmore, 2006) and correlate it with

*Corresponding author. Address: Brain Connectivity Laboratory, IRCCS San Raffaele Pisana, Via Val Cannuta, 247, 00166 Rome, Italy. Tel: +39-06-52253767.
E-mail addresses: fabrizio.vecchio@uniroma1.it, fabrizio.vecchio@sanraffaele.it (F. Vecchio).

Abbreviations: AD, Alzheimer's disease; BAs, Brodmann Areas; EEG, electroencephalogram; eLORETA, exact low-resolution electromagnetic tomography; ICA, independent component analysis; MCI, mild cognitive impairment; MMSE, Mini Mental State Evaluation; MNI, Montreal Neurological Institute; ROIs, Regions of Interests; SW, Small World.

http://dx.doi.org/10.1016/j.neuroscience.2015.12.036

behavior or clinical and tests performances. For instance, it evaluates whether the functional connectivity patterns between brain areas reproduce the organization of more or less strongly bound networks based on the strength of synchronization in time-varying oscillatory neuronal firing of different brain regions as reflected by oscillating electroencephalogram (EEG) rhythms (Vecchio et al., 2014a–c, 2015b).

The human brain consists of complex inhibitory and excitatory circuits of functionally specialized areas with a continuous, time-varying interplay – with millisecond epochs – for sharing and integrating information. The white-matter (axonal) fibers provide the anatomical basis for signal transfer and communication; these connections are not random, but are organized in a ‘‘Small-World” network topology characterized by a high degree of local clustering (segregation) and the presence of long-distance connections (integration).

Previous studies (Sporns and Zwi, 2004; Stam, 2004; Bassett and Bullmore, 2006; Ponten et al., 2007; de Haan et al., 2009) demonstrated that healthy functional as well as structural brain networks have Small-World properties, which are degraded by mechanisms of brain degeneration. Our previous studies (Vecchio et al., 2014b; Miraglia et al., 2015a) suggested that in resting-state condition, Small-World characteristics decreased in AD patients with respect to mild cognitive impairment (MCI) subject in the low-frequency EEG band, namely the MCI connectivity pattern being more small worldnessy than that of the AD group. Furthermore, we found an intermediate trend of the MCI group, with more small worldness with respect to AD and nearer to Nold’s network topology (Miraglia et al., 2015a). The cognitive impairment of MCI is probably causing Small-World architecture alteration, deviating from the Small-World network structure seen in the healthy toward a more ‘‘ordered” type. This is associated with less efficient information exchange between brain areas, supporting the disconnection hypothesis of AD. This trend also supports the idea of a functional impairment of cortical neural synchronization due to the disease processes and the hypothesis of a progressive impairment of cortical reactivity across a MCI and AD subjects.

Keeping also in mind that memory is declining with physiological brain aging and that memory deficits are regarded as an initial symptom of AD (Petersen et al., 2001), the aim of this study was to determine whether the Small World (SW) characteristic of the resting-state brain networks as reflected in the EEG rhythms correlate with memory measures in subjects affected by AD and those in possible prodromic stage of dementia as MCI.

EXPERIMENTAL PROCEDURES

Participants

A dataset of 144 subjects was analyzed. The patients group included 70 AD (MMSE Mini Mental State Evaluation 21.4 ± 0.6 SEM), while the amnesic MCI group included 50 subjects (MMSE 25.2 ± 0.5). In the EEG control group, 24 healthy subjects Nold – Normal old – (MMSE 29.8 ± 0.2) was selected. Mean age was paired in the three groups: 73.2 ± 2.1 years for AD, 73.5 ± 1.5 years for MCI and 72.9 ± 1.6 years for Nold.

All subjects were right-handed at Handedness Questionnaire. Informed consent was obtained from each subject and the study was approved by local Ethics Committee. Experimental procedures were conformed to the Declaration of Helsinski and national guidelines.

Inclusion and exclusion criteria

All subjects took part in a battery of neuropsychological tests to assess attention, memory, executive function, visuo-construction abilities and language. Memory was assessed by means of the immediate and delayed recall of the Rey Auditory Verbal Learning Test (Carlesimo et al., 1996) the delayed recall of Rey figures (Rey, 1968), the delayed recall of a 3-word list (Chandler et al., 2004), and the delayed recall of a story. Furthermore, specific short-term memory performance was assessed via digit spanning both forward and backward tasks (Monaco et al., 2013) in subgroups including 34 AD (MMSE 21.42 ± 0.7) and 20 amnesic MCI (MMSE 25.15 ± 0.6). Pathological performances on memory tasks were set below the 5th percentile of the normal population.

AD was diagnosed according to the National Institute on Aging-Alzheimer’s Association workgroups (McKhann et al., 2011) and DSM IV TR criteria.

Amnesic MCI was diagnosed according to guidelines and clinical standards (Flicker et al., 1991; Zaudig, 1992; Petersen et al., 1997, 2001; Portet et al., 2006). The exclusion criteria for MCI included: (i) mild AD; (ii) evidence of concomitant dementia such as frontotemporal, vascular, reversible dementias, marked fluctuations in cognitive performance compatible with Lewy body dementia and/or features of mixed dementias; (iii) evidence of concomitant extra-pyramidal symptoms; (iv) clinical and indirect evidence of depression as revealed by the Geriatric Depression Scale GDS (Yesavage et al., 1982); (v) other psychiatric diseases, epilepsy, drug addiction, alcohol dependence, use of neuro/psychoactive drugs including acetylcholinesterase inhibitors; and (vi) current or previous uncontrolled or complicated systemic diseases (including diabetes mellitus) or traumatic brain injuries.

Data recordings and preprocessing

The EEG recording was performed at rest, with closed eyes no task conditions (at least 5 min), and while the subject was seated and relaxed in a sound-attenuated and dimly lit room. Electroencephalographic signals were measured from at least 19 electrodes positioned according to the International 10–20 system, 32 electrodes for the subgroup of patients that also performed specific short-term memory tests. Eye movements were monitored from vertical and horizontal EOGs. Skin/electrode impedances were lowered below 5 K Ω. Data were analyzed by Matlab R2011b software (MathWorks), using scripts based on EEGLAB 11.0.5.4b toolbox (http://www.sccn.ucsd.edu/eeglab). Recordings

were band-pass filtered (FIR, 0.1–47 Hz), and the sampling rate frequency was set up at 256 or 512 Hz. In order to avoid potential bias in the results, we obtained the same sampling frequency across the whole study downsampling at 256 Hz. EEG data were then fragmented in 2-s epochs, cleaning artifacts (i.e., eye movements, EKG activity, and muscle contraction) using an independent component analysis (ICA) procedure performed in EEGLAB Infomax ICA algorithm (Bell and Sejnowski, 1995; Jung et al., 2000; Iriarte et al., 2003). Subjects with at least 80 artifact-free epochs were selected.

Functional connectivity analysis

EEG functional connectivity analysis has been performed using the exact low-resolution electromagnetic tomography (eLORETA) (Vecchio et al., 2014a–c) software (freely available at http://www.uzh.ch/keyinst/NewLORETA/LORETA01.htm). The eLORETA algorithm is a linear inverse solution for EEG signals that has no localization error to point sources under ideal (noise-free) conditions (Pascual-Marqui, 2002).

Based on the scalp-recorded electric potential distribution, the exact low-resolution brain electromagnetic tomography (eLORETA) software was used to compute the cortical three-dimensional distribution of current density. The description of the method and the proof of its exact zero-error localization property are described in Pascual-Marqui (2009).

In the current implementation of eLORETA, computations were made in a realistic head model (Fuchs et al., 2002) using the MNI152 template (Mazziotta et al., 2001), with the three-dimensional solution space restricted to cortical gray matter, as determined by the probabilistic Talairach atlas (Lancaster et al., 2000). The standard electrode positions on the MNI152 scalp were taken from Jurcak et al. (2007). The intracerebral volume is partitioned in 6239 voxels at a 5-mm spatial resolution. Thus, eLORETA images represent the electric activity at each voxel in the neuroanatomic Montreal Neurological Institute (MNI) space as the exact magnitude of the estimated current density. Anatomical labels as Brodmann Areas (BAs) are also reported using MNI space, with correction to Talairach space (Brett et al., 2002).

To obtain a topographic view of the whole brain, brain connectivity was computed with sLORETA/eLORETA software in 84 regions positioning the center in the available 42 BAs (1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 13, 17, 18, 19, 20, 21, 22, 23, 24, 25, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47) in left and right hemispheres.

Regions of Interests (ROIs) are needed for the estimation of electric neuronal activity that is used to analyze brain functional connectivity. The signal at each cortical ROI consisted of the average electric neuronal activities of all voxels belonging to that ROI, as computed with eLORETA.

For each hemisphere, among the eLORETA current density time series of the 42 ROIs, intracortical Lagged Linear Coherence, extracted using a sphere with 19-mm radius (Pascual-Marqui, 2007), was computed between all possible pairs of the ROIs for each of the five independent EEG frequency bands of delta (2–4 Hz), theta (4–8 Hz), alpha 1 (8–10.5 Hz), alpha 2 (10.5–13 Hz), beta 1 (13–20 Hz), beta 2 (20–30 Hz) and gamma (30–45 Hz) for each subject in line with previous studies (Miraglia et al., 2015b; Vecchio et al., 2015c).

Starting with the definition of the complex valued coherence between time series x and y in the frequency band ω—which is based on the cross-spectrum given by the covariance and variances of the signals—the lagged linear coherence in the frequency band ω is reported in accordance with the following equation (Pascual-Marqui, 2007):

$$\mathrm{LagR}^2_{xyw} = \frac{[\mathrm{ImCov}(x,y)]^2}{\mathrm{Var}(x) * \mathrm{Var}(y) - [\mathrm{ReCov}(x,y)]^2}$$

where Var and Cov are variances and covariance of the signals.

It was developed as a measure of true physiological connectivity not affected by volume conduction and low spatial resolution (Pascual-Marqui, 2007). The values of lagged linear connectivity computing between all pairs of ROIs for each frequency band were used as weights of the networks built in the graph analysis.

Graph analysis

A network is a mathematical representation of a real-world complex system. It is defined by a collection of nodes (vertices) and links (edges) between pairs of nodes. Nodes in large-scale brain networks usually represent brain regions, while links represent anatomical, functional or effective connections (Friston, 1994), depending on the dataset. Anatomical connections typically correspond to white matter fiber tracts between pairs of gray matter brain regions (cortical areas or subcortical relays). Functional connections correspond to magnitudes of temporal correlations in activity and may occur between pairs of anatomically unconnected regions.

A weighted graph is a mathematical representation of a set of elements (vertices) that may be linked through connections of variable weights (edges).

In the present study, (no thresholded) weighted and undirected networks were built. The vertices of the network are the estimated cortical sources in the BAs, and the edges are weighted by the Lagged Linear value within each pair of vertices. The software instrument used here for the graph analysis was the Brain Connectivity Toolbox (BCT, http://www.brain-connectivity-toolbox.net/), adapted with our own Matlab scripts.

Core measures of graph theory were computed referring to the concepts of brain integration and segregation. In particular, segregation refers to the degree to which network elements form separate clusters and correspond to clustering coefficient (C) (Rubinov and Sporns, 2010). Integration refers to the capacity of network to become interconnected and exchange information (Sporns, 2013), and it is defined

characteristic path length (L) coefficient (Rubinov and Sporns, 2010). The clustering (C) around a vertex i is quantified by the number of triangles in which vertex i participates, normalized by the maximum possible number of such triangles (Onnela et al., 2005; Rubinov and Sporns, 2010).

As triangles are one type of subgraph, the definition of C may be used to yield the weighted clustering coefficient C^w by replacing the number of triangles with the sum of triangle intensities as (Onnela et al., 2005; Rubinov and Sporns, 2010) follows:

$$C^w = \frac{1}{n}\sum_{i\in N}\frac{2t_i^w}{k_i(k_i-1)}$$

where

$$t_i^w = \frac{1}{2}\sum_{j,h\in N}(w_{ij}w_{ih}w_{jh})^{1/3}$$

is the geometric mean of triangles around i, w_{ij} are connection weights associated to links (i,j), assuming that weights are normalized, such that $0 \leqslant w_{ij} \leqslant 1$ for all i and j. The mean clustering coefficient is computed for all nodes of the graph and then averaged. It is a measure for the tendency of network elements to form local clusters (de Haan et al., 2009).

Characteristic path length of the network and weighted characteristic path length L^w are defined as (Onnela et al., 2005; Rubinov and Sporns, 2010) follows:

$$L^w = \frac{1}{n}\sum_{i\in N}\frac{\sum_{j\in N, j\neq i}d_{ij}^w}{n-1}$$

with

$$d_{ij}^w = \sum a_{uv} \in g_{i\leftrightarrow j}^w f(w_{uv})$$

that represents the shortest weighted path length between i and j. f is a map (e.g., an inverse) from weight to length and $g_{i}^{w}\leftrightarrow j$ is the shortest weighted path between i and j.

The S^w coefficient describes the balance between local connectedness and global integration of a network. When S^w is larger than 1, a network has Small-World properties. Small-World organization is intermediate between that of random networks, the short overall path length of which is associated with a low level of local clustering, and that of regular networks or lattices, and the highlevel of clustering of which is accompanied by a long path length (Vecchio et al., 2014b). This means that nodes are linked through relatively few intermediate steps, and most nodes maintain few direct connections (Miraglia et al., 2015a). Small-worldness (S^w) parameter is defined as the ratio between normalized C^w and L^w with respect to the frequency bands. To obtain individual normalized relative measures, the values of characteristic path length and of clustering coefficient were divided by the mean values obtained by the average of themselves in all bands of each subjects.

Statistical evaluation

eLORETA statistical evaluation was made on a graph analysis pattern extracted with sLORETA/eLORETA from the brain network (including 84 ROI, 42 ROIs of the left and 42 ROIs of the right hemisphere). The normality of the data was tested using the Kolmogorov–Smirnov test, and the hypothesis of Gaussianity could not be rejected. In order to confirm the goodness of the data, a statistical ANOVA design was addressed for the SW between the factors Group (AD, MCI, Nold) and Band (delta, theta, alpha 1, alpha 2, beta 1, beta 2, gamma).

Pearson's linear correlations were tested between memory test scores and Small-World coefficient considering all subjects as a whole group (Bonferroni corrected to obtain $p < 0.05$).

RESULTS

With an illustrative purpose, Fig. 1 reports the connectivity patterns from the eLORETA connectivity maps for the groups of subjects in the explored frequencies. The maps illustrated only the connections (among the mentioned 84 ROIs: 42 left and 42 right BAs) that resulted in higher than an arbitrary threshold for each frequency band. The arbitrary threshold was selected only by a visual inspection in order to show the differences among groups. A visual inspection shows that AD subjects present a higher number of connections in the lower frequency bands with respect to Nold. Moreover, alpha bands present a focal localization in the posterior areas that decreases the number of tracts in AD respect to Nold group.

ANOVA suggested that SW showed statistically significant interaction ($F_{12,846} = 5.85$, $p < 0.00001$) between the factors Group (AD, MCI, Nold) and Band (delta, theta, alpha 1, alpha 2, beta 1, beta 2, gamma; Fig. 2). Duncan planned post hoc testing showed that, in line with previous evidence (Miraglia et al., 2015a) the pattern Nold > MCI > AD was fitted in delta ($p < 0.05$) band, while Nold and MCI were higher than AD in theta, beta 1 and beta 2 ($p < 0.01$); in alpha bands Nold presented lower values only with respect to AD ($p < 0.05$).

Behavioral analysis of short-term memory tasks showed a statistical t test between the two subgroups of Alzheimer patients and MCI subjects, founding significant differences in both digit span forward ($p < 0.05$) and backward ($p < 0.0335$).

Correlation analyses were performed on the weighted SW coefficient in all seven EEG frequency bands. Considering all subjects as a group, gamma rhythm SW positively correlate with the memory tests' scores. Results show that an increase of gamma Small worldness is linked to a better performance to digit span both forward ($r = 0.2739$, $p = 0.045$) and backward ($r = 0.2861$, $p = 0.036$). Fig. 3 reports the scatterplots of these two correlations.

Finally, as a first step of a further individual analysis possibility, we evaluated z score of digit span tests (both forward and backward) with respect to normative data of hundreds of subjects divided for gender and education (Choi et al., 2014), the same was done for the gamma SW parameter with respect to the normal data of the Nold subjects of this study. We considered for each subject whether the z score indicated differences higher than

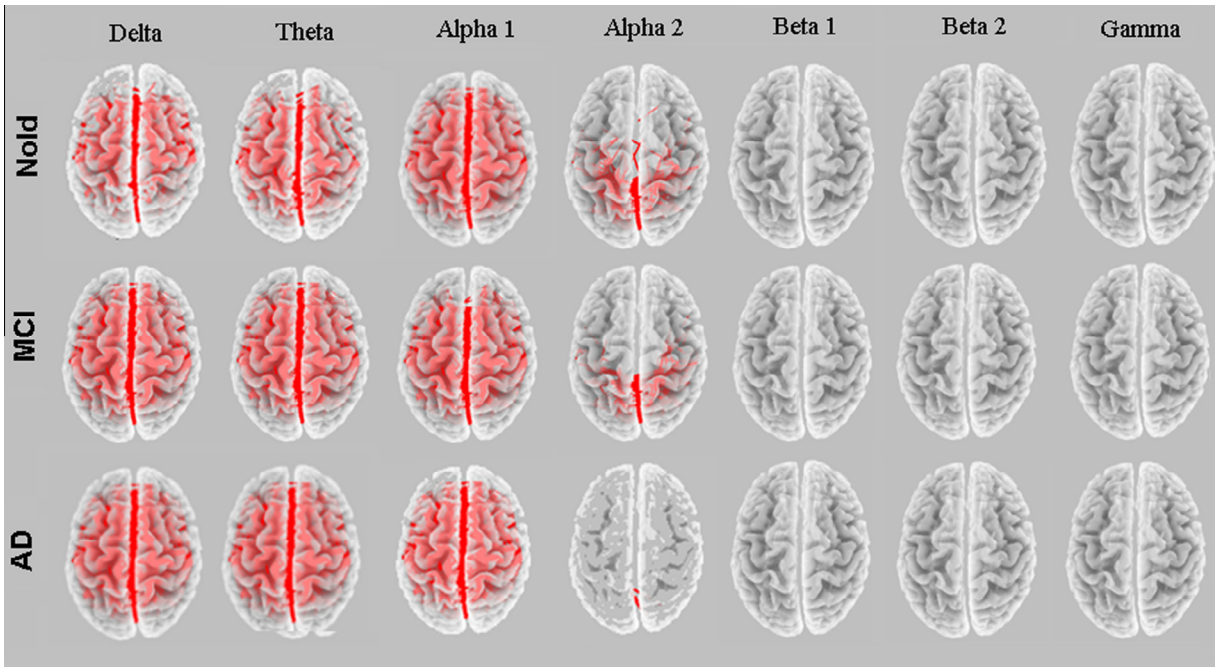

Fig. 1. Small World trends in the three groups of subjects.

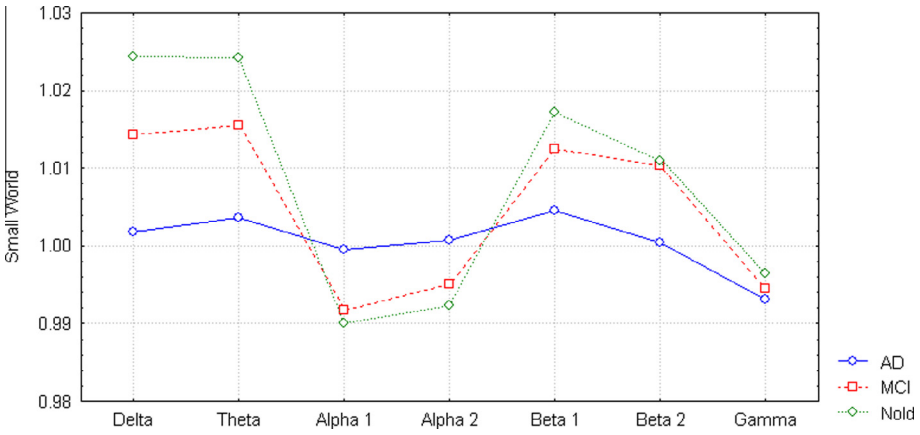

Fig. 2. Small World trends in the three groups of subjects.

95% (one tail considering lower number in patients than in healthy) for both tests and EEG parameters. Results showed that in 42.8% of patients presenting both tests far from the controls the gamma SW where lower than in controls (12 of 28 patients); in 88.5% of patients presenting at least one test (forward and/or backward) within the normative frame, the gamma SW where in line with controls (23 of 26 patients); finally 100% of patients (two patients), that presented both forward and backward scores similar to controls, gamma SW was also within normal limits.

DISCUSSION

Functional brain abnormalities producing memory loss are associated with pathological changes in neural connectivity and network structures. The human brain includes complex inhibitory and excitatory circuits consisting of functionally specialized regions that continuously interact to acquire, share and integrate information in a constant state of dynamic fluctuations also governed by a number of variables including attention, emotions, motivation, arousal which finally influence network performance. Furthermore, the connections between brain areas are not random but reflect segregation and integration characteristics, as revealed by local clustering (segregation) and path length (integration). A well-designed anatomical network could combine the occurrence of functionally specialized (segregated) modules with a robust number of intermodular (integrating) links. Such a design is commonly termed Small-World and indeed appears to be a ubiquitous facet of anatomical connectivity. It is commonly thought that such an organization reflects an optimal balance of functional integration and segregation (Sporns and Honey, 2006).

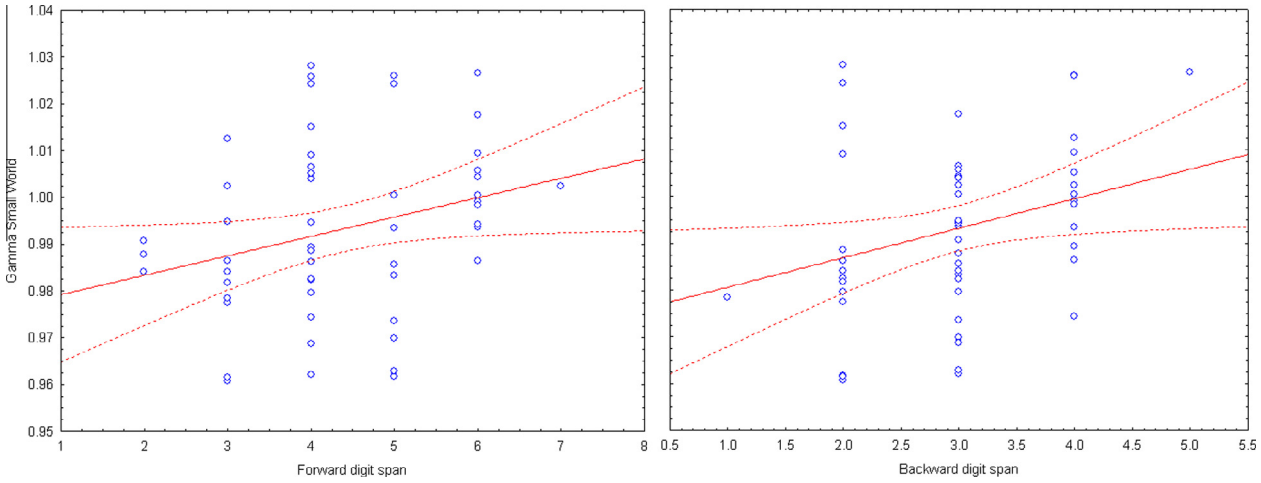

Fig. 3. Scatterplots of Small World correlation with memory tasks.

Results of the present study suggested that, in line with previous evidence (Miraglia et al., 2015a), processes of cerebral integration and segregation in AD are deranged. SW properties of the network had different patterns in pathological aging, with different trends in the EEG frequency bands. Delta low frequency pathological (during wakefulness) band presented lower values of SW in AD, intermediate in MCI and higher in Nold, the opposite was true in the cognitive alpha bands. Keeping in mind the fact that lower values of SW represent a more ordered structure, it is possible to speculate that in delta band it represents a sort of functional disconnection while in alpha band it could be seen as a marker of high performance of the cortical networks (Miraglia et al., 2015a; Vecchio et al., 2015a).

Here, it is not only confirmed a different trend in the EEG of Nold, MCI and Alzheimer subjects regarding the SW distributions on the frequency bands of interest, but it is also – and more importantly – shown the correlation of the SW properties with short-term memory performance. Namely, higher the gamma band SW characteristic during the resting state, better the performance to short-term memory tasks as evaluated by the digit span tests.

AD brain topology can be represented by a progressive derangement of the brain organization in hub regions and long-range connections to spoke nodes causing Small-World architecture alteration. In fact, decreasing local and global connectivity parameters, the large-scale functional brain network organization in AD deviates from the optimal Small-World architecture toward a more ‘‘ordered” type (as reflected by lower values of SW) leading to a less efficient information exchange between brain areas in line with the disconnection hypothesis of AD. These results are reflected on the EEG by the observation that a less ordered brain network (as reflected by increasing value of SW) in gamma band is associated to better memory performance although no significant difference was observed when comparing the three groups of subjects (as a possible sign of not sufficient sensibility at group level).

Time-varying oscillations of the neuronal assemblies rhythmic firing characteristics probably represent the ‘‘scaffold” for transient network interactions during complex cognitive tasks. Several evidences suggested that oscillations in the gamma range mediate information transfer between cortical and hippocampal structures for memory processes. Both animal and human literature provided evidence for a pivotal role of gamma (> 30 Hz) oscillations in memory tasks. These principles were integrated into a model of the cortical–hippocampal network leading to the encoding and retrieval of episodic memories. Oscillatory neural activity in the gamma frequency range is involved in numerous cognitive functions, including visual object processing, attention, and memory (Tallon-Baudry et al., 1998; Gruber et al., 1999; Keil et al., 1999; Nyhus and Curran, 2010). Recently, several studies demonstrated that gamma-band activity is strongly associated with behavioral performance (reaction time and accuracy) in several memory tasks, including episodic, encoding, retrieval (Gruber et al., 2004; Kaiser et al., 2008). Furthermore, a higher gamma-band activity was demonstrated in participants with an elevated recognition memory performance (Busch et al., 2008). Other findings (Park et al., 2012) suggest that gamma oscillations not only reflect brain activity related to memory processes, but also vary with the memory ability of individuals.

Memory ability declines with age and memory deficits are regarded as an initial symptom of dementia of AD type, one of the most prevalent cognitive disorders in older people (Petersen et al., 2001). Within this frame, the present study demonstrated that also the resting-state SW characteristic in EEG gamma band correlates with memory ability. It is concluded that such SW pattern could represent a promising biomarker of memory impairment as also indicated by the individual analysis based on the *z* scores.

CONCLUSIONS

Understanding the role of EEG gamma oscillations in the network dynamics involved in memory performance is not

only important for understanding memory in cognitive decline patients, but can also serve as a model for understanding large-scale brain network dynamics and their relation to other cognitive phenomena. This study opens interesting avenues for future researches investigating eventual modifications of brain connectivity in the evolution of neurodegenerative processes starting from very early, pre-clinical stages.

CONFLICT OF INTEREST

None of the authors have potential conflicts of interest to be disclosed.

Acknowledgments—Dr. Francesca Miraglia participated to this study in the framework of her Ph.D. program at the Doctoral School in Neuroscience, Department of Neuroscience, Catholic University of Rome, Italy. This work was supported by the Italian Ministry of Health for Institutional Research (Ricerca Corrente) and by the Italian Ministry of Instruction, University and Research MIUR ("Approccio integrato clinico e sperimentale allo studio dell'invecchiamento cerebrale e delle malattie neurodegenerative: basi molecolari, epidemiologia genetica, neuroimaging multimodale e farmacogenetica. (Merit)" and "Functional connectivity and neuroplasticity in physiological and pathological aging. Prot. 2010SH7H3F (ConnAge)" PRIN project).

REFERENCES

Aisen PS, Petersen RC, Donohue MC, Gamst A, Raman R, Thomas RG, Walter S, Trojanowski JQ, Shaw LM, Beckett LA, Jack Jr CR, Jagust W, Toga AW, Saykin AJ, Morris JC, Green RC, Weiner MW (2010) Clinical core of the Alzheimer's disease neuroimaging initiative: progress and plans. Alzheimers Dement 6:239–246.

Basar E, Schurmann M (2001) Toward new theories of brain function and brain dynamics. Int J Psychophysiol 39:87–89.

Bassett DS, Bullmore E (2006) Small-world brain networks. Neuroscientist 12:512–523.

Bell AJ, Sejnowski TJ (1995) An information-maximization approach to blind separation and blind deconvolution. Neural Comput 7:1129–1159.

Binder JR, Desai RH (2011) The neurobiology of semantic memory. Trends Cogn Sci 15:527–536.

Brett M, Johnsrude IS, Owen AM (2002) The problem of functional localization in the human brain. Nat Rev Neurosci 3:243–249.

Busch NA, Groh-Bordin C, Zimmer HD, Herrmann CS (2008) Modes of memory: early electrophysiological markers of repetition suppression and recognition enhancement predict behavioral performance. Psychophysiology 45:25–35.

Carlesimo GA, Caltagirone C, Gainotti G (1996) The Mental Deterioration Battery: normative data, diagnostic reliability and qualitative analyses of cognitive impairment. The Group for the Standardization of the Mental Deterioration Battery. Eur Neurol 36:378–384.

Chandler MJ, Lacritz LH, Cicerello AR, Chapman SB, Honig LS, Weiner MF, Cullum CM (2004) Three-word recall in normal aging. J Clin Exp Neuropsychol 26:1128–1133.

Choi HJ, Lee DY, Seo EH, Jo MK, Sohn BK, Choe YM, Byun MS, Kim JW, Kim SG, Yoon JC, Jhoo JH, Kim KW, Woo JI (2014) A normative study of the digit span in an educationally diverse elderly population. Psychiatry Investig 11:39–43.

de Haan W, Pijnenburg YA, Strijers RL, van der Made Y, van der Flier WM, Scheltens P, Stam CJ (2009) Functional neural network analysis in frontotemporal dementia and Alzheimer's disease using EEG and graph theory. BMC Neurosci 10:101.

Dubois B, Feldman HH, Jacova C, Cummings JL, DeKosky ST, Barberger-Gateau P, Delacourte A, Frisoni G, Fox NC, Galasko D, Gauthier S, Hampel H, Jicha GA, Meguro K, O'Brien J, Pasquier F, Robert P, Rossor M, Salloway S, Sarazin M, de Souza LC, Stern Y, Visser PJ, Scheltens P (2010) Revising the definition of Alzheimer's disease: a new lexicon. Lancet Neurol 9:1118–1127.

Dubois B, Feldman HH, Jacova C, Hampel H, Molinuevo JL, Blennow K, DeKosky ST, Gauthier S, Selkoe D, Bateman R, Cappa S, Crutch S, Engelborghs S, Frisoni GB, Fox NC, Galasko D, Habert MO, Jicha GA, Nordberg A, Pasquier F, Rabinovici G, Robert P, Rowe C, Salloway S, Sarazin M, Epelbaum S, de Souza LC, Vellas B, Visser PJ, Schneider L, Stern Y, Scheltens P, Cummings JL (2014) Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. Lancet Neurol 13:614–629.

Flicker C, Ferris SH, Reisberg B (1991) Mild cognitive impairment in the elderly: predictors of dementia. Neurology 41:1006–1009.

Friston KJ (1994) Functional and effective connectivity in neuroimaging: a synthesis. Hum Brain Mapp 2:56–78.

Fuchs M, Kastner J, Wagner M, Hawes S, Ebersole JS (2002) A standardized boundary element method volume conductor model. Clin Neurophysiol 113:702–712.

Gruber T, Muller MM, Keil A, Elbert T (1999) Selective visual–spatial attention alters induced gamma band responses in the human EEG. Clin Neurophysiol 110:2074–2085.

Gruber T, Tsivilis D, Montaldi D, Muller MM (2004) Induced gamma band responses: an early marker of memory encoding and retrieval. NeuroReport 15:1837–1841.

Iriarte J, Urrestarazu E, Valencia M, Alegre M, Malanda A, Viteri C, Artieda J (2003) Independent component analysis as a tool to eliminate artifacts in EEG: a quantitative study. J Clin Neurophysiol 20:249–257.

Jahn H (2013) Memory loss in Alzheimer's disease. Dialogues Clin Neurosci 15:445–454.

Jung TP, Makeig S, Humphries C, Lee TW, McKeown MJ, Iragui V, Sejnowski TJ (2000) Removing electroencephalographic artifacts by blind source separation. Psychophysiology 37:163–178.

Jurcak V, Tsuzuki D, Dan I (2007) 10/20, 10/10, and 10/5 systems revisited: their validity as relative head-surface-based positioning systems. Neuroimage 34:1600–1611.

Kaiser J, Heidegger T, Lutzenberger W (2008) Behavioral relevance of gamma-band activity for short-term memory-based auditory decision-making. Eur J Neurosci 27:3322–3328.

Keil A, Muller MM, Ray WJ, Gruber T, Elbert T (1999) Human gamma band activity and perception of a gestalt. J Neurosci 19:7152–7161.

Khan ZU, Martin-Montanez E, Navarro-Lobato I, Muly EC (2014) Memory deficits in aging and neurological diseases. Prog Mol Biol Transl Sci 122:1–29.

Lancaster JL, Woldorff MG, Parsons LM, Liotti M, Freitas CS, Rainey L, Kochunov PV, Nickerson D, Mikiten SA, Fox PT (2000) Automated Talairach atlas labels for functional brain mapping. Hum Brain Mapp 10:120–131.

Mazziotta J, Toga A, Evans A, Fox P, Lancaster J, Zilles K, Woods R, Paus T, Simpson G, Pike B, Holmes C, Collins L, Thompson P, MacDonald D, Iacoboni M, Schormann T, Amunts K, Palomero-Gallagher N, Geyer S, Parsons L, Narr K, Kabani N, Le Goualher G, Boomsma D, Cannon T, Kawashima R, Mazoyer B (2001) A probabilistic atlas and reference system for the human brain: International Consortium for Brain Mapping (ICBM). Philos Trans R Soc Lond B Biol Sci 356(1412):1293–1322.

McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack Jr CR, Kawas CH, Klunk WE, Koroshetz WJ, Manly JJ, Mayeux R, Mohs RC, Morris JC, Rossor MN, Scheltens P, Carrillo MC, Thies B, Weintraub S, Phelps CH (2011) The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 7:263–269.

Miller EK, Wilson MA (2008) All my circuits: using multiple electrodes to understand functioning neural networks. Neuron 60:483–488.

Miraglia F, Vecchio F, Bramanti P, Rossini PM (2015a) EEG characteristics in ''eyes-open'' versus ''eyes-closed'' conditions: Small-world network architecture in healthy aging and age-related brain degeneration. Clin Neurophysiol. http://dx.doi.org/10.1016/j.clinph.2015.07.040.

Miraglia F, Vecchio F, Bramanti P, Rossini PM (2015b) Small-worldness characteristics and its gender relation in specific hemispheric networks. Neuroscience 310:1–11.

Monaco M, Costa A, Caltagirone C, Carlesimo GA (2013) Forward and backward span for verbal and visuo-spatial data: standardization and normative data from an Italian adult population. Neurol Sci 34:749–754.

Nyhus E, Curran T (2010) Functional role of gamma and theta oscillations in episodic memory. Neurosci Biobehav Rev 34:1023–1035.

Onnela JP, Saramaki J, Kertesz J, Kaski K (2005) Intensity and coherence of motifs in weighted complex networks. Phys Rev E Stat Nonlin Soft Matter Phys 71:065103.

Park JY, Lee KS, An SK, Lee J, Kim JJ, Kim KH, Namkoong K (2012) Gamma oscillatory activity in relation to memory ability in older adults. Int J Psychophysiol 86:58–65.

Pascual-Marqui RD (2002) Standardized low-resolution brain electromagnetic tomography (sLORETA): technical details. Methods Find Exp Clin Pharmacol 24(Suppl D):5–12.

Pascual-Marqui RD (2007) Instantaneous and lagged measurements of linear and nonlinear dependence between groups of multivariate time series: frequency decomposition. *arXiv preprint arXiv:0711.1455*.

Pascual-Marqui RD (2009) Theory of the EEG inverse problem. In: Tong S, Thakor NV, editors. Quantitative EEG analysis: methods and clinical applications. Artech House B. p. 121–140.

Petersen RC, Smith GE, Waring SC, Ivnik RJ, Kokmen E, Tangelos EG (1997) Aging, memory, and mild cognitive impairment. Int Psychogeriatr 9(Suppl 1):65–69.

Petersen RC, Doody R, Kurz A, Mohs RC, Morris JC, Rabins PV, Ritchie K, Rossor M, Thal L, Winblad B (2001) Current concepts in mild cognitive impairment. Arch Neurol 58:1985–1992.

Ponten SC, Bartolomei F, Stam CJ (2007) Small-world networks and epilepsy: graph theoretical analysis of intracerebrally recorded mesial temporal lobe seizures. Clin Neurophysiol 118:918–927.

Portet F, Ousset PJ, Visser PJ, Frisoni GB, Nobili F, Scheltens P, Vellas B, Touchon J, MCI Working Group of the European Consortium on Alzheimer's Disease (2006) 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. J Neurol Neurosurg Psychiatry 77:714–718.

Rey A (1968) Reattivo Della Figura Complessa Manuale.

Rubinov M, Sporns O (2010) Complex network measures of brain connectivity: uses and interpretations. Neuroimage 52:1059–1069.

Sporns O (2013) Structure and function of complex brain networks. Dialogues Clin Neurosci 15:247–262.

Sporns O, Honey CJ (2006) Small worlds inside big brains. Proc Natl Acad Sci U S A 103:19219–19220.

Sporns O, Zwi JD (2004) The small world of the cerebral cortex. Neuroinformatics 2:145–162.

Stam CJ (2004) Functional connectivity patterns of human magnetoencephalographic recordings: a 'small-world' network? Neurosci Lett 355:25–28.

Tallon-Baudry C, Bertrand O, Peronnet F, Pernier J (1998) Induced gamma-band activity during the delay of a visual short-term memory task in humans. J Neurosci 18:4244–4254.

Vecchio F, Miraglia F, Bramanti P, Rossini PM (2014a) Human brain networks in physiological aging: a graph theoretical analysis of cortical connectivity from EEG data. J Alzheimers Dis 41:1239–1249.

Vecchio F, Miraglia F, Marra C, Quaranta D, Vita MG, Bramanti P, Rossini PM (2014b) Human brain networks in cognitive decline: a graph theoretical analysis of cortical connectivity from EEG data. J Alzheimers Dis 41:113–127.

Vecchio F, Miraglia F, Valeriani L, Scarpellini MG, Bramanti P, Mecarelli O, Rossini PM (2014c) Cortical brain connectivity and B-type natriuretic peptide in patients with congestive heart failure. Clin EEG Neurosci.

Vecchio F, Miraglia F, Piludu F, Granata G, Romanello R, Caulo M, Onofrj V, Bramanti P, Colosimo C, Rossini PM (2015a) ''Small World'' architecture in brain connectivity and hippocampal volume in Alzheimer disease: a study via graph theory from EEG data. Brain Imag Behav. submitted for publication.

Vecchio F, Miraglia F, Curcio G, Altavilla R, Scrascia F, Giambattistelli F, Quattrocchi CC, Bramanti P, Vernieri F, Rossini PM (2015b) Cortical brain connectivity evaluated by graph theory in dementia: a correlation study between functional and structural data. J Alzheimers Dis.

Vecchio F, Miraglia F, Curcio G, Della MG, Vollono C, Mazzucchi E, Bramanti P, Rossini PM (2015c) Cortical connectivity in fronto-temporal focal epilepsy from EEG analysis: a study via graph theory. Clin Neurophysiol 126:1108–1116.

Watts DJ, Strogatz SH (1998) Collective dynamics of 'small-world' networks. Nature 393:440–442.

Yesavage JA, Brink TL, Rose TL, Lum O, Huang V, Adey M, Leirer VO (1982) Development and validation of a geriatric depression screening scale: a preliminary report. J Psychiatr Res 17:37–49.

Zaudig M (1992) A new systematic method of measurement and diagnosis of ''mild cognitive impairment'' and dementia according to ICD-10 and DSM-III-R criteria. Int Psychogeriatr 4(Suppl 2): 203–219.

(Accepted 18 December 2015)
(Available online 24 December 2015)