

BRAIN NEURAL SYNCHRONIZATION AND FUNCTIONAL COUPLING IN ALZHEIMER'S DISEASE AS REVEALED BY RESTING STATE EEG RHYTHMS

Babiloni Claudio^{1,2}, Lizio Roberta², Marzano Nicola³, Capotosto Paolo⁴, Soricelli Andrea^{3,5}, Triggiani Antonio Ivano⁶, Cordone Susanna⁶, and Del Percio Claudio²

1 Department of Department of Physiology and Pharmacology, "University of Rome "La Sapienza", Rome, Italy;

2 Department of Neuroscience, IRCCS San Raffaele Pisana, Rome, Italy;

3 IRCCS "SDN", Naples, Italy;

4 Department of Neuroscience and Imaging, University G. D'Annunzio, Chieti, Italy;

5 Department of Studies of Institutions and Territorial Systems, University of Naples Parthenope, Naples, Italy;

6 Department of Clinical and Experimental Medicine, University of Foggia, Foggia, Italy;

Corresponding author:

Prof. Claudio Babiloni

Department of Physiology and Pharmacology "V. Erspamer"

University of Rome "La Sapienza"

P.le A. Moro 5, 00185, Rome, Italy

Email: claudio.babiloni@uniroma1.it

Tel. (fax): +39 06 49910989 (0917)

Running title: Brain synchronization, functional connectivity, EEG rhythms and Alzheimer's disease

Keywords: Electroencephalography (EEG), Drug treatments, Alzheimer's disease

Acknowledgments. The present study was developed and granted in the framework of the following projects: "Does rehabilitation with a 10-Hz sensory stimulation improve brain rhythms and cognitive-motor performance in neurological patients? Towards Internet-based clinical applications at subjects", (Italian Ministry of Health, GR-2008-1143090), "Smart Health 2.0" (Italian Ministry of University and Technological Research, Pon04a2_C-MIUR D.D. 626/Ric e 703/Ric), "CONNAGE" (Italian Ministry of University and Technological Research, PRIN2010-2011, prot. 2010SH7H3F).

Abstract

Alzheimer's disease (AD) is the most frequent neurodegenerative disorder and cause of dementia along aging. It is characterized by a pathological extracellular accumulation of A β amyloid peptides that affects excitatory and inhibitory synaptic transmission. It also triggers aberrant patterns of neuronal circuit activity at the network level. Growing evidence shows that AD targets cortical neuronal networks related to cognitive functions including episodic memory and visuospatial attention. This is partially reflected by the abnormal mechanisms of cortical neural synchronization and coupling that generate resting state electroencephalographic (EEG) rhythms. The cortical neural synchronization is typically indexed by EEG power density. The EEG coupling between electrode pairs probes functional (inter-relatedness of EEG signals) and effective (casual effect from one over the other electrode) connectivity. The former is typically indexed by EEG spectral coherence (linear) or synchronization likelihood (linear-nonlinear), the latter by granger causality or information theory indexes. Here we revised resting state EEG studies in mild cognitive impairment (MCI) and AD subjects as a window on abnormalities of the cortical neural synchronization and functional and effective connectivity. Results showed abnormalities of the EEG power density at specific frequency bands (<12 Hz) in the MCI and AD populations, associated to an altered functional and effective EEG connectivity among long range cortical networks (i.e. fronto-parietal and fronto-temporal). These results suggest that resting state EEG rhythms reflect the abnormal cortical neural synchronization and coupling in the brain of prodromal and overt AD subjects, possibly reflecting dysfunctional neuroplasticity of the neural transmission in long range cortical networks.

1. Introduction

The human brain contains an intricate network of about 100 billion neurons. Aging of the brain is characterized by a combination of synaptic pruning, loss of cortico-cortical connections and neuronal apoptosis that provoke an age-dependent decline of cognitive functions (D'Amelio and Rossini, 2012). Neural/synaptic redundancy and plastic remodeling of brain networking, also secondary to mental and physical training, promotes maintenance of brain activity and cognitive status in healthy elderly subjects for everyday life (D'Amelio and Rossini, 2012).

Pathological processes at cellular level can alter physiological brain aging. It is well known that Alzheimer's disease (AD) is the most frequent neurodegenerative disorder and cause of dementia along aging. It is characterized by a pathological accumulation of A β amyloid and hyperphosphorylated tau peptides that affect excitatory and inhibitory synaptic transmission (Daulatzai, 2010; Shen, 2004). The pathological accumulation of these peptides also triggers aberrant patterns of neuronal circuit activity at the network level (Palop and Mucke, 2010). Growing evidence shows that AD targets cortical neuronal networks related to cognitive functions including episodic memory and visuospatial attention (Pievani et al., 2011). Specifically, AD is related to neurodegeneration within the basal forebrain, parietal, prefrontal, entorhinal cortices, amygdala and hippocampus, and is characterized by an impairment of the cholinergic neurotransmission associated with a pathological production of beta amyloid (A β) and phosphorylated tau (Daulatzai, 2010; Shen, 2004).

The diagnosis of AD on the basis of overt dementia symptoms reasonably comes after 5–6 years from probable disease onset and this delay is very negative from a therapeutic point of view. Towards an early diagnosis of AD, there has been great progress in identifying the AD-associated structural, functional and molecular changes in the brain and their biochemical footprints well before the symptoms of overt dementia. New research criteria for the diagnosis of prodromal AD have been advanced in revising the NINCDS-ADRDA criteria (Dubois et al. 2007; Albert et al, 2011; Jack et al., 2011; McKhann et al, 2011; Sperling et al., 2011). The new criteria include fluid and neuroimaging biomarkers of AD. Fluid biomarkers can be extracted from the blood and the cerebrospinal fluid by lumbar puncture (CSF; Clark et al., 2003; Fagan et al., 2006; Schoonenboom et al., 2008; Tapiola et al., 2009). Validated blood biomarkers probe genetic vulnerability for dementia. Genotyping for apolipoprotein E4 (ApoE), cystatin B and homocysteine represent independent risk factors for sporadic late-onset AD, whereas presenilins (PSEN1 and PSEN2) have autosomal dominant inheritance (high penetrance >85%), and lead to A β amyloid aggregation and early-onset AD (γ -secretase-mediated proteolytic cleavage of APP). Genotyping of ApoE and homocysteine have some impact also for late onset cerebrovascular dementia (VaD) (Dubois et al.

2007). Validated CSF biomarkers probe A β amyloid and total phosphorylated tau as signs of the amyloid cascade towards neural injury and neurodegeneration (Tapiola et al., 2009). On the other hand, the validated neuroimaging biomarkers include structural MRI to probe neurodegeneration as revealed by hippocampal atrophy (Frisoni et al., 2010; Silbert et al., 2003; Zarow et al., 2005; Schuff et al., 2009; Van de Pol et al., 2006) and resting-state PET-fluoro-deoxy-glucose (FDG) mapping of temporo-parietal and precuneous hypometabolism (Jagust et al., 2007; Minoshima et al., 1997); PET-amyloid Pittsburgh Compound B (PIB) is also used for the visualization of A β amyloid deposition in the brain (Klunk et al., 2004; Rowe et al., 2007; Ikonovic et al., 2008). It is important to note that the approaches above are relatively expensive and invasive, so that they cannot be systematically applied to all elderly subjects with memory complaints or very mild objective decline, due to numerous potential patients and limited financial resources of the public health services. Moreover, these approaches are not especially suited to investigate neuronal/synaptic dysfunction along brain networks, which is thought to underlie cognitive and functional deficits. In typical AD, the progression of symptoms follows a relatively stereotyped order which mirrors the topographic progression of neurodegeneration across specific long-range brain neural networks (Frisoni et al., 2010). Namely, the sequence includes episodic memory loss (hippocampus and medial temporal lobe, posterior cingulate cortex), followed by semantic memory loss (lateral temporal cortex), aphasic, apraxic, and visuospatial symptoms (frontal, temporal, and parietal neocortex), and then motor and visual deficits (sensorimotor and occipital cortex). Although atypical variants exist (Alladi et al., 2007), this orderly progression may support the notion that AD reflects a progressive impairment of interconnected regions within large-scale networks, and ultimate spread into adjacent or upstream regions (Pievani et al., 2011).

Because brain functions rely on the integrity of dynamic communication among the nodes of interconnected brain regions and circuits, a network perspective accounting for such interactions has the potential to provide novel and meaningful intermediate phenotypes of pathology even at earlier stages of AD, including preclinical (i.e. pre-symptomatic) and prodromal (i.e. mild cognitive impairment) AD (Palop and Mucke, 2010). Indeed, neural/synaptic redundancy and plastic remodeling of brain networking guarantees functional maintenance, so that neuronal death and synaptic loss can occur in the absence of cognitive symptoms for several years (D'Amelio and Rossini, 2012). These neuro-protective mechanisms are facilitated by mental and physical training, and constitute a form of “cognitive or brain reserve” possibly related to greater amounts of specific pre-synaptic proteins and distinct protein-protein interactions (Honer et al., 2012). The lack of objective cognitive impairment at the earlier stages of prodromal AD motivates the use of instrumental markers of altered functional connectivity and neural transmission across long range

neural networks in association with standard assessment of cognitive functions with “paper and pencil” neuropsychological batteries (Rossini et al., 2007). To this aim, digital electroencephalography (EEG) has very interesting features to provide useful information on the functioning of neural transmission and cortical neuronal synchronization and coupling across long range neural networks when compared to other classical neuroimaging techniques (Babiloni et al., 2009a).

Standard EEG techniques are characterized by low spatial resolution (several centimeters) when compared to structural MRI and PET techniques producing relatively non-invasive views of “in vivo” brain anatomy (millimeters to a few centimeters). However, structural MRI does not provide functional information about the brain, and PET scan of brain glucose metabolism/rCBF is limited in its temporal resolution (i.e. seconds to minutes for PET) compared to EEG (i.e. milliseconds; Rossini et al., 2004). It should be noted that high temporal resolution of EEG is crucial for the study of an emerging property of brain activity, namely the spontaneous and event-related oscillatory gross electromagnetic activity at different frequency ranges, categorized as 1-4 Hz (delta), 4-8 Hz (theta), 8-13 Hz (alpha), 13-30 Hz (beta), and >30 Hz (gamma). Any EEG frequency band conveys particular physiological information on brain functional state during sleep and wake periods (Nunez, 1999).

In recent years, great attention has been focused on the evaluation of quantitative EEG (qEEG) and/or event-related potentials (ERPs) as clinical markers of the early stages of AD (Celesia et al., 1987; Rossini et al., 2007, 2009; Yener et al., 2008, 2009). In this regard, the recording of resting state eyes-closed cortical EEG rhythms represents a fully standardized procedure that may be carried out easily and rapidly in a clinical environment. In contrast to ERPs, the recording of the resting state EEG rhythms does not require stimulation devices or registration of subject’s behavior, and is not affected by fatigue and anxiety typically associated with task performance. Also, the recording of the resting state EEG rhythms can be repeated countless times along the disease progression and the resting state EEG markers are virtually not affected by meta-learning relative to task processes. These are ideal requisites when EEG recordings are performed in elderly vulnerable or diseased subjects. Furthermore, resting state cortical EEG rhythms can be recorded in highly comparable experimental conditions in normal subjects, individuals with subjective memory complaints, objective mild cognitive impairment (MCI), and overt AD (Rossini et al., 2007). Moreover, resting state EEG rhythms have been found to partially restore together with patients’ cognitive performance after the administration of AchetylCholinesterase inhibitors licensed for the symptomatic treatment of AD (Rodriguez et al., 2002, 2004; Kogan et al., 2001; Reeves et al., 2002; Brassens and Adler, 2003, Onofrij et al., 2003; Babiloni et al., 2006e).

It has been proposed that the effects of AD neurodegeneration on cortical neuronal networks is partially reflected by the abnormal mechanisms of cortical neural synchronization and coupling that generate resting state EEG rhythms (Rossini et al., 2007). In the experimental and clinical applications, the cortical neural synchronization is typically indexed by EEG power density (Babiloni et al., 2009a), whereas the EEG coupling between electrode pairs is measured by different approaches to account for the so called functional and effective brain connectivity. In the framework of the EEG techniques, functional brain connectivity captures the statistical dependence between scattered and often spatially remote EEG rhythms by measuring their correlations in either time or frequency domain (Babiloni et al., 2009a). Effective connectivity describes how the EEG rhythms recorded at one electrode affects the EEG rhythms recorded at another remote electrode, as a reflection of a causal hierarchical interaction between the two corresponding cortical generators (Babiloni et al., 2009a). In the framework of the EEG techniques, the functional brain connectivity is typically indexed by EEG spectral coherence (linear) or synchronization likelihood (linear-nonlinear), while the latter is indexed by granger causality (Rossini et al., 2007).

Here we revised previous resting state EEG studies in subjects with amnesic mild cognitive impairment (MCI) at risk of prodromal AD and in AD patients, as a window on the abnormalities of the cortical neural synchronization and functional and effective connectivity due to AD neurodegeneration. This window is expected to reflect the abnormal plasticity of the synaptic neurotransmission within long range cortical networks underpinning cognition along the AD progression.

2. Physiological generation of the resting state electroencephalographic (EEG) rhythms

The word EEG refers to the measurement of brain electrical activity recorded from electrodes placed on the surface of the head. In 1929, Hans Berger reported a dominant 10-Hz oscillating voltage difference between two electrodes placed on the scalp in healthy subjects during a wakeful eyes-closed relaxed state (the so-called alpha rhythm). Berger showed that 10-Hz oscillations (10-50 microvolts) are reduced in amplitude when subjects open their eyes or perform a cognitive task. Nowadays, EEG is largely employed for basic scientific research and clinical applications since it is easy to use, non invasive, cheap, and totally safe.

As an important limitation, the EEG voltage measured depends on the position of the reference electrode. Furthermore, EEG is characterized by a low spatial resolution as compared to other measures of brain function such as functional magnetic resonance imaging (fMRI). Indeed, different conductivities of head tissues (brain, meninges, skull, and scalp) attenuate and blur the spatial distribution of neural currents from brain to scalp electrodes. As a consequence, scalp EEG

data present enhanced low-spatial components and negligible values of high-frequency brain oscillations (>40 Hz, gamma rhythms). To minimize these effects of head volume conduction, mathematical procedures have been developed to obtain reference-free measurements with attenuated head volume conductor effects, namely estimation of common average reference, source current density, and inverse EEG source solutions (Babiloni et al., 2009).

Technical requirements make the EEG equipment a non invasive and non expensive device, with an overall present price of few tens of thousands of Euro needed for high-resolution EEG recording. EEG signals are derived from electric activity of neurons in the cerebral cortex. Specifically, these signals are mainly produced by post-synaptic ionic currents of synchronously active cortical pyramidal neurons reflecting the integrative information processing of signals coming from thalamus, brainstem, and other cortical modules. EEG signals are very large-scale measures of brain source activity, reflecting synaptic activity synchronized over macroscopic (centimeter) regional spatial scales (Nunez, Wingeier, & Silberstein, 2001). Synchrony among neural populations in compact regions of the brain produces localized dipole current sources. Synchrony among neural populations distributed across the cortex results in regional or global networks consisting of many dipole sources.

EEG signals have a high temporal resolution (< 1ms) ideal to investigate an important property of brain physiology, namely brain rhythms during passive wakefulness and task performance. Spectral analysis methods allow the estimation of EEG dynamics in terms of the dominant frequencies, power (or amplitude), phase, and coherence of EEG rhythms. The background spontaneous oscillatory activity of brain neurons at about 10 Hz generates the dominant alpha rhythm of resting-state EEG activity first described by Berger. In the classical studies by Jasper and Penfield (1949), alpha rhythms ranging from about 8 to 12 Hz were recorded from nearly the entire upper cortical surface (including the frontal and prefrontal areas) in a large population of patients awake during surgery.

High-resolution EEG studies have shown long- and short-range correlations of alpha rhythms depending on age, the subject's condition, and performance of a cognitive task (Babiloni et al., 2004a; Nunez et al., 2001; Salenius, Kajola, Thompson, Kosslyn, & Hari, 1995; Salmelin, Hari, Lounasmaa, & Sams, 1994). In the condition of slow-wave sleep, cortico-fugal slow oscillations (<1 Hz) are effective in grouping thalamic-generated delta rhythms (1–4 Hz) and spindling activity (7–14 Hz) rhythms (Steriade, 2003). In the condition of brain arousal, spindles as well as high and low components of the delta rhythms are blocked by the inhibition of oscillators within, respectively, reticulo-thalamic (7–14 Hz), thalamo-cortical (1–4 Hz), and intra-cortical (<1 Hz), neuronal circuits. These rhythms are replaced by fast (beta and gamma) cortical oscillations, which

are mainly induced by forebrain (nucleus basalis) cholinergic inputs to hippocampus and cortex as well as by thalamo-cortical projections (Steriade, 2003 and Steriade et al., 1996). In the condition of awake rest, low frequency (8–10.5 Hz) alpha would be mainly related to subject's global attentional readiness (Klimesch, 1996; Klimesch et al., 1997, 1998; Rossini et al., 1991; Steriade and Llinas, 1988). Noteworthy, there is consensus that alpha rhythms represent the dominant resting oscillations of the adult, awake human brain (Rossini et al., 1991; Steriade and Llinas, 1988; Klimesch, 1996; Klimesch et al., 1997, 1998), and have been linked to intelligence quotient, memory, and cognition (Klimesch, 1999). This background activity is desynchronized during sensory and cognitive-motor events (Babiloni et al., 2005, 2006, 2008; Pfurtscheller & Lopes da Silva, 1999). Oscillations in other frequency bands, e.g., delta (1-4 Hz), theta (4–7 Hz) and gamma bands (30–70 Hz) also exhibit complex patterns of power that are modulated by cognitive processes such as working memory and perceptual binding (Srinivasan, Winter, & Nunez, 2006). Unless otherwise specified, spontaneous EEG activity during resting state condition is indexed by spectral power density in given narrow frequency bands (per electrode, scalp region of interest or cortical source).

3. Cortical neural synchronization in MCI and AD subjects as revealed by EEG power density

Resting state eyes-closed cortical EEG rhythms typically change with physiological aging, with gradual modifications observable as variation of EEG power density spectrum computed at scalp electrodes or in mathematically estimated cortical sources (Rossini et al., 2007). The majority of the following studies addressed the differences of EEG power density between the control and the AD group as an index of the abnormal global synchronization of pyramidal cortical neurons during the spontaneous fluctuation of the cortical arousal in AD patients (Pfurtscheller and Lopes da Silva, 1999).

Along the physiological aging, healthy elderly subjects were characterized by a marked decrease of alpha power density (8–13 Hz) with respect to young controls (Dujardin et al., 1994, 1995; Klass and Brenner, 1995; Klimesch, 1999). Such changes in alpha power density were confirmed in a large sample of healthy subjects (N = 215, 18–85 years), showing an age-dependent decrement of the EEG power density in the posterior low-frequency alpha (alpha 1; 8–10.5 Hz) and delta rhythms (Babiloni et al., 2006a). These results are in line with those of several studies showing a shift of alpha power density toward frontal brain regions in resting state EEG rhythms of AD patients (Dierks et al., 1993) as well as during cognitive processes in physiological aging (Yordanova et al., 1996, 1998; Kolev et al., 2002; Başar et al., 2010). Of note, parieto-occipital alpha power density presumably reflects the dominant oscillatory activity of brain networks in the

resting state eyes-closed condition as a result of massive synchronization of cortical pyramidal neurons (Pfurtscheller and Lopes da Silva, 1999). This activity is modulated by thalamo–cortical and cortico–cortical interactions facilitating/inhibiting the transmission of sensorimotor information and the retrieval of semantic information from cortical storage (Steriade and Llinas, 1988; Brunia, 1999; Pfurtscheller and Lopes da Silva, 1999). In the condition of wake resting state, the low-frequency alpha rhythms (about 8-10 Hz) can be observed in widely distributed brain networks, and reveal the spontaneous fluctuation of the general brain arousal and subject's global attentional readiness (Klimesch, 1996; Klimesch et al., 1997; Klimesch et al., 1998; Rossini et al., 1991; Steriade and Llinas, 1988). The power density of these rhythms also reflects intelligent quotient, memory, and global cognition status (Klimesch, 1999). In parallel, the power density of the high-frequency alpha rhythms (about 10-12 Hz) denotes the oscillation of more selective neural systems for the elaboration of sensorimotor or semantic information (Klass and Brenner, 1995; Klimesch, 1996, 1997). Of note, the topology of the EEG rhythms should be carefully taken into account. The alpha rhythms at different frequency bands (i.e. 8-10 Hz, 10-12 Hz) is not an overall phenomenon and can be completely different in anterior and posterior areas, as reported in several experiments in both humans and animals (Başar et al., 2010; Schürmann et al., 2000).

At group level, resting state eyes-closed cortical EEG rhythms present topographical and frequency differences in the EEG power density spectra of healthy normal elderly (Nold), MCI, cerebrovascular dementia (CVD), Parkinson disease with dementia (PDD), and AD subjects. When compared to the Nold subjects, the AD subjects showed a power density increase of topographically widespread delta and theta rhythms and a power density decrease of posterior alpha (8–13 Hz) and/or beta (13–30 Hz) rhythms (Babiloni et al., 2004a; Dierks et al., 2000; Huang et al., 2000; Ponomareva et al., 2003; Jeong, 2004; Prichep, 2005). Posterior alpha rhythms were lower in power density in the AD than in the CVD and PDD subjects, whereas topographically widespread theta rhythms were higher in power density in the CVD and PDD subjects than in the AD subjects (Babiloni et al., 2004a, 2011a).

Resting state EEG power density differed between AD patients and amnesic MCI subjects, who were considered to be at high risk to suffer from prodromal AD. There was an “intermediate” power density of low-frequency alpha rhythms (8–10.5 Hz) in parietal and occipital regions in MCI compared to mild AD and Nold subjects (Babiloni et al., 2006b). Furthermore, maximum alpha and beta power density shifted more anteriorly in AD patients compared to Nold and MCI subjects (Huang et al., 2000). Moreover, longitudinal studies have shown that increased delta or theta power density, decreased alpha and beta power density, and slowing of mean EEG frequency were in some way predictors of the progression from MCI to dementia at about 1-year follow up (Huang et al.,

2000; Jelic et al., 1996, 2000; Grunwald et al., 2001; Kwak, 2006; Rossini et al., 2006). High power density of the posterior alpha rhythms also predicted a stable global cognitive function in MCI subjects at 1-year follow-up (Babiloni et al 2010a).

Some EEG studies assessed the changes in the resting state eyes-closed EEG rhythms with disease progression, namely during the period from “baseline” to “follow-up” at about 1-year or longer. In the MCI subjects, the EEG markers of disease progression included an increase of the power density at theta and delta rhythms in temporal and occipital regions as well as a decrease of the power density at beta rhythms in temporal and occipital regions (Jelic et al., 2000). AD patients were characterized by an increase of the power density at parieto-occipital theta and delta rhythms as well as by a reduction of the power density at alpha and beta rhythms in parieto-occipital regions (Coben et al., 1985). Furthermore, the AD patients showed an increase of the power density at theta and delta rhythms in temporal-occipital regions (Soininen et al., 1989, 1991). Power density of the resting state eyes-closed EEG rhythms was correlated to brain atrophy in the typical track of AD neurodegeneration, as revealed by structural MRI. In the AD patients with global cognitive impairment, the hippocampal atrophy was associated with increased power density at delta and theta rhythms in temporal and parietal regions (Helkala et al., 1996), in line with recent magnetoencephalographic (MEG) evidence (Fernandez et al., 2003). Furthermore, a volume decrement of hippocampus was related to the decreased power density at alpha rhythms in temporal, parietal, and occipital regions in MCI and AD subjects (Babiloni et al., 2009b). The same was true for the relationship between the power density of the resting state eyes-closed EEG rhythms and the volumetric changes of sub-cortical white matter (i.e. connection pathways to and from the cerebral cortex) and cortical grey matter. The total volume of the frontal white matter was negatively correlated to the frontal power density at delta rhythms in AD patients; namely, the higher the white matter volume, the lower the (pathological) delta power density, thus suggesting that reduced modulation/regulatory inputs to frontal cortex through white matter might dis-inhibit the intrinsic delta oscillations of the cerebral cortex (Babiloni et al., 2006d). Furthermore, the global delta and alpha power density was related to the total amount of atrophy of cortical grey matter in the amnesic MCI and in the AD subjects, as revealed by MRI voxel-to-voxel volumetry of lobar brain volume; the higher the total grey matter volume, the lower the global delta power density and the higher the global alpha power density (Babiloni et al., 2012). Of note, these modifications of the delta and alpha power density in the MCI and AD subjects were not merely due to vascular brain lesions of the white matter (Babiloni et al., 2008a,b, Babiloni et al., 2011b). Keeping in mind the above findings, it can be speculated that the posterior delta/theta and alpha power density of the

resting state eyes-closed EEG rhythms reflect the neurodegenerative processes along the time course of AD, at least at group level.

The power density of the resting state eyes-closed EEG rhythms was repeatedly found to be correlated to cognitive status in MCI and AD subjects. It has been shown that the posterior alpha power density was positively correlated to the subjects' global cognitive status, as measured by ADAS-cog in the MCI or AD subjects; namely, the lower the alpha power density, the lower the cognitive status (Luckhaus et al., 2008). This relationship can be extended to the cognitive health condition. Furthermore, the posterior delta and alpha power density was correlated to the MMSE score in the Nold, MCI and AD subjects; namely, the lower the alpha power, the higher the delta power and the lower the cognitive status (Babiloni et al., 2006b). Moreover, the lower cognitive performance in the AD subjects, as revealed by CAMCOG scores, was associated with the poor alpha power density in parieto-occipital and fronto-central regions (Claus et al., 2000).

These findings suggest that the power density of delta and alpha rhythms may be used alone or in combination with structural MRI, SPECT, and PET markers to corroborate and support the standard clinical and neuropsychological assessment of MCI and AD subjects. In this line, a first important study has combined EEG, structural MRI, and PET markers using an ensemble of classifiers based on a decision-fusion approach, in order to determine whether a strategic combination of these different modalities can improve the diagnostic accuracy over any of the individual data sources when used with an automated classifier (Polikar et al., 2010). The results showed an improvement of up to 10%-20% using this multi-modal approach, compared to the classification performance obtained when using separately the modal data sources (Polikar et al., 2010).

Few longitudinal studies have evaluated the resting state eyes-closed EEG rhythms to determine the changes in the baseline EEG power density that might be able to predict a cognitive decline at follow-up. It has been shown that in the MCI subjects, the markers of disease progression included an increase of the power density at theta and delta rhythms in the temporal and occipital lobes as well as the reduction of the beta power density in the temporal and occipital lobes (Jelic et al., 2000). AD patients were characterized by an increase of theta and delta power density and by a reduction of the alpha and beta power density in the parieto-occipital lobes (Coben et al., 1985). Furthermore, half of the AD patients showed an increase of the theta and delta power density in the temporal-occipital lobe (Soininen et al., 1989).

On the whole, the results of this section show that the power density of the resting state EEG rhythms in MCI and AD subjects is an effective index of the abnormal global synchronization of pyramidal cortical neurons during the spontaneous fluctuation of cortical arousal.

4. Functional brain connectivity in MCI and AD subjects as revealed by linear and non-linear coupling of the resting state EEG rhythms

Power density of the resting state EEG rhythms does not capture one of the main features of the AD process, namely the impairment of functional or effective connectivity within long range brain networks underlying the cognitive dysfunction in prodromal and manifest AD patients. Indeed, the majority of the cognitive processes are highly distributed and dynamic process, depending on the selective interplay among many neural populations distributed across several cortical and sub-cortical regions. In the same line, it is expected that temporally-coordinated brain networks underpinning cognitive functions do become more and more abnormal along the progression of AD neurodegeneration, so that AD can be viewed as a disconnection syndrome (Bokde et al., 2009). An ideal methodological approach is, therefore, the extraction of some functional indexes of the abnormalities of the functional brain connectivity across long term neural networks (Varela et al, 2001; Le van Quyen, 2003; Börner et al, 2007).

In this theoretical framework, promising markers of functional neural connectivity derive from the measurement of the functional coupling of resting state eyes-closed EEG rhythms between pairs of electrodes. These indexes of the EEG functional coupling should be able to capture linear and nonlinear relationships among brain regions (Stam et al., 2010). The linear index of the EEG functional coupling should model the phase relationship between the EEG rhythms recorded at electrode pairs, whereas the nonlinear index should model the complex relationships between these EEG rhythms (Stam et al., 2010).

Linear components of such coupling can be evaluated by the analysis of EEG spectral coherence, which evaluates the functional co-ordination and mutual information exchange of the cortical generators of EEG rhythms (Gerloff et al., 1998; Gevins et al., 1998; Thatcher et al., 1986; Rappelsberger and Petsche, 1988). EEG spectral coherence is a normalized value that quantifies the temporal synchronization of two EEG time series between pairs of electrodes in the frequency domain, and can be derived by fast Fourier transform -FFT- (Rappelsberger and Petsche, 1988; Pfurtscheller and Andrew, 1999). Its basic theoretical assumption is that, when the oscillatory activity of two cortical areas is functionally coordinated, the EEG rhythms of these cortical areas show linear correlation and high spectral coherence. In general, decreased EEG coherence reflects reduced linear functional coupling and information transfer (i.e. functional uncoupling or unbinding following) among cortical areas or the reduced modulation of common areas by a third region. In contrast, an increase of the EEG coherence values is interpreted as an enhancement of the linear functional connections and information transfer (i.e. functional coupling or binding), which reflects

the interaction of different cortical structures for a given task (Rossini et al., 2007). Indeed, it has been repeatedly demonstrated that perceptive, cognitive, and motor processes are associated with enhanced EEG spectral coherence in the cortical regions involved in the intensive task-related information processing (Sauseng et al., 2005; Babiloni et al., 2006c; Vecchio et al., 2007, 2010, Vecchio and Babiloni, 2011), as a function of the extension and type of the neural networks engaged (Pfurtscheller and Lopes da Silva, 1999; von Stein and Sarnthein, 2000). In addition, EEG spectral coherence may reflect the integrity of cortical neural pathways (Locatelli et al., 1998) and the modulating effects of cholinergic systems on the functional coupling of the activity of brain neural populations (Xiang et al., 1998).

At group level, spectral coherence of the resting state eyes-closed EEG rhythms differs among the Nold, MCI, and AD subjects. The majority of previous EEG studies have reported a prominent decrease of the spectral coherence at alpha rhythms in the AD than in the Nold subjects (Cook and Leuchter, 1996; Jelic et al., 1997; Almkvist et al., 2001; Locatelli et al., 1998; Wada et al., 1998a,b; Knott et al., 2000; Adler et al., 2003; Leuchter et al., 1987, 1992; Jelic et al., 2000). This effect was found to be associated with ApoE genetic risk, which is hypothesized to be mediated by cholinergic deficit (Jelic et al., 1997). On the other hand, some previous studies have shown contradictory results, with either a decrease or an increase of EEG coherence at delta and theta rhythms (Locatelli et al., 1998; Adler et al., 2003; Leuchter et al., 1987; Brunovsky et al., 2003). A recent study has reconciled these conflicting results by computing “total coherence”, obtained by averaging the EEG spectral coherence across all combinations of electrode pairs (Babiloni et al., 2009d). The latter may better take into account, frequency band-by-frequency band, the global impairment of brain networks and cognition along the AD process, which is presumed to affect the functional integration within cerebral neural networks supporting cognition. In the mentioned recent study, the delta total coherence was higher in AD than MCI subjects and in MCI than Nold subjects (Babiloni et al., 2009d). Furthermore, the low-frequency alpha total coherence was lower in AD than in MCI and Nold subjects. Of note, these EEG coherence values were negatively correlated to (moderate to high) cholinergic lesion across the MCI subjects (Babiloni et al., 2010c). Unpublished data of our research group indicated that the spectral delta coherence was higher in the AD than in the MCI and Nold subjects, while the spectral alpha coherence was lower in the AD than in the MCI and Nold subjects.

With respect to the spectral coherence as a linear measurement of the functional coupling of EEG rhythms, the so-called ‘synchronization likelihood’ (SL) is an index capturing both linear and non-linear dimensions of this coupling. SL is a measure of the dynamical interdependencies between EEG signals recorded at a given electrode and one or more other EEG signals recorded at

other electrodes (Stam and van Dijk, 2002). Its basic theoretical assumption is that the state of one dynamical system (X), thought as neural networks underlying the EEG recorded at two different electrodes, is a function F of the state of another dynamical system (Y): $X = F(Y)$. The concept of “state of the system” is expressed in terms of the level of neural synchronization, as indexed by the amplitude of the EEG voltage, in the neural networks generating the EEG potentials recorded at the two mentioned electrodes. Function F does not need to be linear; the only requirement is that it is locally smooth. This concept can be put in practice by synchronization likelihood, which is simply the chance that, if system X is in the same state at two different times i and j , then system Y will also be in the same state at time i and j (Stam and van Dijk, 2002; Takens, 1981).

SL analysis of the resting state EEG rhythms has shown that the cognitive impairment in AD and MCI subjects is associated with a loss of functional connectivity at high-frequency alpha and beta bands), but not at the gamma band (Stam et al., 2003). Noteworthy, the application of this measure on MEG data showed that the AD patients were characterized by the reduction of SL not only at the high-frequency alpha and beta bands but also at the gamma band (Stam et al., 2002). Furthermore, decrease of the SL at beta rhythms occurred in the mild AD subjects, both in a resting condition and during a working memory task (Pijnenburg et al., 2004). Moreover, the patients with vascular dementia and mild AD presented poor SL at both fronto-parietal (delta-alpha) and inter-hemispherical (delta-beta) electrode pairs (Babiloni et al., 2004b). The feature distinguishing the patients with mild AD with respect to the patients with VaD was a more prominent reduction of SL at fronto-parietal alpha rhythms; these results suggest that mild AD patients are characterized by an abnormal fronto-parietal coupling of the dominant human alpha rhythms (Babiloni et al., 2004b). Another study reported a poor SL in the AD patients at delta, theta, alpha and beta rhythms (Babiloni et al., 2004d). In detail, SL was lower in the MCI than in the Nold subjects. Furthermore, it was lower in the AD than in the MCI subjects at midline and right fronto-parietal electrodes (Babiloni et al., 2006c). The same was found for the SL of delta rhythms at the right fronto-parietal electrodes. For these EEG bands, the SL values correlated with those indexing the global cognitive status, as measured by mini mental state evaluation (MMSE). In a recent study, the SL of the resting state EEG rhythms was compared between patients with Parkinson’s disease and dementia (PDD) and PD without dementia (Bosboom et al., 2009). Results showed that the PPD patients were characterized by lower values of fronto-temporal SL at alpha rhythms, of inter-hemispherical temporal SL at delta, theta and alpha rhythms, as well as of centro-parietal SL at gamma rhythms (Bosboom et al., 2009). In contrast, parieto-occipital SL at high-frequency alpha and beta bands was higher in the PDD than in the PD without dementia.

Previous EEG studies using different nonlinear indexes such as mutual information have also reported loss of functional connectivity in AD patients in different frequency bands, with a special engagement of the alpha frequencies (Jeong, 2004). A study (Jeong et al., 2001) used some indexes of mutual information as indexes of both linear and nonlinear statistical dependencies between resting state EEG rhythms recorded at electrode pairs. The local cross-mutual information (CMI) quantified the information transmitted from one EEG time series to the other. CMI was lower in the AD patients than that in normal controls, especially over the EEG rhythms recorded in frontal and antero-temporal regions (Jeong et al., 2001). Furthermore, there was a prominent decrease in information transmission between distant EEG electrodes in the right hemisphere and between corresponding inter-hemispheric electrodes (Jeong et al., 2001). In addition, the auto-mutual information (AMI), which estimates how much on average the value of the time series can be predicted from values of the time series at preceding points, throughout the cerebrums of the AD patients decreased significantly more slowly with delay than did the AMIs of normal controls. In addition, the auto-mutual information (AMI), which estimates how much on average the value of the EEG rhythms at a given time instant can be predicted from those at preceding time points, was lower in the AD patients than in the control subjects (Jeong et al., 2001).

Figure 1 (top) illustrates the principal models of functional brain connectivity as indexed by linear or nonlinear functional coupling of the resting-state eyes-closed EEG rhythms.

INSERT THE FIGURE 1 HERE

5. Effective brain connectivity in MCI and AD subjects as revealed by the estimation of the directional information flow with the EEG coupling and by the combination of transcranial magnetic stimulation and EEG activity

Both linear and nonlinear indexes of the EEG functional brain connectivity have an important limitation: they do not reflect neither the causal aspects of the relationships among brain regions nor the direction of the information among these regions. One can overcome this limitation by two main methodological approaches. The first approach is based on the estimation of the directional information flow with the EEG coupling (Kaminski et al., 1991). The second approach stems upon the combination of transcranial magnetic stimulation (TMS) over a given scalp site of interest and the recording of interference effects on the EEG activity collected at another electrode (Capotosto et al., 2009, 2011; Romei et al., 2008; Paus et al., 2001; Brignani et al., 2008; Fuggetta et al., 2008). These approaches allow the estimation of the so called “effective brain connectivity” in

which “causality” can be understood in terms of a “flow” of neural signals from a cortical population to another one as expressed in mathematical terms.

The estimation of the directional information flow with the EEG coupling relies on two main mathematical theories, namely the information theory and Granger causality (Shannon, 1948; Kaminski et al., 1991). The information theory is based upon the concept of entropy introduced by Claude Shannon, namely the uncertainty associated with a random variable (Shannon, 1948). Several procedures measuring the joint information of two processes have been proposed from Shannon’s theory. Among them, a popular procedure is the so called mutual information (MI), which was defined as:

$$I(X;Y)=H(X)+H(Y)-H(X,Y)$$

Where $H(X)$ and $H(Y)$ is the Shannon entropy of X and Y respectively, and $H(X,Y)$ is the joint entropy of X and Y (Cover and Thomas, 1991). This value is always positive, but it is equal to zero if X and Y are statistical independent, and it is equal to 1 if X and Y have the same information. An important limitation of this procedure is that X and Y are random variables but not signals. To apply the entropy theory to real signals, several methods are available. A recent method has been proposed by Kraskov and colleagues to compute MI in the time domain (Kraskov et al., 2004). Another method has been introduced to quantify the mutual information also in time–frequency domain (Aviyente, 2005) from the normalized spectrograms. In the framework of the theory of information, the “distance” between two EEG signals or their “dissimilarity” was defined by several procedures. Among them, the Kullback–Leibler divergence is an asymmetric index of how two signals or distributions are disjoint (Blanco et al., 1995; Quiroga et al., 1999). This method is generalized with Rényi entropy. Another procedure is the Jensen–Shannon divergence (symmetric), which uses an arithmetic mean of normalized signal spectrograms. (Dauwels et al., 2010). Finally, the Jensen–Rényi divergence extended the Jensen–Shannon method from arithmetic to geometric mean (Dauwels et al., 2010). Keeping in mind the above procedures, the information-theoretic notion of transfer entropy was formulated by Schreiber (2000) as an alternative measure of effective connectivity. It can be seen as a measure of directed (time-asymmetric) information transfer between joint processes (i.e. the EEG rhythms recorded at two electrodes). Noteworthy, the transfer entropy is a rigorous derivation of Wiener’s definition of causal dependencies (Wiener, 1956), which uses Kullback-Leibler divergence defined above, keeping directional and dynamical information due to its transition probabilities and asymmetry. An important property of the transfer entropy is that it does not require any particular model for the interaction between the two processes of interest (i.e. the EEG signals recorded at two

electrodes). Furthermore, the transfer entropy works well when the detection of some unknown non-linear interactions is required (Vicente et al., 2011).

Differently from transfer entropy, the Granger causality for the linear estimation of the directional information flow within a matrix of EEG electrodes refers to the notion that, if the prediction of one time series could be improved by incorporating the knowledge of past values of a second one, then the latter is said to have a causal influence on the former (Granger, 1969). Initially developed for econometric applications, the Granger causality has gained popularity also among physicists and eventually became one of the methods of choice to study brain connectivity in neuroscience (Kamiński and Blinowska, 1991; Kamiński and Liang, 2005). Whereas the linear interdependence measures of the correlation coefficient section to the coh-entropy and wav-entropy coefficient section are bivariate (i.e., they can only be applied to pairs of EEG signals), the Granger causality measures are multivariate in that they can be applied to multiple signals simultaneously (Granger, 1969; Kamiński and Blinowska, 1991; Kamiński and Liang, 2005). Interestingly, non-linear extensions of Granger causality have been proposed recently (see, e.g., (Ancona et al., 2004; Chen et al., 2004), but we will not consider such extensions in this review for sake of brevity and since they are less commonly used.

A very popular procedure derived from the Granger causality is the so called directed transfer function (DTF), which has been proven to be reliable for the modeling of directional information flux within linear EEG functional coupling on the basis of autoregressive model (DTF; Kaminski and Blinowska, 1991; Korzeniewska et al., 1997; Kamiński et al., 1997; Mima et al., 2000; Blinowska et al., 2010; Blinowska, 2011; Blinowska and Zygierevicz, 2011; Brzezicka et al., 2011). Before computing the DTF, the EEG data are usually preliminarily normalized by subtracting the mean value and dividing by the variance (Kaminski and Blinowska, 1991). An important step of the DTF method was the computation of the so-called Mvar model (Kaminski and Blinowska, 1991; Korzeniewska et al., 1997; Kamiński et al., 1997). EEG data are simultaneously given as an input to the Mvar model towards the computation of the directional information flux among all the pair combinations of the electrodes selected. This model is used to estimate the “direction” of the information flow within the EEG rhythms between the brain regions. 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 than directionality from B to A (Vecchio and Babiloni, 2011). 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 (Babiloni et al., 2004b, 2006e; Jeong et al., 2004).

In the eyes-closed resting state, the resting state EEG rhythms propagate mainly from posterior to anterior cortical regions (Kaminski et al., 1997). This finding may be a reference point for the assessment of changes in propagation for demented patients. As a matter of fact, it has been reported a reduction of the parietal-to-frontal directional information flow within the EEG functional coupling in the amnesic MCI and mild AD subjects compared to the Nold subjects (Babiloni et al., 2009c), in line with the idea of a common patho-physiological background linking, on average, the groups of MCI and AD subjects (Vecchio and Babiloni, 2011). It is noteworthy that such a direction of the fronto-parietal functional coupling is relatively preserved in the amnesic MCI subjects in whom the cognitive decline is mainly explained by the extent of white-matter vascular disease (Babiloni et al., 2008b). This finding supports the additive model posing that MCI subjects would result from the combination of cerebrovascular and neurodegenerative lesions (Babiloni et al., 2008b). In addition, other EEG studies used Granger causality and stochastic event synchrony as models of the directional information flux showing a loss of EEG synchrony between electrode pairs in MCI and AD patients with respect to age-matched control subjects (Dauwels et al., 2009, 2010). Noteworthy, this procedure resulted in a successful leave-one-out classification rate of 83% and 88%.

Summarizing, the transfer entropy is an information theoretic measure of time-directed information transfer between jointly dependent processes such as those generating EEG signals at electrode pairs. On the other hand, the Granger causality is a statistical notion of causal influence based on prediction via vector autoregression. Interestingly, the two concepts are expected to be related, and the exact relationship has recently been formally described (Barnett et al., 2009). For Gaussian variables, the transfer entropy and the Granger causality are entirely equivalent, thus bridging autoregressive and information-theoretic approaches to data-driven causal inference (Barnett et al., 2009).

As mentioned above, the correlation analysis of the resting state EEG rhythms does not enlighten the causal relationships among the brain neural populations within the long range neural networks. And the estimation of the directional flow of information between two or more neural generators of the EEG signals is based on the concept of “synchrony” as well. To go beyond towards the estimation of the effective brain connectivity, a promising experimental strategy is based on the excitation or inhibition of a given cortical region by repetitive transcranial magnetic stimulation (rTMS), and then on the recording of its interferential effects on the ongoing EEG

activity recorded from multiple sites (Capotosto et al, 2009, 2011; Romei et al., 2008; Paus et al., 2001; Brignani et al., 2008; Fuggetta et al, 2008).

TMS is the most effective, non-invasive and tolerated procedure for the stimulation of human cortex through the intact skull (Barker et al., 1985). It utilizes a rapidly changing magnetic field to transmit a short lasting electrical current pulse into the brain. This field can induce a synchronized activation of cortical neurons followed by a long-lasting inhibition, especially in superficial cortical layers. Single pulses or short bursts of TMS can perturb ongoing neuronal processing in the stimulated cortex, producing a transient and fully interference with underlying cortical synchronization mechanisms (Pascual-Leone et al., 2000; Rossini et al., 2007; Rossini and Rossi, 2007). This perturbation has been extensively used by cognitive neuroscientists to examine the functional relevance of the stimulated area for cognitive processes and behavior (Pascual-Leone et al., 2000, Walsh and Cowey, 2000, Jahanshahi and Dirnberger, 1999).

Studies combining TMS with functional neuroimaging techniques in humans revealed that these effects occur both in the main cortical stimulated region as well as, due to trans-synaptic effects, in other distant areas (Paus et al., 1997). TMS has been shown to impact episodic memory, which is the most vulnerable cognitive domain in AD and amnesic MCI. Although mnemonic processes are crucially related to the integrity of medial temporal lobe structures, other brain areas including the dorsolateral prefrontal cortex also have a relevant role both in encoding and retrieval mechanisms of long-medium term episodic memory as revealed by fMRI and PET (Brewer et al., 1998; Buckner et al., 1999; Fletcher and Henson, 2001; Spaniol 2009). It has been shown that rTMS applied over the left dorsolateral prefrontal cortex results in distal changes of neural activity, relative to the site of stimulation, and that these changes depend on the patterns of brain network activity during resting-state (van der Werf et al., 2010).

In the framework of the estimation of the effective brain connectivity, the combined use of TMS and EEG allows a better understanding of the causal effects of TMS on cortical activity. Several approaches of combined TMS-EEG are available. Firstly, EEG activity can be compared before and after TMS over a cortical region to understand how spontaneous EEG activity and causal modulation of that activity affect sensory and cognitive processes. For example TMS over occipital cortex evoked phosphenes as a function of alpha activity before TMS (Romei et al., 2008). Secondly, the comparison of EEG activity before and after TMS has revealed changes in the EEG power spectrum. A single TMS pulse has been reported to transiently synchronized activity in the beta (14-30 Hz) range (Paus et al., 2001). Furthermore, rTMS trains of 1 Hz (Brignani et al., 2008) and 5 Hz rTMS (Fuggetta et al, 2008) were associated with concurrent changes in cortical alpha (about 8-12 Hz) and beta activity. Third, a single TMS-pulse evokes in the EEG a cortical evoked

potential that strongly differs in polarity and amplitude of its peak components. This is dependent on several factors including position and orientation of the TMS coil, stimulation intensity, and electrode position (Casarotto et al., 2011).

The TMS-EEG procedure has been recently used to demonstrate the causal role of Dorsal Attention Network (DAN) nodes (FEF, IPS) in the control of the modulation of the alpha rhythms in occipital-parietal cortex during a spatial attention task (Capotosto et al., 2009, 2011). Furthermore, it has been used to test the hypothesis that interference with spontaneous ongoing, i.e. not task-driven, activity in the Angular Gyrus (AG), one of the core regions of the Default Mode network (DMN), can modulate the dominant electroencephalographic (EEG) alpha rhythms observed in the resting state (Capotosto et al., 2012, submitted). Compared to sham stimulation, magnetic stimulation (1 Hz for 1 min) over both left and right AG, but not over FEF or IPS enhanced the dominant alpha power density in occipito-parietal cortex (Capotosto et al., 2012, submitted). Furthermore, right AG-rTMS enhanced intra-hemispheric alpha coherence (Capotosto et al., 2012, submitted). These results suggest that AG as a part of DMN plays a causal role of “effective connectivity” in the modulation of dominant low-frequency parieto-occipital alpha rhythms in the resting state condition.

To our knowledge, the only application of TMS-EEG for the study of “effective connectivity” has recently appeared to study how the excitability of the frontal cortex changes during healthy and pathological aging (Casarotto et al., 2011). The TMS-evoked EEG potentials were collected in healthy young and elderly individuals as well as in AD subjects. Results showed that the EEG potentials evoked by the TMS of the left superior frontal cortex were not affected by physiological aging but were markedly altered by cognitive impairment in the AD patients (Casarotto et al., 2011).

Figure 2 sketches the mentioned two approaches to the study of effective brain connectivity, namely the estimation of the directional flow of information within the functional coupling of the resting-state eyes-closed EEG rhythms and the rTMS combined with the recording of EEG activity.

INSERT THE FIGURE 2 HERE

6. The topology of the brain connectivity in MCI and AD subjects as revealed by graph theory

As mentioned above, brain cognitive functions rely on the integrity of dynamic communication among the nodes of interconnected brain regions within circuits. It can be speculated that an effective network perspective accounting for the global features of the brain networks would have the potential to provide novel and meaningful intermediate phenotypes of the pathology even at earlier stages of AD, including preclinical (i.e. pre-symptomatic) and prodromal

(i.e. mild cognitive impairment) AD (Stam, 2010). There is consensus that a novel approach applying the concepts of the network theory to neurophysiological data is a promising new way to characterize the topology of the functional and effective brain connectivity and their changes due to the plasticity induced by the AD neurodegeneration (Bassett and Bullmore, 2006; Stam and Reijneveld, 2007; Bullmore and Sporns, 2009).

The modern network theory is a branch of the mathematical graph theory (Stam, 2009). In this theory, the graphs are simplified representations of networks denoted by ensembles of nodes (vertices) and connections (edges). Furthermore, edges exist between any pair of vertices with probability p . On the whole, the graph theory provides a method to evaluate whether the functional connectivity patterns between brain areas resemble the organization of theoretically efficient, flexible or robust networks. Concerning the present review, a fundamental hypothesis of the graph theory is that cognitive dysfunction in the individual MCI and AD patients can be formally represented by abnormal brain networks reflected by altered topology of the functional coupling of the EEG or MEG rhythms between the electrode pairs (Stam et al., 2010).

An important contribution to the mathematical formalization of the graphs was made by Watts and Strogatz when they published their model of ‘small-world’ networks (Watts and Strogatz, 1998). Their demonstration started with the description of a ring network model. In this model, each vertex is connected to a fixed number ($N=4$) of neighbors and has a high clustering coefficient defined as the probability that the neighbors of a vertex are connected to each other. In contrast, the ring model has a long path length defined as the average number of the edges that have to be traveled to get from one vertex to another. For the next steps of their demonstration, Watts and Strogatz posited that the edges from the starting ring model are picked with a rewiring probability p , and randomly attached to another vertex. When $p = 1$, all edges are rewired each other, and a fully ER random graph like network results. This fully random network has low clustering, but short path length. For small values of p , when only a few edges are randomly rewired, the path length drops strongly, while the clustering is hardly affected. The edges randomly rewired acts a sort of “hubs” ensuring long path connectivity between remote regions of the network. This intermediate type of network with high clustering and short path lengths is called ‘small-world’ networks. Small-world networks are optimal in the sense that they allow efficient information processing, are (wiring) cost-effective, and relatively resilient to network damage. Indeed, the high clustering of the ‘small world network’ is associated with robustness of a network measure of the local connectivity of a graph. Many real-life systems appear to have small-world properties (Watts et al., 1998; Boccaletti et al., 2006; Humphries et al., 2008).

The 'small-world' networks represent the combination of properties not observed in many real networks but also by neural networks such as brains of healthy humans (Stam et al., 2007; Bullmore et al., 2009, Bassett et al., 2006; Smit et al., 2008; Stam et al., 2007; Gong et al., 2008; Sporns et al., 2004). Examining the overall organization of the brain network using the graph analysis, it has been shown a strong negative association between the normalized characteristic path length of the resting-state brain network and intelligence quotient (IQ), thus suggesting that human intellectual performance is likely to be related to how efficiently our brain integrates information between multiple brain regions (van den Heuvel et al., 2009). Applied to patient data, this technique might provide more insight in the patho-physiological processes underlying the various forms of dementia, and potentially lead to the development of new diagnostic or monitoring tools. A few studies have recently shown that different types of brain pathology interfere with the normal small-world architecture (Bartolomei et al., 2006; Micheloyannis et al., 2006; Ponten et al., 2007).

The application of graph theory to AD research provided quite interesting results. It has been shown a loss of 'small-world' network properties in AD patients as revealed by the resting state EEG and MEG rhythms (Stam et al., 2007, 2009). These properties were replaced by a more 'random' overall network structure (Stam et al., 2007, 2009). Compared to the control non-demented individuals, the AD patients were characterized by the mean clustering coefficient decreased at the lower-frequency (EEG) alpha and beta bands, and by the characteristic path length (i.e. global connectivity) decreased at the lower-frequency alpha and gamma bands (de Haan et al., 2009). With decreasing the above local and global connectivity parameters, the large-scale functional brain network organization in AD deviates from the optimal 'small-world' network structure towards a more 'random' type (de Haan et al., 2009). Furthermore, the modeling results suggest from a parallel MEG study showed that in the AD patients this pathological change was brought about by a preferential decrease of connections between high degree nodes ('hubs'), rather than a non-specific decrease of connection strength (Stam et al., 2009). In another MEG study, network analysis was used to investigate the role of functional sub-networks (modules) in the brain with regard to cognitive failure in AD (de Haan et al., 2012). It was shown that the parietal cortex was the most highly connected network area in both control subjects and AD patients, but it was characterized by the strongest intra-modular clustering losses in AD patients. Furthermore, weakening of inter-modular connectivity was even more outspoken, and more strongly related to cognitive impairment (de Haan et al., 2012). These results support the idea that the loss of communication and relative less efficient information exchange among different functional brain regions reflects an abnormal synaptic plasticity, neural loss, and cognitive decline in AD

(de Haan et al., 2009, 2012). Noteworthy, loss of small-world structure in AD was also demonstrated in recent MRI studies applying graph theory (He et al., 2008; Supekar et al., 2008).

Figure 3 plots a model of the results of graph theory reported in this chapter. Normal control subjects are characterized by a 'small-world' network structure of the functional coupling of the resting-state EEG rhythms (left). With respect to the normal control subjects, the AD patients manifest the deviation of 'small-world' network properties towards a more 'random' overall network structure (right).

INSERT THE FIGURE 3 HERE

7. New directions: high spatial resolution of the functional brain connectivity as revealed by the correlation between resting state EEG rhythms and hemodynamic activity

As described above, EEG at rest (eyes closed) is a low-cost, easy to perform, and widely available neurophysiological approach to the study of functional brain connectivity in AD and MCI subjects (see Rossini et al., 2007 for a review). Furthermore, the resting state EEG rhythms seem to provide -at least at group level- useful markers/end points to evaluate disease progression in MCI and AD subjects. However, low spatial resolution (centimeters) of the EEG techniques prevents a reliable and precise spatial estimation of the cortical sources and of the functional coupling of the EEG rhythms. In this sense, functional magnetic resonance imaging (fMRI) has an insufficient temporal resolution (seconds) for the study of the brain rhythms but a very high spatial resolution (millimeters). For this reason, the combination of the EEG and fMRI techniques has been performed in the past years. In this line, several simultaneous EEG/functional MRI (fMRI) studies have investigated the correlation between EEG alpha rhythms in the resting state and low-frequency (about 0.1 Hz) fluctuations of the blood oxygenation signal (BOLD) in healthy subjects, showing that these fluctuations are temporally correlated across large-scale distributed networks (Biswal, 1996; Raichle and Mintun, 2006; Fox & Raichle, 2007; Raichle and Snyder, 2007; Smith et al., 2009; Deco & Corbetta, 2010). Furthermore, these fluctuations are considered as changes in brain activity not externally induced or voluntarily generated by the subject and represent about 90-95% of the total amount of brain activity (Raichle and Snyder, 2007; Biswal et al., 1995). One of such networks, the so-called default mode network (DMN), has been originally identified as a set of regions consistently suppressed during goal-driven behaviour (Shulman et al., 1997; Demonet et al., 2001; Damoiseaux et al., 2006; Fox et al., 2005, 2006; Mantini et al., 2007) and tonically active (Raichle et al 2001; Vaishnavi et al., 2010) during the resting state condition. This metabolic profile is consistent with peculiar functions of the DMN during restful wakefulness, a conclusion

confirmed by more recent local field potential recordings from the cortical surface (Miller et al., 2010; Dastjerdi et al 2011). In the resting-state eyes-closed condition, some studies have reported a positive correlation between the alpha power and the BOLD signal time series in the DMN (Mantini et al., 2007), whereas other evidence pointed to negative or mixed correlations (Gonçalves et al., 2006; Laufs et al., 2003). Less clear correlations of the EEG and fMRI data were also seen in the resting-state eyes-open condition (Knyazev et al., 2011; Wu et al., 2010).

In contrast, the alpha power was negatively correlated with activity in the Dorsal Attention Network (DAN) during the resting state condition (Sadaghiani et al., 2010; Mantini et al., 2007; Laufs et al., 2003). This is a set of control regions recruited during goal-driven behavior and perceptual selection (Corbetta & Shulman, 2011). The DAN, which is bilaterally centered on the intraparietal sulcus (IPS) and the frontal eye fields (FEF), appears to be involved in the endogenous goal-driven attention orienting (top-down) process and responsible for the preparation and selection for stimuli and responses (Astafiev et al., 2003; Corbetta and Shulman, 2002). The same negative correlation is observed between the alpha power and the ventral fronto-parietal cortical network (VAN; Corbetta and Shulman, 2002, 2008). The VAN includes the right lateralized temporal-parietal junction (TPJ) and the ventral frontal cortex (VFC), appears to be involved in an exogenous stimuli-driven attention reorienting (bottom-up) process, and is activated when detecting the unexpected salient targets (Astafiev et al., 2003, 2004; Corbetta and Shulman 2002). Finally, the resting state alpha power also correlated to BOLD activity in the cingulo-insular-thalamic network, the so called Control network (Gonçalves et al., 2006; Sadaghiani et al., 2010).

Correlation between the resting state EEG power and the brain BOLD activity was not limited to alpha rhythms. It has been shown that the power of several EEG bands (i.e. delta, theta, alpha, beta, and gamma) correlated to fMRI time courses within the resting state networks identified by the use of independent component analysis (Mantini et al., 2007). Analogously to the alpha power, the beta power was positively correlated to the BOLD activity in the DMN and self-referential networks, and was negatively correlated with the BOLD activity observed in the DAN (Mantini et al., 2007).

The correlation between the resting state alpha power and the BOLD in the DMN, attentional networks, and cingulate-insular-thalamic networks unveil the functional role of brain EEG oscillatory activity for the functional connectivity and neurotransmission within long-range cortical networks, as a possible basis of the regulation of spontaneous cortical arousal in wakefulness (Fox et al, 2005). Keeping in mind these data, we think that the study of correlation between the resting state alpha power and the BOLD in the Default Mode Network (DMN), Dorsal Attention Network (DAN), and ventral fronto-parietal cortical network (VAN) represent a new

avenue for a better understanding of the clinical neurophysiology of AD patients and for the definition and validation of instrumental markers for diagnostic, prognostic, and therapy monitoring purposes.

Figure 1 (bottom) sketches the approach to the functional brain connectivity by a multimodal approach based on the recording and analysis of the resting-state eyes-closed fMRI hemodynamic curve and EEG rhythms.

8. Conclusions

The outcome of present review of the literature shows that the resting state eyes-closed EEG (MEG) rhythms recorded in MCI and AD subjects is a useful approach to study brain synchronization mechanisms, functional connectivity and neuroplasticity of the neurotransmission in AD patients as revealed by spectral markers of these EEG (MEG) rhythms such as power density, spectral coherence, and other quantitative features. The variables differed among normal elderly, MCI, and AD subjects, at least at group level. The majority of the revised studies pointed to abnormalities of posterior EEG (MEG) power density at specific frequency bands (i.e. especially at alpha band), associated to an altered functional coupling among long-range brain networks (i.e. fronto-parietal and fronto-temporal) as revealed by markers of functional and effective brain connectivity. These abnormalities of the EEG (MEG) functional coupling showed specific topological features. The group of AD patients was characterized by a deviation from the functional organization called ‘small-world’ network, with a reduction of both local and long-range functional connections. This was especially true at the level of “hub” cortical regions, namely the parietal areas. In conclusion, the resting state EEG makers are promising to unveil abnormal functional connectivity and neuroplasticity of neurotransmission in the brain of AD patients.

Table 1 provides an overview of the main bibliographic references on the functional and effective brain connectivity in MCI and AD subjects. The results of these references support a very tentative physiological model of brain synchronization mechanisms and functional connectivity in healthy and AD subjects in the resting-state eyes-closed condition. The dominant posterior alpha rhythms (8–12 Hz) would denote the back-ground, spontaneous synchronization around 10 Hz of neural networks regulating the fluctuation of subject’s global arousal and consciousness states. These networks would span neural populations of cerebral cortex, thalamus, basal forebrain and brainstem, including glutamatergic, cholinergic, dopaminergic and serotonergic parts of the reticular ascending systems. The neurophysiological model posits that AD neurodegenerative processes affect the interactions among these neural populations, thus inducing an amplitude increase of widespread delta (2-4 Hz) and theta (4-8 Hz) rhythms and an amplitude decrease of the

dominant alpha rhythms. This sort of cortical disconnection from sub-cortical structures, working as a thalamo-cortical “disconnection mode” reflected both in a “slowing” of the EEG rhythms and in a local decrease of functional coupling of alpha rhythms. Figure 4 sketches the theoretical neurophysiological models at the basis of the generation of the resting-state eyes-closed EEG rhythms in normal control subjects and in AD patients. Specifically, the models illustrate the effects of the AD neurodegeneration on the amplitude (top) and the functional coupling (bottom) of the EEG rhythms.

INSERT THE TABLE 1 AND THE FIGURE 4 HERE

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Table legend

Table 1. Overview of the main bibliographic evidence on the functional and effective brain connectivity in MCI and AD subjects as revealed by the functional coupling of the resting-state yes-closed EEG rhythms. The results of the main studies using spectral coherence, synchronization likelihood, information theory indexes, directed transfer functions, and others are reported.

Figure legend

Fig. 1. Top: Sketch of main models of functional brain connectivity indexed by linear and nonlinear functional coupling of resting-state eyes-closed electroencephalographic (EEG) rhythms. Bottom: multimodal analysis of fMRI hemodynamic curves and EEG signals.

Fig. 2. Top: Two main different approaches to the study of effective brain connectivity. The estimation of the directional information flow between electrode pairs for the resting-state eyes-closed EEG rhythms. Bottom: effects of the transcranial magnetic stimulation (rTMS) delivered over a given electrode on the evoked EEG activity collected at another electrode (bottom).

Fig. 3. Sketch of the nodes and topologic connections of functional brain connectivity in healthy subjects and in Alzheimer's disease (AD) patients as revealed by electroencephalographic (EEG) or magnetoencephalographic (MEG) rhythms. These nodes and connections show the deviation of the AD patients from the 'small-world' network properties of the control subjects' brain. The features of the AD patients' brain are more similar to those of 'random' networks.

Fig. 4. Theoretical physiological model of cortical neural synchronization and functional coupling in the resting-state eyes-closed condition in healthy subjects and in AD patients as revealed by EEG rhythms. In the resting-state eyes-closed condition, dominant posterior alpha rhythms (8–12 Hz) would reflect the back-ground, spontaneous synchronization around 10 Hz of the neural networks regulating the fluctuation of subject's global arousal and consciousness states. These networks would span neural populations of cerebral cortex, thalamus, basal forebrain and brainstem, including glutamatergic, cholinergic, dopaminergic and serotonergic parts of the reticular ascending systems. It can be speculated that that AD neurodegenerative processes affect the interactions among these neural populations, thus inducing an increase of the power density of widespread delta (2-4 Hz) and theta (4-8 Hz) rhythms and a decrease of the power density of the dominant alpha rhythms. This sort of cortical disconnection from sub-cortical structures, working as a thalamo-cortical "disconnection mode" is reflected both in a "slowing" of the EEG rhythms (top) and in a local decrease of functional coupling of alpha rhythms (bottom).

Tab. 1

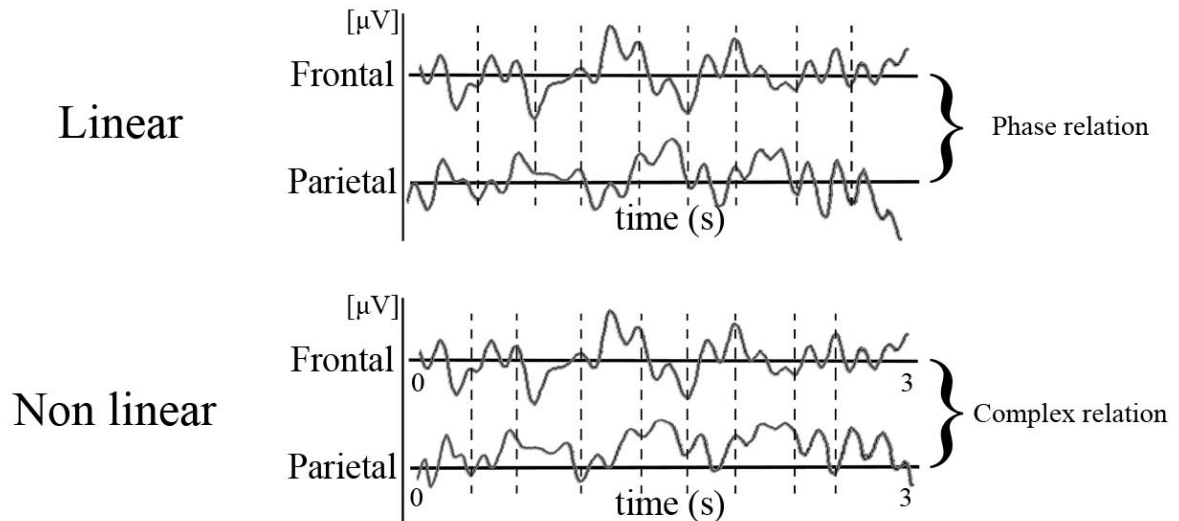
EEG Marker	Group	Main results	Reference
Spectral coherence	N=41 AD and 18 Nold	Decrease of left occipito-parietal, left temporo-parietal, and right temporo-frontal alpha coherence in AD homozygous for the APOEε4 compared to Nold.	Jelic et al., 1997
Spectral coherence	N=10 AD and 10 Nold	Decrease of alpha coherence in AD compared to Nold. Increase of fronto-parietal delta coherence in few AD patients.	Locatelli et al., 1998
Spectral coherence	N=10 AD and 10 Nold	Decrease of alpha and beta coherence in AD compared to Nold.	Wada et al., 1998a
Spectral coherence	N=10 AD and 10 Nold	Decrease of inter-hemispheric delta, theta, alpha, and beta coherence in AD compared to Nold.	Wada et al., 1998b
Spectral coherence	N=35 AD and 30 Nold	Decrease of inter-hemispheric delta, theta, alpha, and beta coherence as well as intra-hemispheric delta and theta coherence in AD compared to Nold.	Knott et al., 2000
Spectral coherence	N=15 AD, 27 MCI and 16 Nold	Decrease of temporo-parietal delta, theta, alpha, and beta coherence in AD compared to Nold and MCI.	Jelic et al., 2000
Spectral coherence	N=31 AD and 17 cognitively unimpaired depressive	Decrease of inter-hemispheric theta coherence in AD compared to cognitively intact depressive subjects.	Adler et al., 2003
Spectral coherence	N=38 AD	Negative (positive) correlation between delta (alpha) total coherence and MMSE across AD patients.	Brunovsky et al., 2003
Spectral coherence	N=47 AD, 52 MCI and 33 Nold	Progressive increase of delta total coherence across Nold, MCI, and AD. Decrease of alpha 1 total coherence in AD compared to MCI and Nold. Negative correlation between delta total coherence and MMSE across Nold, MCI, and AD.	Babiloni et al., 2009c

Spectral coherence	N=57 MCI and 28 Nold	Decrease of alpha 1 total coherence in MCI compared to Nold. Decrease of alpha 1 total coherence in MCI+ (high cholinergic damage) compared to MCI- (low cholinergic damage).	Babiloni et al., 2010b
Synchronization likelihood (SL)	N=14 AD, 11 MCI and 14 subjective	Decrease of alpha and beta SL in AD compared to subjective memory complaint.	Pijnenburg et al., 2004
Synchronization likelihood (SL)	N=82 AD, 25 VAD and 41 Nold	Decrease of fronto-parietal delta and alpha as well as inter-hemispherical delta and beta coherence in AD compared to Nold	Babiloni et al., 2004c
Synchronization likelihood (SL)	N=109 AD, 88 VAD, and 69 Nold	Progressive decrease of fronto-parietal delta and alpha1 SL across Nold, MCI, and mild AD. Correlation between fronto-parietal delta and alpha 1 SL and MMSE across Nold, MCI, and AD.	Babiloni et al., 2006c
Cross and auto mutual information (CMI, AMI)	N=15 AD, and 15 Nold	Decrease of alpha CMI and AMI in AD compared to Nold	Jeong et al., 2001
direct transfer function (DTF)	N=64 AD, 69 VAD and 73 Nold	Reduction of parietal-to-frontal DTF in MCI and AD compared to Nold	Babiloni et al., 2009b
direct transfer function (DTF)	N=73 AD, 69 VAD and 64 Nold	Reduction of parietal-to-frontal DTF in MCI and AD compared to Nold	Vecchio and Babiloni., 2011
Granger causality and stochastic event synchrony	N=17 AD, and 24 Nold	Discrimination between AD and Nold with Granger causality and stochastic event synchrony with a classification rate of 88%	Dauwels et al., 2009
Granger causality and stochastic event synchrony	N=25 MCI and 24 Nold	Discrimination between MCI and Nold with Granger causality and stochastic event synchrony with a classification rate of 83%	Dauwels et al., 2010

Fig. 1

Functional connectivity

EEG signals functional connectivity



Multimodal functional connectivity

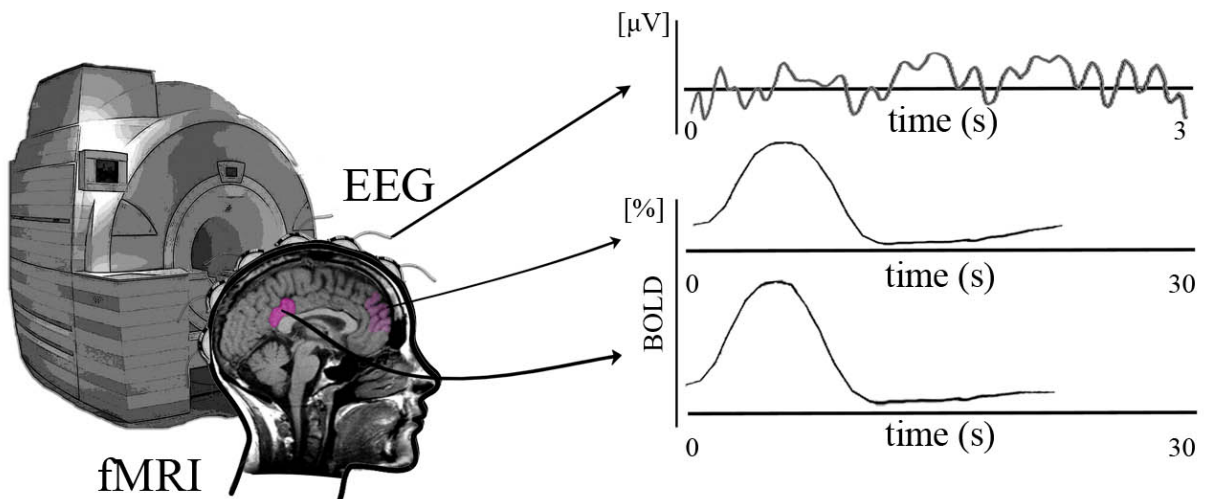
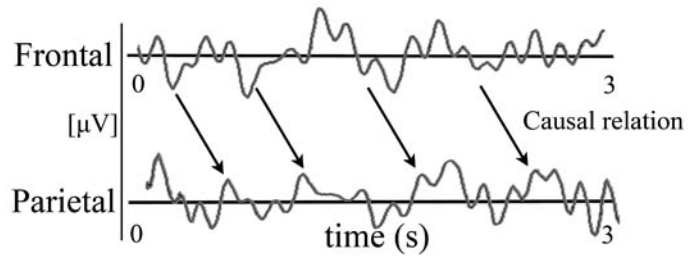


Fig. 2

Effective connectivity

Directed Transfer Function (DTF)



TMS effective connectivity

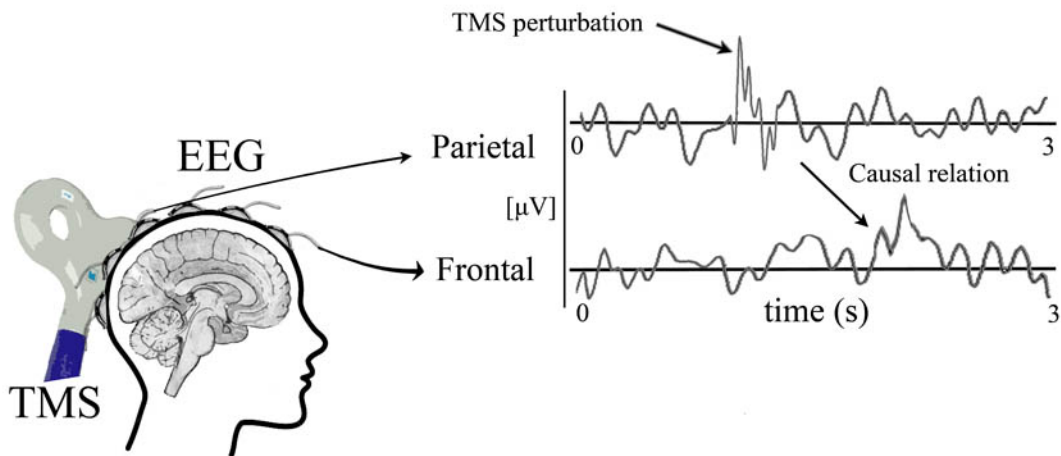


Fig. 3

'Small-world' network

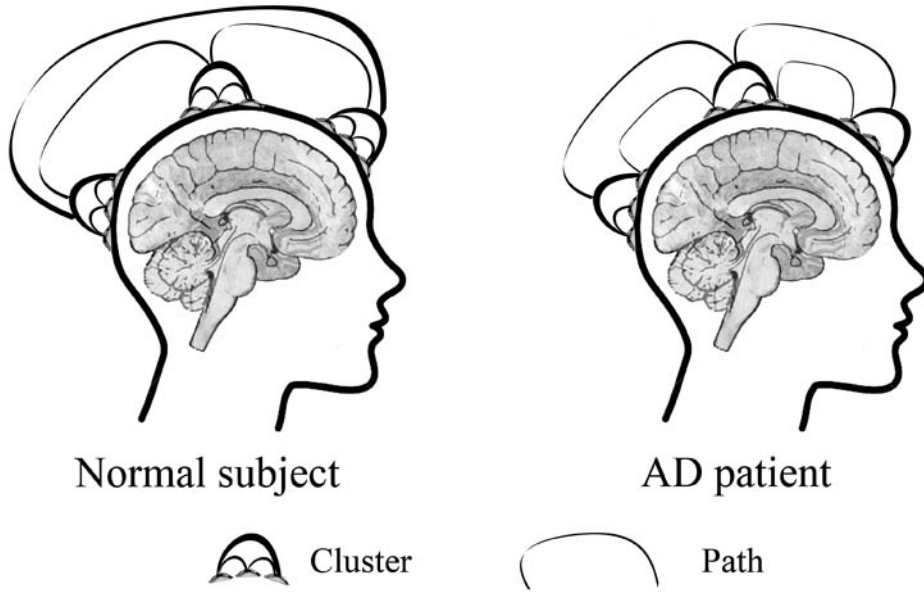


Fig. 4

Dynamics and functional coupling of EEG signals

Normal Vs. AD brain
(resting state eyes closed)

