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Review Paper

Brain neural synchronization and functional coupling in Alzheimer's disease as revealed by resting state EEG rhythms

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ABSTRACT

Alzheimer's disease (AD) is the most common type of neurodegenerative disorder, typically causing dementia along aging. AD is mainly characterized by a pathological extracellular accumulation of amyloid-beta peptides that affects excitatory and inhibitory synaptic transmission, inducing aberrant patterns in neuronal circuits. 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 synchronization likelihood (linear and nonlinear) or spectral coherence (linear), the latter by granger causality or information theory indexes. Here we reviewed literature concerning EEG studies in condition of resting state in AD and mild cognitive impairment (MCI) 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 with 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 is composed of about 100 billion neurons interconnected through a complex and intricate network of synapses. A combination of several factors is responsible for brain aging, typically the synaptic pruning, the neuronal apoptosis, and the loss of cortico-cortical connections, bringing to a decline of cognitive functions (D'Amelio and Rossini, 2012). Neural and synaptic redundancy, as well as plastic remodeling of brain networking, promotes maintenance of brain functions and cognitive status in late life (D'Amelio and Rossini, 2012).

Pathological processes at the cellular level can alter physiological brain aging. It is well known that Alzheimer's disease (AD) is the most common type of neurodegenerative disorder, typically causing dementia along aging. AD is characterized by a pathological accumulation of amyloid-beta (Aβ) and hyperphosphorylated tau peptides that affect excitatory and inhibitory synaptic transmission (Daulatzai, 2010; Shen, 2004). The pathological accumulation of these peptides induces aberrant patterns in neuronal circuits (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 characterized by an impairment of the cholinergic neurotransmission and a pathological production of Aβ and phosphorylated tau. Furthermore, it is related to neurodegeneration within the basal forebrain, prefrontal, parietal, entorhinal cortices, hippocampus, and amygdala (Daulatzai, 2010; Shen, 2004).

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Alzheimer's disease is diagnosed on the basis of overt dementia symptoms, but the disease onset probably started about 5 years before. For a better therapeutic strategy is necessary an early diagnosis of AD. In this line, there has been great progress in identifying the biochemical footprints of the AD-related changes in the brain well before the symptoms of overt dementia. The NINCDS-ADRDA criteria for the diagnosis of prodromal AD have been revised (Dubois et al., 2007; Albert, 2011; Jack et al., 2011; McKhann et al, 2011; Sperling et al., 2011) to include fluid and neuroimaging biomarkers of AD. Fluid biomarkers, from the blood and the cerebrospinal fluid (CSF; Clark and Wagner, 2003; Fagan et al., 2006; Schoonenboom et al., 2008; Tapiola et al., 2009) includes: genotyping for apolipoprotein E4 (ApoE), cystatin B and homocysteine, considered as independent risk factors for sporadic late-onset AD; presenilins (PSEN1 and PSEN2) autosomal dominant inheritance (high penetrance >85%), which cause Aβ aggregation and is related to early-onset AD; changes in the levels of cerebrospinal fluid (CSF) tau protein and beta-amyloid 42 (Abeta42) peptide, which are considered signs of the amyloid cascade that leads to neurodegeneration (Tapiola et al., 2009). The validated neuroimaging biomarkers, instead, include: positron emission tomography-with fluorodeoxyglucose (FDG-PET) to map the temporo-parietal and precuneus hypometabolism (Jagust et al., 2007; Minoshima et al., 1997); structural magnetic resonance imaging (MRI) to evaluate hippocampal atrophy (Frisoni et al., 2010; Silbert et al., 2003; Zarow et al., 2005; Schuff et al., 2000; Van de Pol et al., 2006); PET-amyloid Pittsburg Compound B (PIB), used for the evaluation of Aβ deposition (Klunk et al., 2004; Rowe et al., 2007; Ikonomovic et al, 2008). It is crucial to underline the expensiveness and the invasiveness of the techniques above, so they cannot be applied for serial assessment of a great number of elderly subjects which show objective cognitive impairment, due to limited financial resources of the public health services. Moreover, these approaches are not especially suited to investigate neuronal/synaptic dysfunction, perhaps causing cognitive and functional deficits. Basically, the progression of symptoms of AD often follows the topographic progression of neurodegeneration across specific long-range brain neural networks (Frisoni et al., 2010), including semantic memory loss (lateral temporal cortex), episodic memory loss (posterior cingulate cortex and hippocampus and medial temporal lobe), apraxic, aphasic, and visuospatial symptoms (frontal, temporal, and parietal neocortex), motor (sensorimotor cortex) and visual deficits (occipital cortex). Excluding atypical variants (Alladi et al., 2007), this orderly progression may support the notion that AD reflects the compromised integrity of communication between interconnected brain regions and circuits, and reflect incremental spread into adjacent or upstream regions (Pievani et al., 2011). So, a network perspective accounting for the brain region interactions has the potential to provide a new meaningful intermediate phenotype 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). These neuro-protective mechanisms, such as the neural/synaptic redundancy and plastic remodeling of brain networking, are facilitated by mental and physical training, and constitute a form of "cognitive or brain reserve" possibly related to greater amounts of specific presynaptic proteins and distinct protein–protein interactions (Honer et al., 2012). The absence of objective cognitive impairment at the onset of AD motivates the use of instrumental markers of altered functional connectivity and neutral transmission across long-range neural networks together with "paper and pencil" neuropsychological batteries to assess the cognitive functions (Rossini et al., 2007). To this aim, digital electroencephalography (EEG) has very interesting features to provide useful information on the functioning of neutral transmission and cortical neuronal synchronization and coupling across long-range neural networks when compared to other classical neuroimaging techniques (Babiloni et al., 2009a).

Of note, EEG is characterized by a low spatial resolution (centimeters) compared to other neuroimaging relatively non-invasive techniques, such as structural MRI and PET, producing "in vivo" brain anatomy images with high spatial resolution (millimeters to a few centimeters). On the other hand, EEG can rely on a high temporal resolution (i.e. milliseconds; Rossini et al., 2004), compared to structural MRI, which does not provide any functional information about the brain, and PET scan of brain glucose metabolism/rCBF (seconds to minutes for PET). High temporal resolution of EEG is considered crucial for the study of the spontaneous and event-related oscillatory gross electromagnetic activity at different frequency ranges (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 activity in wake and wake (Nunez et al., 1999).

In the last two decades, the evaluation of quantitative EEG (qEEG) and/or event-related potentials (ERPs) as clinical markers of the early stages of AD has been considered (Celesia et al., 1987; Rossini et al., 2007; Rossini, 2009; Yener et al., 2008, 2009). In particular, the recording of resting state eyes-closed EEG represents a simple standardized procedure that may be carried out rapidly in a clinical environment. The recording of the EEG rhythms at rest does not require stimuli or assessment of subject's behavior, and it does not induce fatigue or anxiety typically associated with common task performance. Also, the recording of the EEG rhythms can be repeated countless times along the disease progression and the 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, 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 (Kogan et al., 2001; Rodriguez et al., 2002, Rodriguez et al., 2004; Reeves et al., 2002; Onofrj et al., 2003; Brassen and Adler, 2003; Babiloni et al., 2006e).

It has been proposed that the effect 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. 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, instead, describes how the EEG rhythms at one electrode affects the EEG rhythms at another remote electrode, as a reflection of a causal interaction between the two corresponding cortical sources (Babiloni et al., 2009a). In the framework of the EEG techniques, the former is typically indexed by synchronization likelihood (linear and nonlinear) or spectral coherence (linear), 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 electrical activity of the brain recorded from electrodes placed on the scalp. In 1929, Hans Berger

reported a dominant 10-Hz oscillating voltage difference between two electrodes placed on the scalp in healthy subjects during 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.

Important limitations are the EEG voltage measured depends on the position of the reference electrode and the low spatial resolution. Furthermore, the spatial distribution of neural currents from the brain to scalp electrodes is attenuate and blur because of varying conductivities of head tissues (brain, meninges, skull, and scalp). So, EEG recording on the scalp is characterized by low values of gamma frequency oscillations and enhanced low-spatial components. Estimation of common average reference, inverse EEG source solutions, and source current density (Babiloni et al., 2009a, 2009b) are examples of mathematical procedures developed to obtain reference-free measurements with attenuated head volume conductor effects, and to minimize the effects of head volume conduction.

Technical requirements make the EEG equipment a noninvasive and nonexpensive device, with an overall present price of few tens of thousands of Euro needed for high-resolution EEG recording. EEG signals are derived from the electric activity of neurons in the cerebral cortex. Specifically, these signals are mainly produced by post-synaptic potentials of synchronously active cortical pyramidal neurons that reflect the integrative information processing of signals coming from brainstem, thalamus, and other cortical modules. Every EEG signal is a very large-scale measure of cortical activity, reflecting synaptic activity synchronized over macroscopic (centimeter) regional spatial scales (Nunez, Wingeier, and 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.

The EEG high temporal resolution (<1 ms) is ideal to investigate an important property of brain physiology, namely cortical rhythms during passive wakefulness and task performance. The estimation of EEG dynamics, in terms of power, phase, dominant frequencies, and coherence of EEG rhythms, is made by spectral analysis. At about 10 Hz, the background spontaneous oscillatory activity of cortical neurons 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 almost 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, and Hari, 1995; Salmelin, Hari, Lounasmaa, and Sams, 1994). During the so-called slow-wave sleep, cortico-fugal slow oscillations (<1 Hz) are responsible for grouping thalamic-generated delta rhythms (1–4 Hz) and spindling activity (7–14 Hz) rhythms (Steriade, 2003). In condition of arousal, spindles are blocked by the inhibition of oscillators within the reticulo-thalamic neuronal circuits, while delta rhythms are blocked by the inhibition of oscillators within the thalamo-cortical neuronal circuits (1–4 Hz), and intra-cortical neuronal circuits (slow wave, <1 Hz). Faster rhythms (beta and gamma), mainly induced by cholinergic inputs from the nuclei basalis to hippocampus and cortex, and thalamo-cortical projections, replaced the slower rhythms (Steriade, 2003 and Steriade et al., 1996). At rest, awake, low-frequency alpha (8–10.5 Hz) would be mainly related to global attention (Steriade and Llinas, 1988; Rossini et al., 1991; Klimesch, 1996; Klimesch et al., 1997, 1998). Noteworthy, alpha oscillations are considered the dominant resting rhythms of the awake adult human brain (Steriade and Llinas, 1988; Rossini et al., 1991; Klimesch, 1996; Klimesch et al., 1997, 1998), related to intelligence quotient, cognition, and memory (Klimesch, 1999). This background activity is desynchronized during sensory and cognitive-motor events (Babiloni et al., 2005, Babiloni et al., 2006a, b, c, d, e; Babiloni et al., 2008a, 2008b; Pfurtscheller and Lopes da Silva, 1999). Delta (1–4 Hz), theta (4–7 Hz) and gamma bands (30–70 Hz) also show complex patterns modulated by cognitive processes such as working memory and perceptual binding (Srinivasan, Winter, and 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

Eyes-closed cortical EEG rhythms at rest undergo gradual modifications with aging, observable as changes in EEG power density spectrum, either evaluated at scalp electrodes, or in 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 people are characterized by a typical decrease of alpha power density (8–13 Hz) with respect to young controls (Klimesch, 1999; Dujardin et al., 1994a, 1994b, 1995; Klass and Brenner, 1995). A large sample study of 215 healthy subjects, ranged between 18 and 85 years, showed an age-related decrease of the EEG power density in the posterior alpha at low frequencies (alpha 1; 8–10.5 Hz) and in delta rhythms (Babiloni et al., 2006a). These studies are in line with the shift of alpha power density towards frontal brain regions in EEG rhythms at rest found in AD patients (Dierks et al., 1993), and during cognitive processes in healthy elderly people (Yordanova et al., 1996, 1998; Kolev et al., 2002; Başar, 2011). Of note, parieto-occipital alpha power density presumably reflects the dominant oscillatory activity of cerebral networks in the condition of resting state with eyes closed, as a result of high synchronization of cortical pyramidal neuronal activity (Pfurtscheller and Lopes da Silva, 1999), modulated by cortico-cortical and thalamo-cortical interactions with the transmission of sensorimotor signals and the cortical recovery of semantic information (Steriade and Llinas, 1988; Brunia, 1999; Pfurtscheller and Lopes da Silva, 1999). At awake rest, the low alpha rhythms (alpha 1; 8–10.5 Hz) characterize widely distributed brain networks, and reveal the spontaneous fluctuation of the general brain arousal and global attentional readiness (Steriade and Llinas, 1988; Rossini et al., 1991; Klimesch, 1996; Klimesch et al., 1997; Klimesch et al., 1998). If the power density of these rhythms is related to memory, intelligent quotient, and global cognition status (Klimesch, 1999), the power density of the high alpha rhythms (alpha 2; 10.5–13 Hz) denotes the oscillation of more selective neural circuits responsible for sensorimotor and semantic information (Klimesch, 1996, 1997; Klass and Brenner, 1995). 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: they can completely differ in anterior and posterior areas as reported in studies involving both humans and animals (Başar, 2011; Schürmann et al., 2000).

At group level, cortical EEG rhythms at rest in healthy normal elderly (Nold), MCI, Parkinson disease with dementia (PDD), cerebrovascular dementia (CVD), and AD subjects present topographical and frequency differences in power density spectra. 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 (about 8–13 Hz) and/or beta (about 13–30 Hz) rhythms (Huang et al., 2000; Dierks et al., 2000; Ponomareva et al., 2003; Babiloni et al., 2004a; Jeong, 2004; Prichep, 2005). AD showed lower power density of posterior alpha rhythms

than CVD and PDD subjects, whereas CVD and PDD subjects showed widespread higher power density theta rhythms in the than in the AD subjects (Babiloni et al., 2004a, 2011a).

EEG power density at rest differed between AD and amnesic MCI subjects, considered at high risk of prodromal AD. Low-frequency alpha rhythms (8–10.5 Hz), in parietal and occipital regions, was at an "intermediate" level of power density in MCI compared to Nold and mild AD subjects (Babiloni et al., 2006b). In AD patients was observed an anterior shift of maximum alpha and beta power density compared to Nold and MCI subjects (Huang et al., 2000).

Changes in the EEG rhythms in a condition of resting state with eyes closed were studied along the progression of the disease, at least at 1-year. In the MCI subjects, the most changes in were: temporal and occipital theta and delta power density increase as well as a temporal and occipital beta power density decrease (Jelic et al., 2000). In the AD patients, a parieto-occipital theta and delta power density increase was observed as well as a parieto-occipital alpha and beta power density decrease (Coben et al., 1985). Moreover, the AD patients showed an increase in the power density at theta and delta rhythms in temporal and in occipital regions (Soininen et al., 1989, 1991). In the typical track of AD neurodegeneration was found a relationship between brain atrophy, as revealed by structural MRI, and power density of the resting state eyes-closed EEG rhythms. In the AD patients with global cognitive impairment, the hippocampal atrophy was positively correlated with delta and theta power density in temporal and parietal regions (Helkala et al., 1996), in line with recent magnetoencephalographic (MEG) evidence (Fernandez et al., 2003). Hippocampal atrophy was also related to a reduction of power density at alpha rhythms in parietal, temporal, and occipital regions in AD and MCI subjects (Babiloni et al., 2009b). A similar relationship was observed between the volumetric changes of sub-cortical white matter (i.e. connection pathways to and from the cerebral cortex), cortical gray matter, and the power density of the resting state eyes-closed EEG rhythms. Moreover, the volume of the white matter was negatively correlated to the delta power density in frontal region in AD patients, suggesting that reduction of the modulation in frontal cortex through white matter might dis-inhibit the intrinsic delta oscillations of the cerebral cortex (Babiloni et al., 2006d). Furthermore, a relationship was found between the global alpha and delta power density and the total amount of atrophy of cortical gray matter (computed by MRI voxel-to-voxel volumetry of lobar brain volume) in the AD subjects and in the amnesic MCI subjects; the higher the total gray matter volume, the higher the global alpha power density, and the lower the global delta power density (Babiloni et al., 2012). These modifications of the delta and alpha power density in the MCI and AD subjects were not due only to vascular lesions of the white matter (Babiloni et al., 2008a,b; Babiloni et al., 2011b). From the above findings, it seems that the posterior delta and theta power density, together with the alpha power density of EEG in a condition of resting state with eyes closed, reflect, at least at group level, the neurodegenerative processes along the time course of AD.

The power density of the resting state eyes-closed EEG cortical rhythms was found to be related to cognitive status in AD and MCI subjects. It has been shown that the posterior alpha power density was positively correlated with the subjects' global cognitive status, as measured by ADAS-cog in AD and MCI subjects: the lower the power density of alpha rhythms, the lower the cognitive status (Luckhaus et al., 2008). Moreover, in the Nold, MCI and AD subjects the posterior delta was negatively correlated with the MMSE score; conversely, the alpha power density was positively correlated with the MMSE score (Babiloni et al., 2006b). Furthermore, low CAMCOG scores for cognitive performance in the AD subjects was associated with low-alpha power density in frontal, parietal, occipital, and central regions (Claus et al., 2000).

Taking into account those results, it can be speculated that the use of power density of alpha and delta rhythms, alone or with structural MRI, SPECT, or PET markers, may corroborate and support the standard assessment of MCI and AD. An important study, first in his field, has combined EEG, PET, and structural MRI markers using an ensemble of classifiers based on a decision-fusion approach, to determine whether a multi-modal approach can improve the diagnostic accuracy over any of the individual data sources when used with an automated classifier. This strategic combination of different modalities improved the classification up to 10%–20%, compared to the performance obtained using separately those unimodal data sources (Polikar et al., 2010).

Some longitudinal studies investigated the power density of baseline eyes-closed EEG rhythms at rest as a predictor of 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). In AD patients, an increase of theta and delta power density and a reduction of the alpha and beta power density were found in the parietal and in the occipital regions (Coben et al., 1985). Another study found that the 50% of the AD group showed an increase of the delta and theta power in the occipital and in the temporal regions (Soininen et al., 1989). Furthermore, longitudinal studies demonstrated that are considered predictors of the progression from MCI to dementia, at about 1-year follow-up, the increase of delta or theta power density, the decrease of alpha and beta power density, and the slowdown of mean EEG frequency (Jelic et al., 1996, 2000; Grunwald et al., 2001; Kwak, 2006; Rossini et al., 2006). Moreover, high power density of the posterior alpha rhythms also predicted the stability of the global cognitive status in MCI subjects at 1-year follow-up (Babiloni et al, 2010a).

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

The 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 et al., 2003; Börner et al, 2007).

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

Linear components of such coupling can be obtained by the analysis of EEG spectral coherence, which evaluates the functional co-ordination and mutual information exchange of the cortical generators of EEG rhythms (Thatcher et al., 1986; Rappelsberger and Petsche, 1988; Gevins et al., 1998; Gerloff et al., 1998). EEG spectral coherence is a

normalized value used to estimate the temporal synchronization in the frequency domain (obtainable by fast Fourier transform, FFT) of two EEG time series recorded in two different pairs of electrodes (Rappelsberger and Petsche, 1988; Pfurtscheller and Andrew, 1999). As a theoretical assumption, the functional coordination of oscillatory activity of two cortical areas is related to a high linear correlation and subsequent high spectral coherence of the EEG rhythms of these cortical areas show. Reduced linear functional coupling and, in general, information transfer (i.e. functional uncoupling or unbinding following) among cortical areas or reduced modulation of common areas by a third region are reflected by a decreased EEG coherence. Conversely, an enhancement of the linear functional connections and information transfer (i.e. functional coupling or binding), a reflection of the interaction of different cortical structures for a given task, produced an increase of the EEG coherence (Rossini et al., 2007). It has been proved an association between high EEG spectral coherence in the cortical regions responsible for the information processing during intensive task, and cognitive, perceptive, and motor processes (Sauseng et al., 2005; Vecchio et al., 2007, 2010; Vecchio and Babiloni, 2011), as a function of the type and the extension of the neural networks involved (Pfurtscheller and Lopes da Silva, 1999; von Stein and Sarnthein, 2000). Moreover, EEG spectral coherence may be a reflection of 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).

The spectral coherence of the resting state eyes-closed EEG cortical rhythms is different among Nold, MCI, and AD groups. In the majority of previous EEG studies a prominent decrease of the spectral coherence at alpha rhythms in the AD than in the Nold subjects was observed (Leuchter et al., 1987, 1992; Cook and Leuchter, 1996; Wada et al., 1998a; Locatelli et al., 1998; Knott et al., 2000; Jelic et al., 2000; Almkvist et al., 2001; Adler et al., 2003). Such values of low coherence were also associated with ApoE genetic risk, hypothesized to be mediated by cholinergic deficit (Jelic et al., 1997). Conversely, some previous studies showed divergent results, with either a decrease or an increase of EEG delta and theta coherence (Leuchter et al., 1987; Locatelli et al., 1998; Brunovsky et al., 2003; Adler et al., 2003). More recently, these conflicting results were reconciled by averaging the EEG spectral coherence of all combinations of electrode pairs, as an index of "total coherence" (Babiloni et al., 2009d), that may better take into account the global impairment of brain networks and cognition during the development of AD, which is presumed to affect the functional integration within cerebral neural networks involved in cognition process. In the mentioned recent study, the delta total coherence followed the path AD > MCI > Nold (Babiloni et al., 2009d). On the other hand, total coherence in low alpha frequency was decreased in AD respect to the MCI and Nold subjects. In MCI subjects, this EEG coherence was negatively correlated with cholinergic lesion (Babiloni et al., 2010c). Furthermore, 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.

The so-called 'synchronization likelihood' (SL) is an index capturing both linear and non-linear dimensions of the functional coupling of EEG rhythms. 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 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. F does not have to be necessarily linear; the only requirement is that it is locally smooth. In this line synchronization likelihood is the chance that, if system X is in the same state at two different time instants, then system Y will be in the same state at the same time instants (Stam and van Dijk, 2002; Takens, 1981).

SL analysis of the EEG rhythms at rest has shown that the cognitive impairment in AD and MCI subjects is associated with a loss of functional connectivity at high 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, a 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 mild AD from the VaD was a higher 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). Conversely, parieto-occipital high alpha SL and beta bands were higher in the PDD than in the PD without dementia.

Previous EEG studies using different nonlinear indexes such as mutual information have also reported a loss of functional connectivity in AD patients in different frequencies, especially in the alpha band (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 demonstrated to be lower AD than in Nold, in particular in frontal and antero-temporal regions (Jeong et al., 2001). In addition, there was a major decrease in information transmission between corresponding inter-hemispheric electrodes and between distant electrodes in the right hemisphere (Jeong et al., 2001). Moreover, the auto-mutual information (AMI), i.e. the estimation of how much the average value of the time series can be predicted from values of the same time series at preceding points, throughout the cerebrums of the AD patients, decreased significantly more slowly with delay respect to a group of normal controls (Jeong et al., 2001).

Fig. 1 (top) depicts the principal models of functional brain connectivity expressed as linear or nonlinear functional coupling of the EEG rhythms in a condition of resting state with eyes closed. Fig. 1 (bottom) also sketches the approach to the functional brain connectivity by a multimodal approach based on the recording and analysis of the fMRI hemodynamic curve and EEG rhythms in a condition of resting state with eyes closed.

5. Effective brain connectivity in AD patients and MCI 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

Linear and nonlinear EEG indexes of functional brain connectivity have both a significant limitation: they cannot reflect neither the

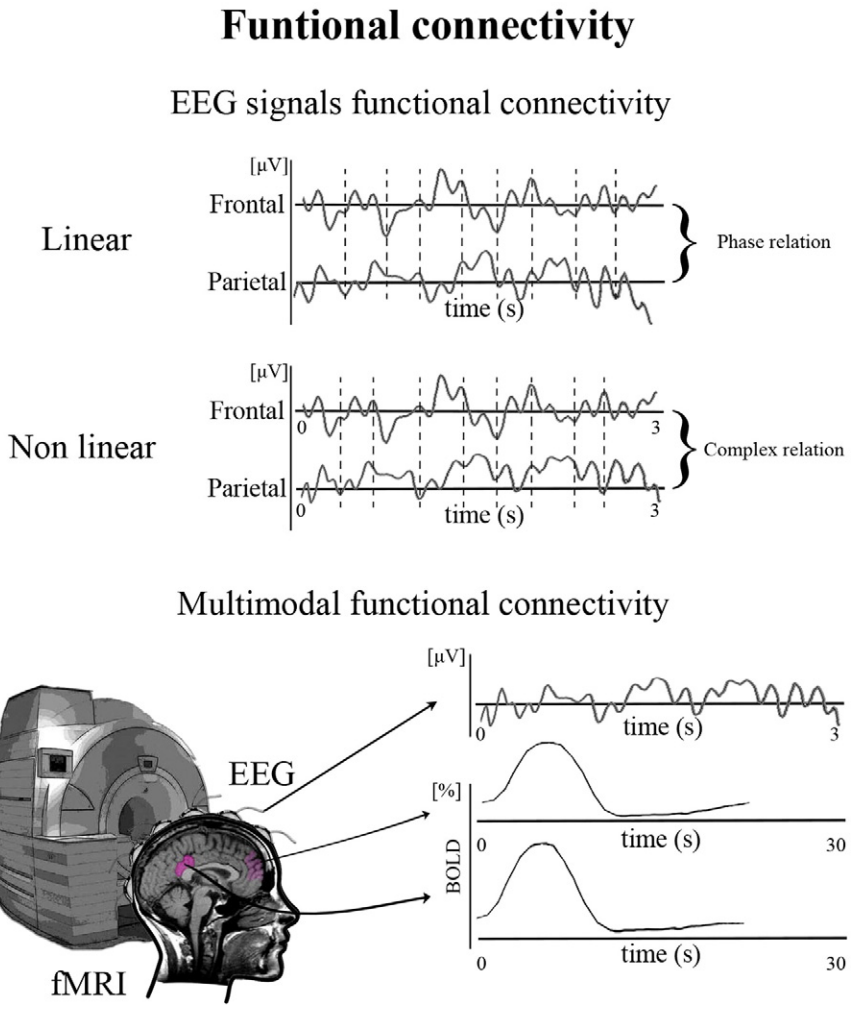

Fig. 1. Top: Sketch of main models of functional brain connectivity indexed by linear and nonlinear functional coupling of resting-state eyes-closed electroencephalographic (EEG) rhythms. Bottom: multimodal analysis of fMRI hemodynamic curves and EEG signals.

causality of the relationships nor the direction of the information among cortical regions. The overcome of this limitation is represented 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 involves 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, 2012, 2014; 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). At the base of the information theory, there is the concept of entropy introduced by Claude Shannon, namely the uncertainty related to 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:

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

With H(X) and H(Y), respectively, the Shannon entropies of X and Y, and with H(X,Y), the joint entropy of X and Y (Cover and Thomas, 1991). This value is between zero and 1: equal to zero when X and Y are statistically independent, equal to 1 when 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 information transfer between two joint processes (i.e. the EEG recordings 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 a specific 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 to detect unknown non-linear interactions (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 a time series can be considered causal another time series, if the prediction of the latter could be improved by incorporating the knowledge of past values of 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 be applied only to pairs of EEG signals), the Granger causality is a multivariate methodology applicable to multiple signals simultaneously (Kamiński and Blinowska, 1991; Kamiński and Liang, 2005). Recently, non-linear extensions of Granger causality have been proposed (Ancona et al., 2004; Chen et al., 2004), not considered here for sake of brevity and since they are less commonly used.

The directed transfer function (DTF) is a very popular method related to Granger causality, with the difference that it transforms the autoregressive model into the spectral domain. This procedure showed reliability in characterizing the directional information flux within EEG functional coupling, using a multivariate autoregressive linear modeling (Korzeniewska et al., 1997; Kamiński et al., 1997; Mima et al., 2000; Blinowska et al., 2010; Blinowska, 2011; Blinowska and Zygierewicz, 2011; Brzezicka et al., 2011). EEG data are usually normalized (z-score), before computing the DTF (Kaminski and Blinowska, 1991). EEG data are simultaneously given as an input to the so-called Mvar model (Kaminski and Blinowska, 1991; Kamiński et al., 1997; Korzeniewska et al., 1997) to obtain the estimation, among all the combinations of the electrodes pair, of the "direction" of the information flow within the EEG rhythms between different brain regions. In other terms, Mvar model can provide an evaluation of the influence of the electrode A signal on the electrode B signal (information flow between electrodes A and B), to be interpreted as a causal influence. The information flow from A to B is considered causal when the directionality from A to B is statistically more likely than directionality from B to A (Vecchio and Babiloni, 2011). About the functional role of intrinsic directional connectivity in cognition, a dominant directional flux from parietal to frontal regions has been reported in healthy awake subjects during a visuospatial EEG task (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), finding that may represent a reference point for the evaluation of changes in propagation in demented patients. As a matter of fact, a reduction of the directional information flow from frontal to parietal regions was observed in the mild AD and amnesic MCI compared to the Nold subjects (Babiloni et al., 2009c), in line with the idea of a common pathophysiological background that links, on average, the groups of AD and MCI subjects (Vecchio and Babiloni, 2011). Such a direction of the fronto-parietal functional coupling was found to be partially preserved in the amnesic MCI subjects whereas the cognitive decline was mainly explained by the white matter vascular disease extent, a finding that supports the additive model posing that MCI subjects would result from the combination of cerebrovascular and neurodegenerative lesions (Babiloni et al., 2008b). Other EEG studies using Granger causality and stochastic event synchrony as models of the directional information flux, showed a loss of EEG synchrony between electrode pairs in AD and MCI with respect to Nold 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 a theoretic measure of time-directed information transfer between jointly dependent processes such as those generating EEG recorded 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, being the exact relationship recently studied (Barnett et al., 2009). For Gaussian variables, the transfer entropy and the Granger causality are entirely equivalent, connecting 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, 2012, 2014; 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 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 superficial cortical layers long-lasting inhibition. Single pulses or short bursts of TMS can produce an interference with the ongoing neuronal processing in the cortex, perturbing the 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 (Walsh and Cowey, 2000; Pascual-Leone et al., 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 (Sestieri et al., 2013), 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 and medium term episodic memory as revealed by fMRI and PET (Brewer et al., 1998; Buckner et al., 1999; Fletcher and Henson, 2001; Spaniol et al., 2009). It has been shown that rTMS over the left dorsolateral prefrontal cortex results in distal modification of neural activity related to the site of stimulation. These changes are linked to the patterns of resting-state brain network activity (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, very different for polarity and amplitude from its peak components. This is dependent on several factors including the position and orientation of the TMS coil, the stimulation intensity, and the position of the electrodes (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 parieto-occipital cortex during a spatial attention task (Capotosto et al, 2009, 2012). 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., 2014). Compared to sham stimulation, magnetic stimulation (1 Hz for 1 min) over both left and right AG, but not over FEF or IPS, enhanced both dominant alpha power density in parieto-occipital cortex and intra-hemispheric alpha coherence (Capotosto et al., 2014). 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 regions changes during pathological and healthy 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 applied on the left superior frontal cortex did not changes along physiological aging but were altered by cognitive impairment in the AD patients (Casarotto et al., 2011).

Fig. 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 EEG rhythms in a condition of resting state with eyes closed and the rTMS combined with the recording of EEG activity.

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 a 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 may represents a promising 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 part of the mathematical graph theory (Stam, 2009), in which the graphs represents simplified networks using groups of nodes (vertices) linked by 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

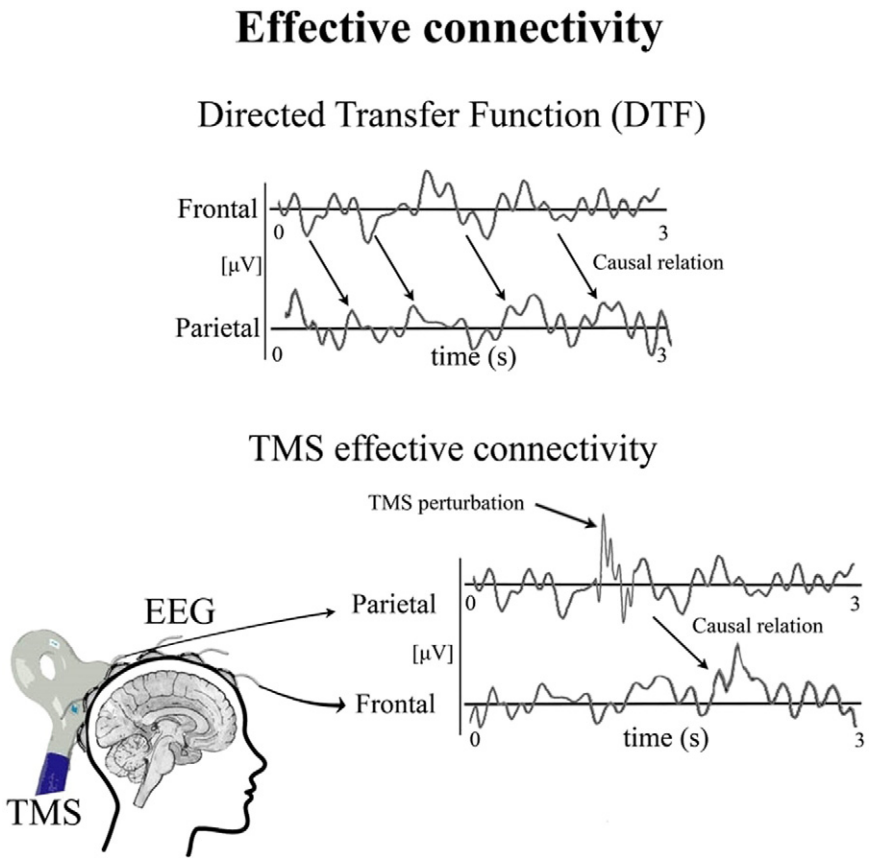

Fig. 2. Top: Two main different approaches to the study of effective brain connectivity. The estimation of the directional information flow between electrode pairs for the resting-state eyes-closed EEG rhythms. Bottom: effects of the transcranial magnetic stimulation (rTMS) delivered over a given electrode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

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 the 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 staring 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 the 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., 2005; Humphries and Gurney, 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 and Sporns, 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 pathophysiological 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). 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. 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).

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). 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 et al., 1996; Raichle and Mintun, 2006; Fox and Raichle, 2007; Raichle and Snyder, 2007; Smith et al., 2009; Deco and 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., 1996). 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 behavior (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, 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 and 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; Corbetta et al., 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 with 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.

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

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.

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 controls	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 memory complaints	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)

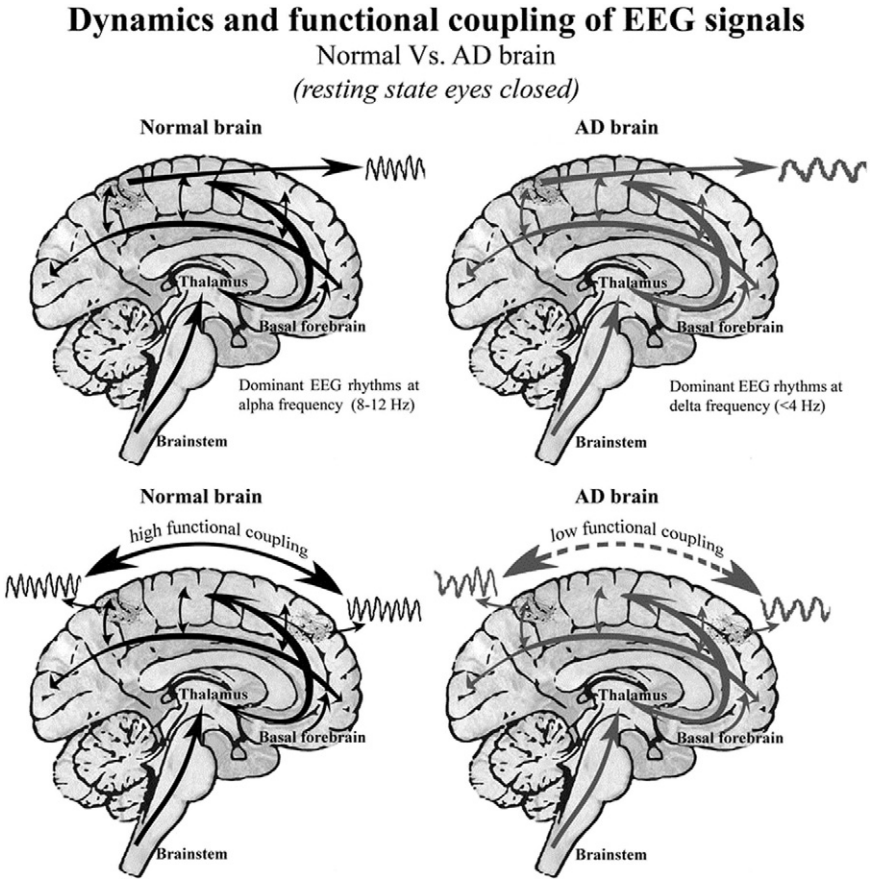

Fig. 3. Theoretical physiological model of cortical neural synchronization and functional coupling in the resting-state eyes-closed condition in healthy subjects and in AD patients as revealed by EEG rhythms. In the resting-state eyes-closed condition, dominant posterior alpha rhythms (8–12 Hz) would 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 serotoninergic 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).

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 a 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 the alpha band), associated with 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 background, 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 the cerebral cortex, thalamus, basal forebrain and brainstem, including glutamatergic, cholinergic, dopaminergic and serotoninergic 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. Fig. 3 sketches the theoretical neurophysiological models that are 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.

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