ELSEVIER
DRUG DISCOVERY TODAY THERAPEUTIC STRATEGIES

Drug Discovery Today: Therapeutic Strategies
Vol. 10, No. 2 2013



Recent advances in the treatment of Alzheimers

# Resting state EEG rhythms as network disease markers for drug discovery in Alzheimer's disease

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**Alzheimer's disease (AD) induces a widespread pathological extracellular accumulation of beta-amyloid (Aβ) peptides that affects cortical networks underpinning cognitive functions. This is related to abnormal functional and effective brain connectivity as revealed by graph markers of resting-state eyes-closed electroencephalographic (EEG) rhythms. Here we revised EEG studies in mild cognitive impairment and AD subjects showing that these markers are promising network disease endpoints for basic research and AD drug discovery.**



## Introduction

Alzheimer's disease (AD) is the most frequent neurodegenerative disorder and cause of dementia along aging. It is characterized by a pathological accumulation of beta-amyloid (Aβ) and hyperphosphorylated tau peptides that affect cortical neuronal networks related to cognitive functions [1]. For this reason, a network disease perspective has the potential to provide novel markers of the pathology at preclinical and prodromal AD stages [2], as well as instrumental targets for drug discovery. In this line, resting-state eyes-closed electroencephalographic (EEG) rhythms provide useful information on functional and effective brain connectivity across long-range neural networks [3,4].

The hypothesis of this review is that global topological features of functional and effective brain connectivity as revealed by the functional coupling of resting-state eyes-closed EEG rhythms could build a platform of promising network disease endpoints for basic research and AD drug discovery.

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

Synchronous activity of oscillating networks arises from the interaction between the intrinsic excitability of neurons and their interconnectivity [5] and correlates with the subjects' behavior and with the stimulating conditions of the environment [6]. In more detail, even single neurons themselves can oscillate at multiple frequencies [7], *a fortiori* cortical regions do not exhibit pure oscillations but a combination

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 http://dx.doi.org/10.1016/j.ddstr.2014.02.003 

of delta (<4 Hz), theta (4–7 Hz), alpha (8–12 Hz), beta (13–30), and gamma (>30 Hz) rhythms, coexisting in the same area or interacting among different structures, and generally attributed to network operations in cortico-cortico and corticothalamic systems [8]. To this theoretical model, joint EEG/functional magnetic resonance imaging (fMRI) analysis showed that large-scale functional-anatomical networks – as revealed by auto-correlation of blood oxygenation level-dependent (BOLD) activity – oscillate in multiple electrophysiological frequency bands [9]. Neurodegenerative disorders impair the synaptic integrity underlying cooperation among neural networks; several studies demonstrated the role of soluble Aβ as a principal causative agent of synaptic and cognitive impairment in AD. Robust evidence demonstrates that soluble Aβ elicits a toxic signaling cascade by the α7-nicotinic acetylcholine receptor (α7nAChR), leading to synaptic impairments, intraneuronal Aβ42 aggregates, and correlated cognitive deficits [10]. This compromised signaling activates kinases ERK2 and JNK1, leading to the formation of neurofibrillary tangles (NFTs) namely aggregates of hyperphosphorylated tau protein. Cognitive impairment and magnitude of synaptic deficit in the AD brain are more highly correlated with soluble Aβ than with the abundance of amyloid plaques, reflecting the fact that soluble Aβ inflicts synaptic impairment [11].

In the field of fMRI research, there is a whole line of study that focuses on differential brain connectivity in AD patients when compared to healthy elders. In this line, BOLD has been reported to be a promising marker for the identification of disrupted functional connectivity patterns in AD patients [12,13]. Moreover, it has been shown that in AD patients, acetylcholinesterase inhibitor donepezil affects functional connectivity of dorsolateral prefrontal cortex [14] and of parahippocampal, temporal, parietal and prefrontal cortices associated to medial cholinergic pathway network [15]. Furthermore, stronger recovery in the network connectivity was correlated with cognitive improvement as measured by Mini-Mental State Examination (MMSE) and AD Assessment Scale-cognitive subscale scores (ADASCog) [15].

In the framework of EEG techniques, functional brain connectivity is reflected by statistical functional coupling of EEG oscillatory activity in various frequency bands [3]. Moreover, effective brain connectivity is reflected by how EEG rhythms recorded at one electrode affects those recorded at another remote electrode, due to a causal hierarchical interaction between the two corresponding cortical generators [3]. In this framework, the functional brain connectivity is typically indexed by EEG spectral coherence (linear) or synchronization likelihood (linear–nonlinear), while the effective brain connectivity is indexed by markers derived by information theory and granger causality [16]. These indexes do capture linear and nonlinear relationships among brain regions [17]. The linear indexes model the phase relationship between the EEG rhythms recorded at electrode pairs, whereas the nonlinear indexes disclose complex relationships between these EEG rhythms [17].

EEG spectral coherence quantifies the temporal synchronization of two EEG time series between pairs of electrodes in the frequency domain, and can be typically derived by fast Fourier transform – FFT – [18]. At group level, spectral coherence of the resting state eyes-closed EEG rhythms differed among the Nold, MCI, and AD subjects [19–22]. The majority of previous EEG studies reported a prominent decrease of the spectral coherence at alpha rhythms in the AD than in the Nold subjects [19,20]. This effect was found to be associated with ApoE genetic risk of AD [19]. Other studies showed decrease or increase of EEG coherence at delta and theta rhythms in AD patients [21]. A recent study averaged EEG spectral coherence across all electrode pairs showing the pathological increase of the 'total coherence' in the AD patients in relation to cholinergic lesions [22]. Although several studies have shown that EEG coherence might be a diagnostic biomarker sensitive to disease severity, it is poorly known the relationship between such EEG markers and specific abnormalities induced by Aβ, partially recovered by active compounds against AD (i.e. donepezil). Only one study described negligible differences between the pre- and post-treatment with donepezil 5 mg daily for 1 month on inter-hemispheric EEG coherence across homologous electrode pairs [23].

'Synchronization likelihood' (SL) is an index capturing both linear and non-linear dimensions of EEG functional coupling. It measures the dynamical interdependencies between EEG signals recorded at electrode pairs [24]. SL relies on the concept of 'state' of one dynamical system expressed in terms of the level of neural synchronization, as indexed by serial measurements of the EEG voltage [24]. Compared to Nold subjects, MCI and AD patients were characterized by lower global SL across all electrode pairs at high-frequency alpha and beta bands [25]. Furthermore, there was a fronto-parietal reduction of SL (delta to alpha) greater in MCI than in AD patients [26]. Moreover, patients with vascular dementia and mild AD showed poor SL at both fronto-parietal (delta to alpha) and inter-hemispherical (delta to beta) electrode pairs [27]. And the fronto-parietal reduction of SL at alpha rhythms was greater in mild AD than in VaD patients [27]. SL was also sensitive to another form of dementia due to neurodegeneration. Compared to Parkinson's disease (PD) patients, PD patients with dementia (PDD) were characterized by lower values of SL in the following electrode pairs and frequency bands: fronto-temporal alpha rhythms; inter-hemispherical temporal delta, theta and alpha rhythms; and centro-parietal gamma rhythms [28]. In contrast, parieto-occipital SL at high-frequency alpha and beta bands was higher in the PDD than in the PD without dementia.

Other non linear indexes of the EEG functional coupling derive from information theory, which is based upon the concept of entropy defined as the uncertainty associated with a random variable. Previous EEG studies using mutual information of the information theory have disclosed a loss of functional connectivity in AD patients in different frequency bands of the resting-state eyes-closed EEG rhythms, with a special engagement of the alpha frequencies [29]. Furthermore, the local cross-mutual information (CMI) quantified the information transmitted from one the EEG rhythms recorded at one electrode over another; CMI was lower in the AD patients than that in normal controls, especially over the EEG rhythms recorded in frontal and antero-temporal regions [30]. Furthermore, there was a prominent decrease in information transmission between distant EEG electrodes in the right hemisphere and between corresponding inter-hemispheric electrodes [30]. In addition, the auto-mutual information (AMI) estimated how much on average the voltage value of the EEG rhythms can be predicted from values of those at preceding points. It decreased significantly more slowly with delay throughout the scalp in AD than in Nold subjects [30].

Fig. 1 (top) illustrates the principal models of functional brain connectivity as indexed by the linear or nonlinear functional coupling of the resting-state eyes-closed EEG rhythms. The linear models reflect the phase relations between the EEG rhythms recorded at electrode pairs. The nonlinear models denote a complex relation between these EEG rhythms.

Both linear and nonlinear indexes of the EEG functional brain connectivity have an important limitation: they do 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 the estimation of the directional information flow with the EEG coupling. Fruitful approaches rely on the information theory and Granger causality [31].

Concerning the information theory, transfer entropy indexes directed (time-asymmetric) information transfer between joint processes (i.e. the EEG rhythms recorded at two electrodes) [32]. It is robust even with unknown nonlinear interactions [33]. On the other hand, the Granger causality 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 [34]. 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 a multivariate autoregressive model (DTF) [31]. Concerning its clinical applications, it has been reported a reduction of the parietal-to-frontal directional information flow within the EEG functional coupling in amnesic MCI and mild AD subjects compared to Nold subjects [35]. This finding suggests a common pathophysiological background linking, on average, the groups of MCI and AD subjects. Noteworthy, 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 [36]. This finding supports the additive model of the cognitive impairment posing that MCI status results from

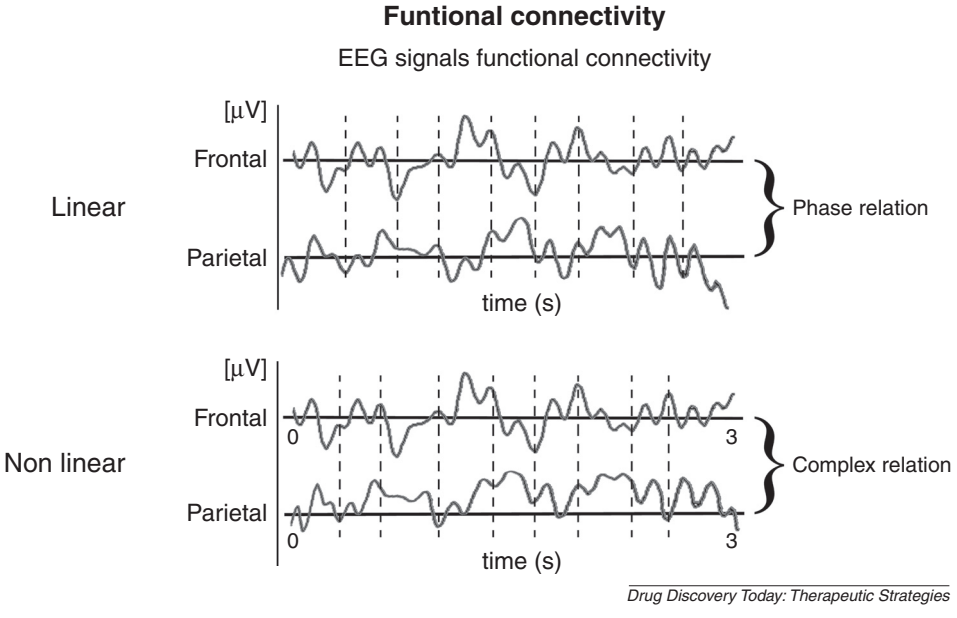


**Figure 1.** Sketch of main models of functional brain connectivity indexed by linear and nonlinear functional coupling of resting-state eyes-closed electroencephalographic (EEG) rhythms.

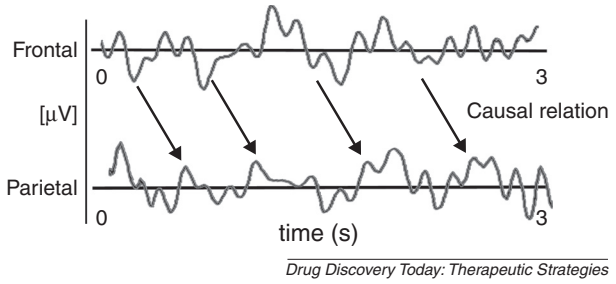


**Figure 2.** Estimation of the directional information flow between electrode pairs for the resting-state eyes-closed EEG rhythms.

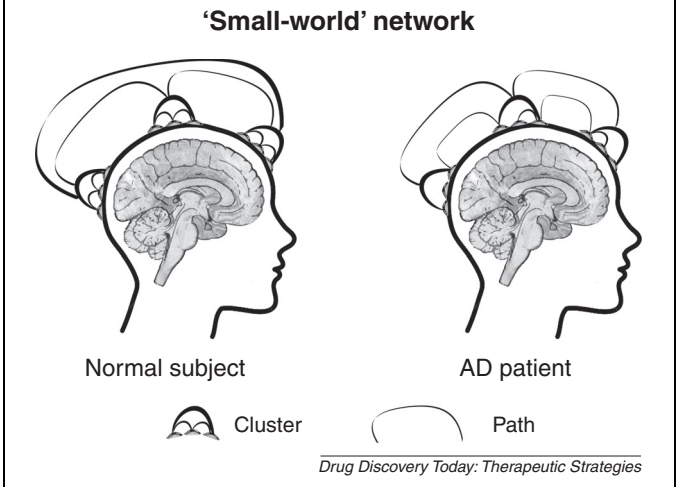


**Figure 3.** Sketch of the nodes and topologic connections of functional brain connectivity in healthy subjects and in Alzheimer's disease (AD) patients as revealed by electroencephalographic (EEG) or magnetoencephalographic (MEG) rhythms. The topology of these nodes and connections show the deviation of the AD patients (i.e. reduction of the local clustering and long-range connectivity) from the 'small-world' network properties observed in the control subjects.

the combination of cerebrovascular and neurodegenerative lesions [36]. In addition, other EEG studies used Granger causality and stochastic event synchrony as models of the directional information flux [37,38]. Results showed a loss of EEG synchrony between electrode pairs in MCI and AD patients with respect to age-matched control subjects [37,38]. Furthermore, these markers provided a successful leave-one-out individual classification rate of 83% and 88%.

Fig. 2 plots an example model of the directional information flow between electrode pairs from the resting-state eyes-closed EEG rhythms.

It should be however remarked that computational measures of functional connectivity are not free from disadvantages. They do not directly estimate metastability and typically use linear mathematical models of the brain signals, even if brain connectivity model cannot be restrict to only linear phenomena [39]. Furthermore, interpretation of the results might be biased by the use of periods of non-stationary EEG signals [40].

## The network disease in MCI and AD subjects as revealed by graph theory

How to integrate the mentioned EEG markers of functional and effective brain connectivity (i.e. spectral coherence, SL, DTF, etc.) into a topological model of the network disease? A promising theoretical framework is offered by graph theory [41]. In this theory, the graphs are simplified representations of networks denoted by ensembles of nodes (vertices) and connections (edges). Using EEG and MEG markers as an input, graph theory studies showed that healthy subjects were characterized by an efficient and robust network called 'small-world', with high clustering among near nodes and relatively few 'hubs' connecting far nodes [41,42]. In AD brains, 'small-world' network properties were replaced by a more 'random' overall network structure [41–43]. Indeed, 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 [43]. 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 [41]. 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 [44]. 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 and long-distance connectivity was even more outspoken, and more strongly related to cognitive impairment [44,45]. 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 [43,44]. Noteworthy, loss of small-world structure in AD was also demonstrated in recent MRI studies applying graph theory [46,47].

Fig. 3 plots a model of the above results of graph theory. 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).

## Conclusions

In conclusion, the deep comprehension of normal EEG dynamics of functional and effective connectivity in healthy with respect of non-healthy subjects and the pharmacological way of restoration of a normal pattern is a useful approach for basic, applied, and drug discovery research. EEG markers of functional and effective connectivity can be used as inputs for an analysis to produce candidate network disease markers to be used as dependent variables for basic research, as well as surrogate endpoints for drug discovery of new symptomatic and disease-modifying compounds against the AD. Future studies should demonstrate how EEG functional coupling could allow identifying novel targets of AD neurodegeneration; how it reflects synaptic plasticity and neuronal network activity; and how it will impact network based strategies for drug discovery. These issues will have to be addressed by simultaneous recording of EEG and spike potentials at different scales in the brain of rodent models of AD (e.g. TASTPM), together with dosing Aβ in the brain and pharmacological manipulations with Aβ lowering drugs.

## Conflict of interest

The authors have no conflict of interest to declare.

## Acknowledgments

We are indebted with Prof. Paolo M. Rossini and Dr. Fabrizio Vecchio for their invaluable critical contribution to the discussion of the topic of this review. The research was supported in part by the San Raffaele S.p.A. The activity of some co-Authors leading to the present review was developed in the framework of the PRIN2010-2011 project 'CONNAGE' and of the GRIDCORE project of Italian Ministry of Health.

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