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EEG characteristics in "eyes-open" versus "eyes-closed" conditions: Small-world network architecture in healthy aging and age-related brain degeneration

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HIGHLIGHTS

- Graph analysis tools for the study of the brain as a complex network.
- Cortical sources of resting EEGin eyes-closed and eyes-open conditions could be different in mild cognitive impairment (MCI) and Alzheimer's disease (AD) patients with respect to normal elderly people.
- Small worldnessy modulation in eyes-open EEG reactivity in pathological aging.

ABSTRACT

Objective: Applying graph theory, we investigated how cortical sources small worldness (SW) of resting EEG in eyes-closed/open (EC/EO) differs in amnestic mild cognitive impairment (aMCI) and Alzheimer's disease (AD) subjects with respect to normal elderly (Nold).
Methods: EEG was recorded in 30 Nold, 30 aMCI, and 30 AD during EC and EO. Undirected and weighted cortical brain network was built to evaluate graph core measures. eLORETA lagged linear connectivity was used to weight the network.
Results: In Nold, in EO condition, the brain network is characterized by more SW (higher SW) in alpha bands and less SW (lower SW) in beta2 and gamma bands. In aMCI, SW has the same trend, except for delta and theta bands where the network shows less small worldness. AD shows a similar trend of Nold, but with less fluctuations between EO/EC conditions. Furthermore, in both conditions, aMCI SW architecture presents midway properties between AD and Nold. At low frequencies (delta e theta bands) in EC, aMCI group presents network's architecture similar to Nold, while in EO aMCI, SW is superimposable to AD ones.
Conclusions: In resting state condition, aMCI small-world architecture presents midway topological properties between AD subjects and healthy controls, confirming the hypothesis that aMCI is an intermediate step along the disease progression.
Significance: We proposed the application of graph theory to EEG in reactivity to EO in order to find a marker of diagnosis that – in association with other techniques of neuroimaging – could be sensitive to the progression of MCI or conversion into AD.

1. Introduction

The identification of specific and quantitative biomarkers for the assessment of brain disease severity has utmost importance to understand age-related brain dysfunctions and to develop new therapeutic approaches; in particular, *Connectomics* can significantly contribute to this development (Bullmore and Sporns,

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2009; Griffa et al., 2013), to map brain from structure to function, for understanding how cognitive processes emerge from their morphological substrates, and for better understanding of structural causes of dysfunction (Sporns et al., 2005).

1.1. Graph theory approach

One of the aims of the early graph theoretical studies has been to promote a change of perspective in how we look at the brain. If brain architecture is equalized to network, graph theory provides measures that describe the overall white matter organization and its alterations at different scales of investigation (Griffa et al., 2013). Graph theory is primarily concerned with the topology of the system, – that is, a general set of elements endowed with some relationship among them, not with its already known anatomy (Papo et al., 2014). Previous studies have applied this modern technique of graph theory to EEG data investigating for both physiological and pathological aging brain network organization; a continuous line from normal elderly (Nold) subjects to demented patients passing through mild cognitive impairment was found (Vecchio et al., 2014b,c) in the measures of both integration (characteristic path length) and segregation (clustering coefficient). On this basis, it was concluded that both global and local measures can discriminate cortical network features distinguishing physiological from pathological neurodegenerative brain aging (Mantini et al., 2007). Given that the small-world model supports both specialized and integrated information processing in the brain (Bassett and Bullmore, 2006; Sporns et al., 2004), in this study, the first aim was to describe the effect of cognitive decline on topological property of small-worldness characteristics derived from EEG connectivity data.

This new approach allows the assessment of functional connectivity patterns and aims to specify whether or not an optimal balance between local independence and global integration can be found in the system, representing favorable conditions for information processing (Gaal et al., 2010).

1.2. Subjects and conditions

Based on recent findings of graph theory applications in healthy humans (Bassett et al., 2006; Sporns and Zwi, 2004; Stam and Reijneveld, 2007), in different types of brain pathology (Micheloyannis et al., 2006; Ponten et al., 2007), and in studies on Alzheimer's disease (AD) patients (He et al., 2008; Stam et al., 2009; Supekar et al., 2008), the second goal of this study was to address the differences in functional brain networks between eyes-closed (EC) and eyes-open (EO) states in Nold people, amnestic mild cognitive impairment (aMCI) (Petersen et al., 2001), and AD patients, in order to find a neurophysiological marker, which is sensitive to the progression of aMCI or conversion into AD (Toth et al., 2014). In particular, it could be very interesting to test the hypothesis that the dementia-related slowing in cognitive processing speed represented by the decrease of reactivity in the EC–EO model (Knyazev et al., 2015)could be described by the small-worldness characteristics of the network topology approach.

In fact, the term "mild cognitive impairment" (MCI) conventionally applies to a condition in which the decline of cognitive abilities is more apparent than that seen in normal aging, but it still does not satisfy the criteria of dementia, whereas MCI maybe regarded as a transitional state from which AD may develop (De Carli, 2003).

Furthermore, opening and closing the eyes are fundamental behaviors for directing attention to the external versus internal world (Xu et al., 2014). Recent findings have demonstrated that there are distinct mental states related to the EO and EC states. Specifically, there is an "exteroceptive" mental activity state characterized by attention and ocular motor activity during EO, and an "interoceptive" mental activity state characterized by imagination and multisensory activity during EC (Marx et al., 2004, 2003; Zhang et al., 2015). Xu and colleagues (Xu et al., 2014) suggested that the topological organization of human brain networks dynamically switches corresponding to the information processing modes when the brain is visually connected/disconnected to the external environment.

However, it remains unclear whether the states of EO relative to EC are associated with different topological organizations of functional neural networks for exteroceptive and interoceptive processing (processing the external world and internal state, respectively).

Although fMRI studies have found different influences of EO and EC on brain flow-metabolism characteristics (Marx et al., 2004, 2003; Wiesmann et al., 2006; Yang et al., 2007), and functional connectivity (Van Dijk et al., 2010; Yan et al., 2009; Zou et al., 2009), brain network topological organizations and corresponding information fluxes exchanged underlying these two states had not yet been fully elucidated. Furthermore, although some authors had already proposed graph theory approach in the study of EO EEG reactivity (Gaal et al., 2010; Knyazev et al., 2015; Tan et al., 2013; Toth et al., 2014), the topic of this reactivity influence in pathological aging has not yet been fully explored.

We expect, for the second aim of this study, to find topological differences in EO EEG reactivity in the three groups; in particular, we aimed to find in the small-worldness parameter a marker that could describe the progressive loss of information flow as represented by the cortical neuronal firing functional impairment across Nold, MCI, and AD subjects in a transversal study.

2. Methods

Ninety subjects were analyzed (coming from Neuropsychological and Alzheimer Unit of Catholic University for memory and cognitive disorders). Patient groups included 30 AD (MMSE 22.3) and 30 aMCI (MMSE 26.8). A control group composed of 30 normal people Nold (MMSE 28.9) was also enrolled. The mean age was about 70 years in the groups (Table 1). All subjects were right-handed at Handedness Questionnaire (Salmaso and Longoni, 1985), and they had informed consent. The study (approved by local ethical committee) conformed to the Declaration of Helsinki and national guidelines.

2.1. Inclusion criteria

All subjects participated in a battery of neuropsychological tests to assess cognitive performance such as attention, memory, executive function, visuoconstruction abilities, and language: immediate and delayed recall measure of the Rey Auditory Verbal Learning Test (Carlesimo et al., 1996), delayed recall of Rey figures (Rey, 1968), delayed recall of a three-word list (Chandler et al., 2004), and delayed recall of a story (Babiloni et al., 2009; Spinnler and Tognoni, 1987). Each subject was visited by expert neurologists, and they underwent complete clinical tests such as brain neuroimaging (CT or MRI), neuropsychological interview, Mini-Mental State Evaluation (MMSE) (Folstein et al., 1975), clinical

Table 1
Demographic and neuropsychological data of healthy elderly (Nold), mild cognitive impairment (aMCI), and mild Alzheimer's disease (AD) subjects.

Group	Age (years)	Female/male	Education (years)	MMSE
Nold	65.4 (±1.75SE)	14/16	9.53 (±0.70SE)	28.90 (±0.16SE)
aMCI	70.7 (±1.26SE)	17/13	8.04 (±0.86SE)	26.84 (±0.30SE)
AD	72.0 (±1.48SE)	20/10	8.17 (±0.72SE)	22.34 (±0.97SE)

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