Título: CHARACTERIZATION OF LOCAL ACTIVATION AND NETWORK DYNAMICS FROM ELECTRICAL BRAIN ACTIVITY: APPLICATION TO SCHIZOPHRENIA, MILD COGNITIVE IMPAIRMENT AND DEMENTIA DUE TO ALZHEIMER'S DISEASE

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Resumen: The field of neuroscience has explored the human brain and its neuronal circuits for centuries, trying to understand the underpinnings of perception, memory, information transfer, and learning, among others. The term has evolved through the years to include novel approaches, such as molecular biology, medical imaging, and computational neuroscience, allowing scientists to study and characterize the nervous system in more unique ways than ever. Ironically, although the increase in available resources and techniques has brought unprecedented advances in our understanding of the brain, it has also served as a constant reminder that it still remains the biggest mystery of human anatomy. Rather than being discouraged by this fact, we should embrace it and employ these tools to gradually uncover its secrets.

The present Doctoral Thesis focuses on the research, development and testing of new methodological

frameworks for the characterization of neural activity by means of electroencephalographic (EEG) signals. In particular, the Thesis focuses on new methods and measures aimed at describing the dynamic behavior of brain networks in in the following diseases that affect to the central nervous system: schizophrenia, mild cognitive impairment (MCI), and dementia due to Alzheimer's disease (AD), by means of EEG recordings. Some aspects of disease-induced alterations of EEG activity are well documented for all three pathologies; these include: relative power shifting towards lower frequency bands or disconnection of static functional connectivity. Nonetheless, neural activity in these diseases has mostly been studied from a static perspective, focusing on aspects of neural activity that remain constant across time. While this is a valid and useful approach that has helped unravel many aspects of cognition, recently there has been a shift in focus towards dynamic analyses. Even though it is reasonable to assume that cognitive tasks elicit a dynamic response in the brain, it is not as straightforward to conceive that the brain displays such changes in activation during rest. Here, we focus on exploring these properties from a granular perspective of local EEG activation to a global view of how brain networks evolve during the resting state and an auditory oddball task, in order to determine whether aberrant behavior can be found in a dynamic context.

Neural oscillations are the main mechanism of synchronized brain activity, providing a window into ongoing brain function, which can help determine aberrant or altered behavior intrinsic to neurological and psychiatric diseases such as schizophrenia, MCI and dementia due to AD. Specifically, several of the findings revealed by previous EEG studies are, among others: aberrant assignment of relevance to stimulus in schizophrenia, global slowing and loss of complexity of neural oscillatory activity in AD (and to a lesser extent in MCI), and general disconnectivity in all three disorders. In the present Doctoral Thesis, alterations to normal dynamic neural oscillations are explored in all three diseases from a two-level perspective: (i) local activation dynamics of individual brain areas; and (ii) \textit{chronnectomic} analysis of neuronal activity, i.e., viewing the brain as a fundamentally dynamic system across both time and space. Current neuroscience research is quickly moving towards this concept, as the brain is increasingly being seen as inherently dynamic, even during the resting state. In this Thesis, we approach the chronnectome in order to characterize how the brain behaves in these three neurological and psychiatric diseases. This analysis was performed on resting-state recordings to study abnormal recurrent brain states and network variability in MCI and dementia due to AD, and auditory oddball task recordings to characterize aberrant predictive coding in schizophrenia.

The studies included in this Doctoral Thesis are all based on two databases of EEG recordings. The first database comprised recordings from 28 cognitively healthy control subjects and 51 patients with schizophrenia, which were obtained during a 3-stimulus auditory oddball task. This enabled the characterization of the dynamic response of the brain to relevant stimuli, which is of interest due to the fact that schizophrenia is associated with an aberrant attribution of salience. The second database was composed of eyes-closed resting-state recordings from cognitively healthy elderly control subjects, patients with MCI due to AD, and patients with dementia due to AD. The number of subjects in this database kept increasing during the course of the Thesis, reaching a total of 43 controls, 67 patients with MCI, and 50 patients with dementia due to AD.

The contributions of the Thesis were structured along the two aforementioned levels of analysis. First, (i) locally activated dynamic EEG non-stationarity and recurrent activity was characterized by means of the Kullback-Leibler divergence, and measures derived from recurrence quantification analysis (RQA). Then, (ii) a chronnectomic approach was followed to characterize dynamic functional EEG activity: first by evaluating the

presence and behavior of dynamic functional connectivity (dFC) in neural activity at rest; and then by introducing a novel method for the extraction of brain meta-states, defined as network configurations that dynamically form and act as attractors for neural activity. Afterwards, the dynamic activation of the meta-states was characterized in both the resting state and the inherently dynamic auditory oddball task.

The main findings of these studies include: (i) schizophrenia patients display frequency-dependent baseline hyperactivation and reduced response activation reflected in the non-stationarity of the EEG activity; (ii) the recurrence structure and the non-stationarity of resting-state EEG activity is altered in MCI and AD, and it could possibly be related to a state of excessive neuronal activity in MCI due to impaired neuronal disinhibition; (iii) dFC can be observed in controls, patients with MCI, and patients with dementia due to AD, and is aberrant in patients from the latter groups; (iv) meta-state network topology is generally not affected by MCI and AD, but their sequencing is altered compared to controls. Furthermore, two novel methodological approaches were introduced: (i) two new RQA measures to characterize the unpredictability and density of the recurrence structure, and (ii) a novel method of meta-state extraction based on community detection algorithms, independent of imaging modality, and with no a priori assumptions on the number of meta-states.

The findings confirmed the hypothesis that dynamic EEG activity displays frequency-dependent aberrant behavior in all three diseases under study. Furthermore, these abnormalities can be found in both levels of analysis (local activation and chronnectome), suggesting that these diseases thoroughly affect all aspects of normal neural processing, from the activation of each region to the integrated behavior of all neuronal assemblies. Evidence to the hypothesis of aberrant predictive coding was added, along with additional proof of hyperactivation in schizophrenia during the pre-stimulus stage. Moreover, non-linear evolution of dynamic activity along the MCI-AD continuum suggested that progression towards AD at a later stage could be related to aberrant extreme behavior leading to neuronal damage.

In summary, the present Doctoral Thesis contributes to the body of work being currently developed to characterize dynamic neuronal behavior in the brain, and provides a holistic framework from which a wide range of future research on the subject may be conducted.