Title: Dynamic functional connectivity as a marker of pathological and cognitive change in Alzheimer's disease

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Abstract

One major problem in cognitive neuroscience is to understand whether a neurophysiological phenomenon like functional connectivity (FC), explains the mechanisms from which emerges cognition by the understanding how invariant properties of the neural system explains a broad diversity of quantifiable cognitive outcomes. Modern neuropsychological theories propose that cognitive functions are implemented at the whole brain, but they arise from the dynamic integration between local cortical functions. In this line, Alzheimer disease (AD) is a network disease, as far as brain local deposition of proteins leads to distributed network dysfunction. In AD, network failure and abnormal brain deposition of proteins lead finally, by an unknown mechanism, to irreversible cognitive decline. In the same line, sleep deprivation acting like a cognitive stressor changes large-scale networks and also associates abnormal deposition of proteins that resemble neuropathological aspects of AD. By using static or time-average functional connectivity, has not been possible to understand individual and task-specific cognitive changes arising in the AD, as far it fails to detect the non-stationary nature of the resting-state FC. We tested the hypothesis of whether domain-specific cognitive decline after a neurological insult, is explained by changes in the resting-state fMRI dynamic connectivity networks (dFC). We found that sleep deprivation and mild cognitive impairment associates dFC changes that explain subject by subject variability in higher-cognitive functions. Importantly, patients with amnestic mild cognitive impairment expressed dFC changes that while interacts with molecular-level biomarkers of AD, predict cognition. Importantly, this interaction explains cognitive variability that can't be explained either by dFC or by the molecular biomarkers alone. This suggests that the mechanism of network dysfunction in aMCI is explained by the synergy of molecular factors with macroscale-level network dynamics. Hence, modular dFC gives a new framework to study the cognitive changes following a neurological insult, and proposes an integrative mechanism of cognitive dysfunction