Exploring the relationship between fatigue and brain network disruptions in patients with multiple sclerosis: An eLORETA study

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Introduction

Patients with multiple sclerosis (MS) are known to be impaired by debilitating fatigue, affecting many aspects of daily living. The source of this fatigue remains unclear. Though there is evidence implicating grey matter atrophy, neural connectivity perturbations have been shown to contribute to fatigue arising from the association between mental effort and hyperconnectivity in the dorsolateral prefrontal cortex in patients with RRMS[1] .

To further explore this question, we examined patients with RRMS to better characterize disruptions in cortical functioning and how the disruptions affect fatigue. Working memory (WM) performance is known to involve perception and action over several distinct sets of brain regions[2], comprising many cortical networks and the CEN is known for its involvement in WM.

A working memory challenge, the N-back task, was therefore used to elicit electrical activity from the cortex, measured with quantitative electroencephalography (qEEG) during task performance. Fatigue was measured prior to the N-Back/qEEG task using the Fatigue Severity Scale.

We hypothesized that RRMS cortical dysfunction and fatigue either directly or indirectly depend on the CEN, and would be abnormal in RRMS. Here, we investigate the hypothesis that both fatigue and disease process in RRMS will be associated with disruptions of cortical connectivity during a working memory challenge using the N-Back task and whether these disruptions are related to fatigue.

To examine cortical dysfunction and fatigue in RRMS we tested:

- **7 patients with Relapsing-Remitting Multiple Sclerosis (52.4 ± 15 y.o., 5 female).**
- **11 adult healthy controls (38.8 ± 10.8 y.o., 8 female).**
- **Future testing will include age, gender and education matching.**

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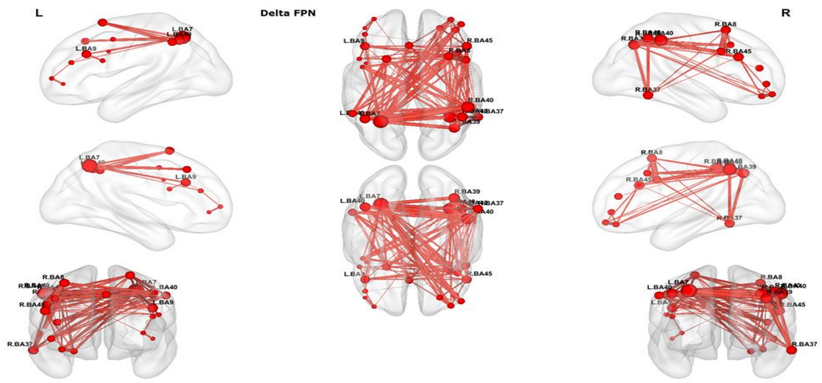
Task Design

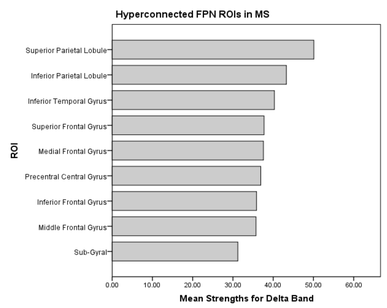
QEEG data were recorded during an N-Back task (0/2 Back) using Geodesic software (version 5.4) with a 256-channel cap, then transformed to Exact Low Resolution Electromagnetic Tomography (eLORETA) for analysis. Graph Theory was likewise used in analysis. The Fatigue Severity Scale [FSS]) was administered following the task.

Significant Cortical Hyperactivation (dysregulation) is present in the CEN of RRMS and is 1.04 times more likely to occur in the CEN of people with RRMS than in people without MS.

RRMS vs. Controls, $\chi^2 = 8.262$, $p < .016$, Odds Ratio = 1.041 95% CI =.925-1.167

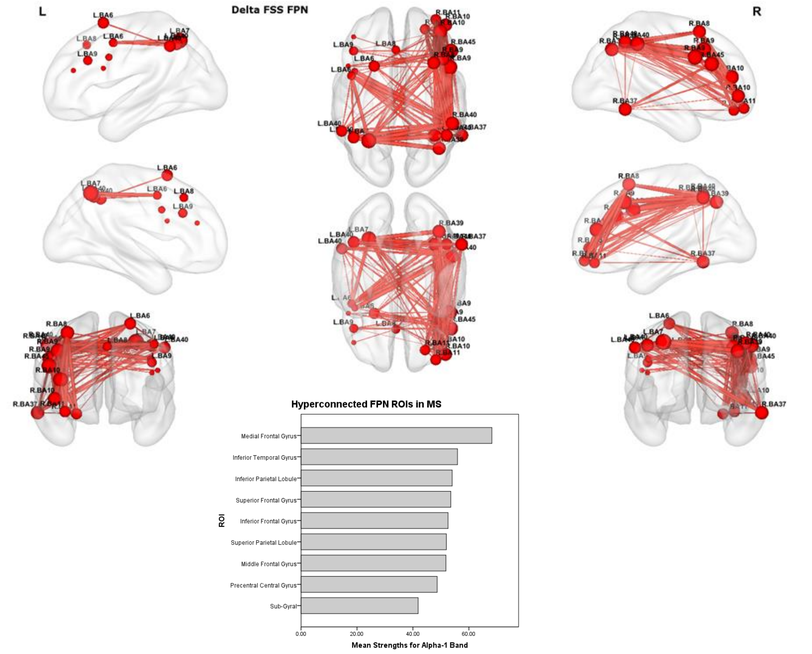
Cognitive processes depend on underlying interactions between distributed networks. Patients with RRMS, during a working memory task, exhibited significantly greater hyper-connectivity in the Central Executive Network than healthy controls in a WM task. This pattern is consistent across the entire network in the delta frequency band (1-3 Hz).





Significant Cortical Hyperactivation (dysregulation) Predicts Fatigue in CEN of RRMS

Linear Regression : FPN hyperconnectivity predicts FSS scores: $r = .416$, $p < .05$



In the brain, there are modules which are clusters of neurons that are talking mostly to themselves, and then there are hubs which have a high level connectivity to other neurons through the modules. **When there is dysregulation of one type or another in those hubs or modules, then there is reduced efficiency of information processing in the associated neurons**.[3] They will still function, but now other groups of neurons (other nodes and hubs) have to compensate for the reduced rate of information processing in the dysregulated nodes, creating a need for more energy expenditure in a system that has been damaged by disease. This situation, in and of itself, is related to central fatigue.

We see different modules and hubs in the brain, which is an estimate of the efficiency of different networks to mediate functions that together give rise to adaptive behavior. During **hyperconnectivity of neurons in the brain,** there is less flexibility and less resource allocation for homeostatic processes, causing information and memory loss, reduced attention, loss of higher order thought, and attenuated cognitive abilities. **This disruption, or inefficient resource allocation in normal connectivity was positively and significantly associated with fatigue in RRMS in our study.**

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