Mechanisms of recovery in the severely injured brain: Physiological correlates of restoration of the anterior forebrain mesocircuit

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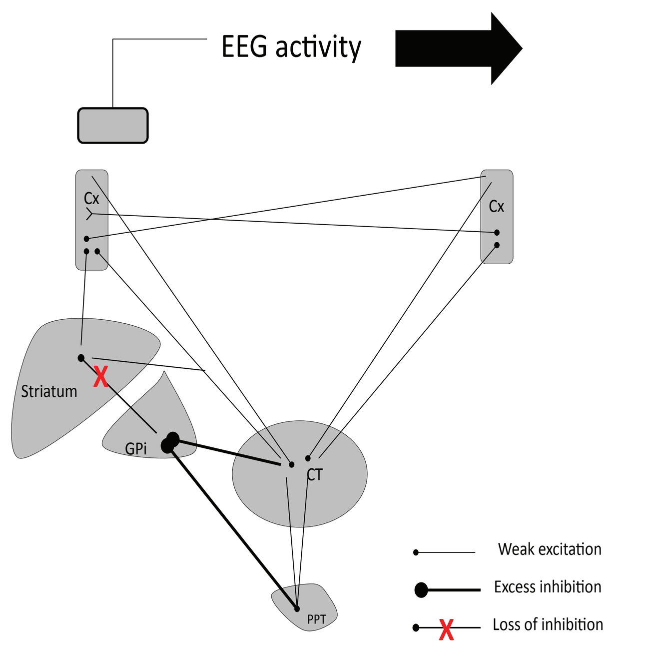
INTRODUCTION

Several observations indicate that common underlying mechanisms of restoration of function can be identified across widely varying patterns of structural brain injury and mechanisms of cellular and circuit dysfunction (Williams et al., 2009; Conte et al., 2010; Drover et al., 2011, 2012; Fridman et al., this meeting). Specifically, the mesocircuit hypothesis proposes that changes in activity across several interconnected structures of the anterior forebrain will index levels of recovery (Schiff 2010). Here we use quantitative electroencephalographic (EEG) measures to identify such changes.

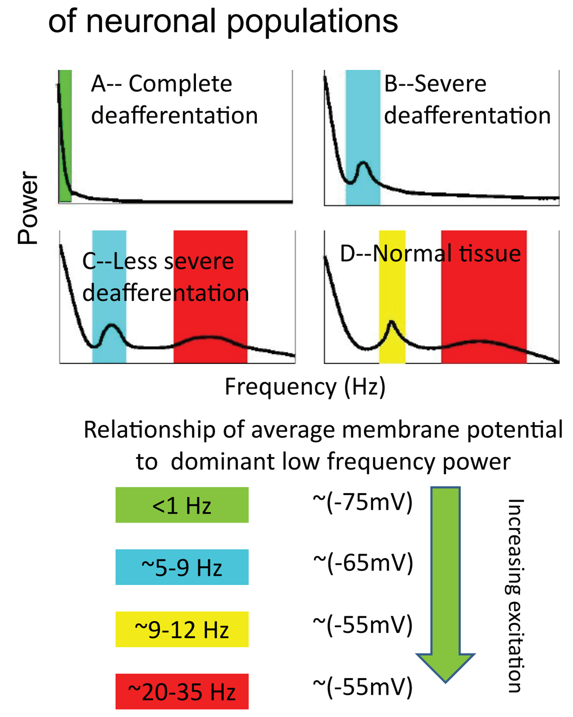
Previous studies identified 1) the presence of low (5-9Hz) frequency oscillations in the resting EEG of patient subjects with severe brain injuries and disorders of consciousness (Drover et al., 2011), 2) reduction of EEG power at these low frequencies and coincident increases in high frequency (15-40Hz) power spatially localized to frontocentral regions in correlation with spontaneous recovery (Conte et al., 2010) and medication-induced improvements in behavioral function (Williams et al., 2009). We now present results of applying hierarchical decomposition (HD), (Repucci et al., 2001) to the EEG records of several longitudinally-studied patient subjects. In contrast to principal component or independent component analysis, HD seeks to identify EEG components that drive others. HD components are linear combinations of the original EEG signal for which an autoregressive model demonstrates a simple causal structure. Here we demonstrate that spontaneous recovery, medication-induced behavior facilitation, and transient salient sensory stimuli (Bardin et al., 2011) can all produce similar patterns of changes in local and global EEG dynamics consistent with the mesocircuit hypothesis: reduction in the causal influence of components with low frequency oscillations. These findings further suggest that HD can provide insight into the underlying mechanisms of the recovery process and be developed as a measure for tracking of recovery of brain function in patients with severe structural brain injuries.

MODEL



Proposed mechanism for downregulation of anterior forebrain mesocircuit in severe brain injuries

Proposed relationship of resting wakeful EEG power spectra to average membrane potentials of neuronal populations



The mesocircuit hypothesis links downregulation of the anterior forebrain (left) to EEG patterns occuring across the recovery process (right). A loss of striatal activity results in over-suppression of an already downregulated central thalamus, resulting in functional de-afferentation of the cortex and consequent changes in the EEG spectra.

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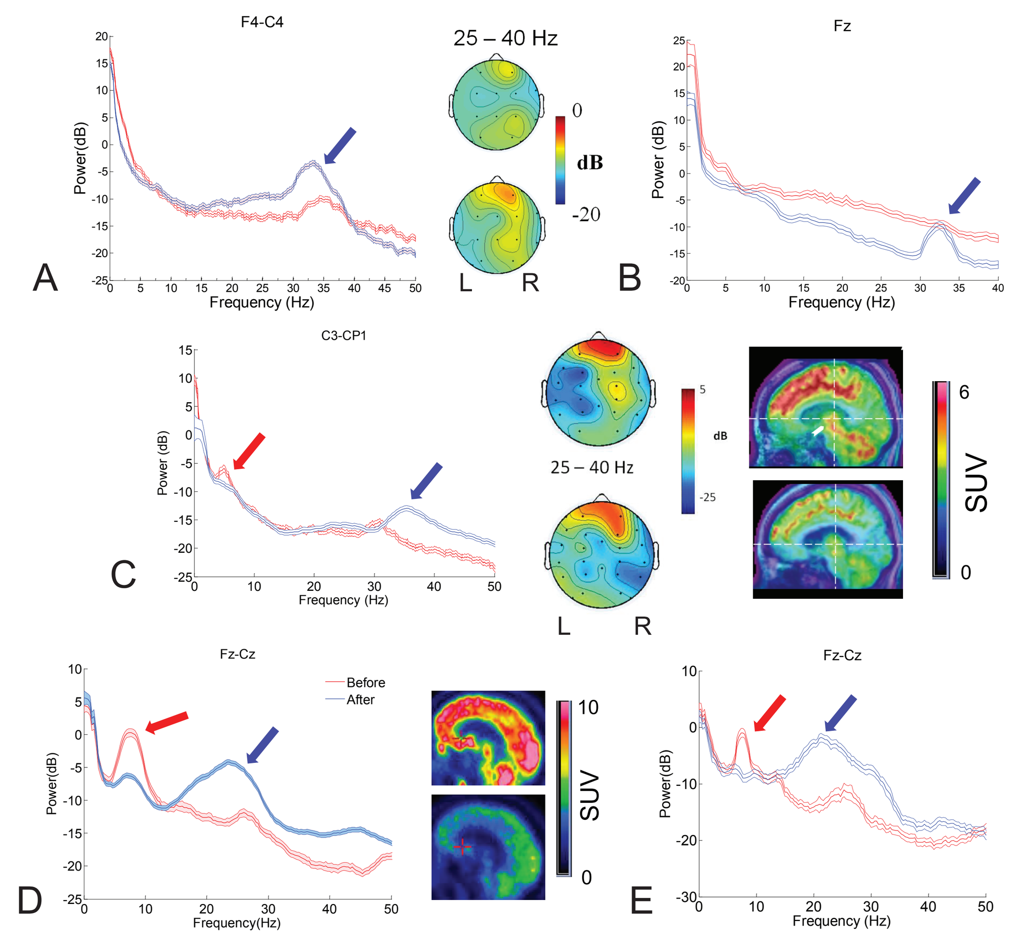
PREDICTIONS



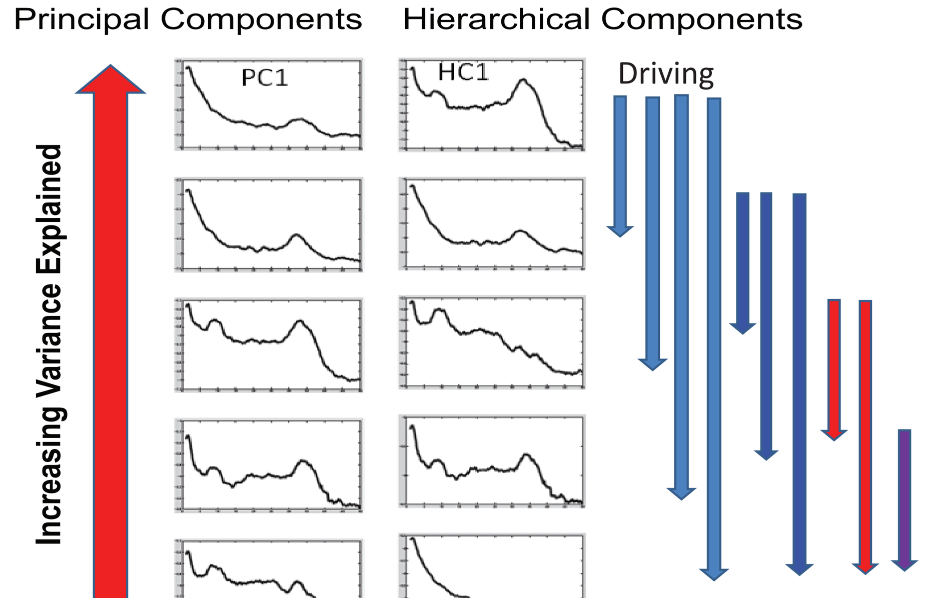
The model predicts that during recovery low-frequency oscillations (5-7Hz, red arrows), if present, will reduce in power over the anterior forebrain, while high-frequency power (15-40 Hz, blue arrows) increase. EEG spectra satisfy these predictions: A,B, and C show spontaneous recovery over time, D and E show changes in response to zolpidem.

METHODS

- Select 10 - 12 hours of awake EEG from each subject
- Decompose into principal components, and retain components based on elbow in the scree plot. 7 components used in all analyses displayed here
- Construct the multi-linear autoregressive model (MLAR) for the principal components

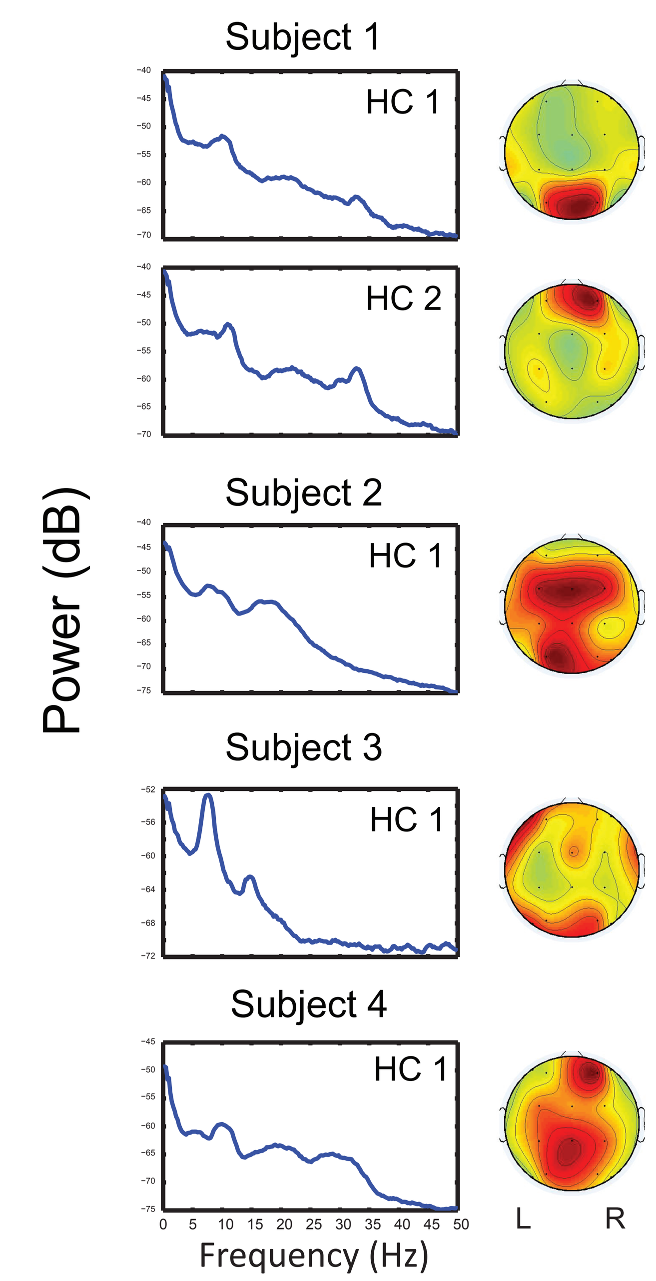
$$X_n = R_n + \sum_{k=1}^{L} A_k X_{n-k}$$

- Pick number of lags (L) in MLAR model so that the power spectrum of the residual time series R is flat
- Rotate the principal components into the hierarchical components using HD
- Repeat for bootstrapped data sets and evaluate stability of estimates



USING HD TO DEMONSTRATE CHANGES IN GLOBAL DYNAMICS

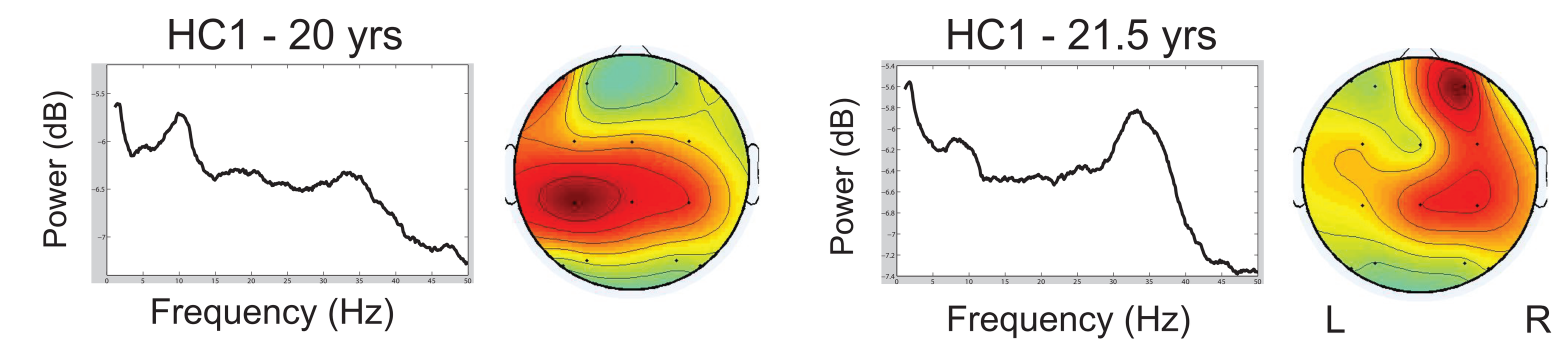
1. Control Subjects



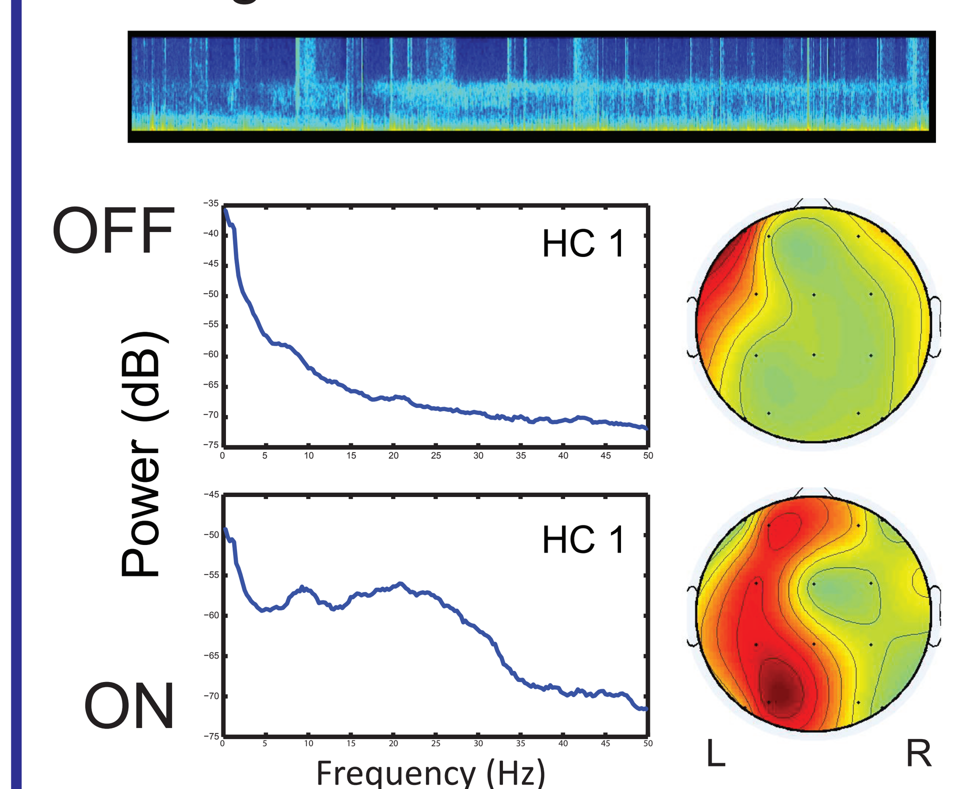
In control subjects (4 shown), components with strong alpha (8-11 Hz) and beta (15-35 Hz) peaks in the power spectrum are at (HC1) or near (HC2) the origin (causal) of the hierarchy identified by HD.

2. Spontaneous Recovery

In a patient subject with spontaneous late recovery from minimally conscious state due to severe traumatic brain injury over an 18-month period, HD reveals increases in ~15-40Hz power in HC1 in right frontocentral regions.

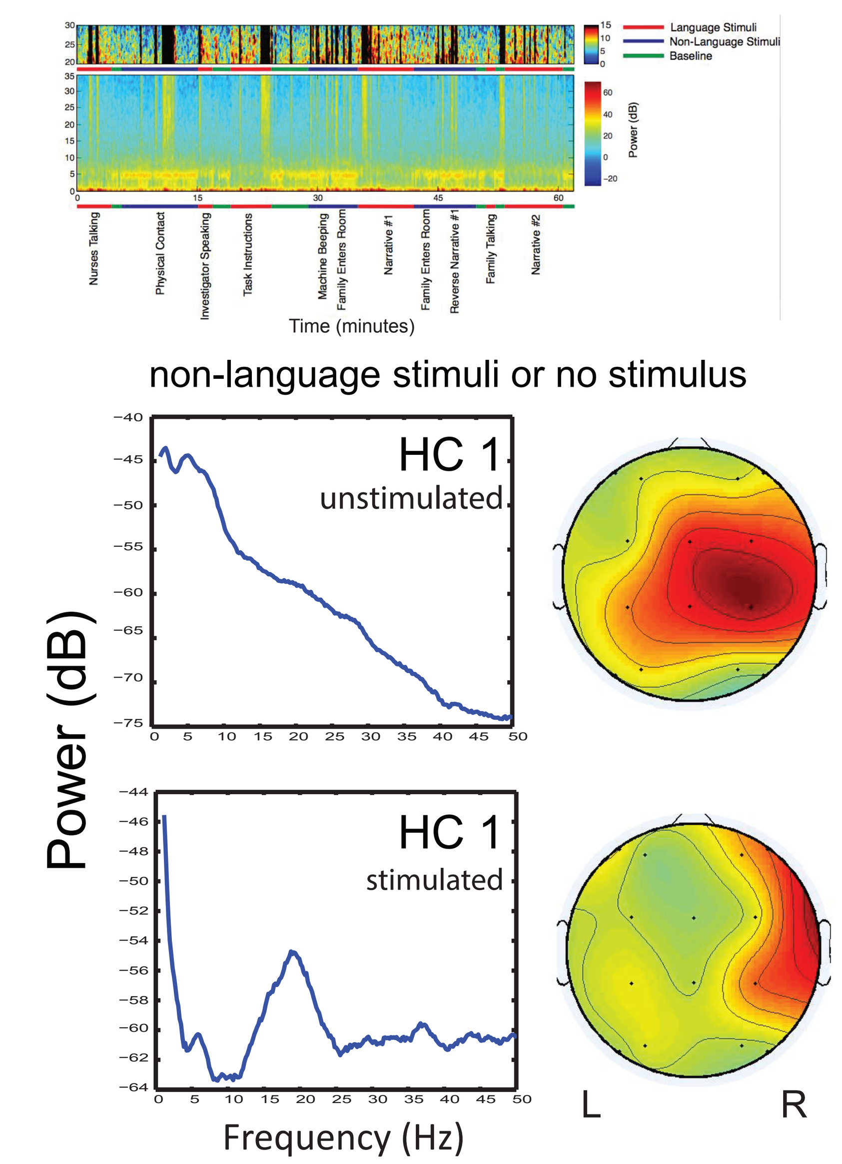


3. Drug Induced



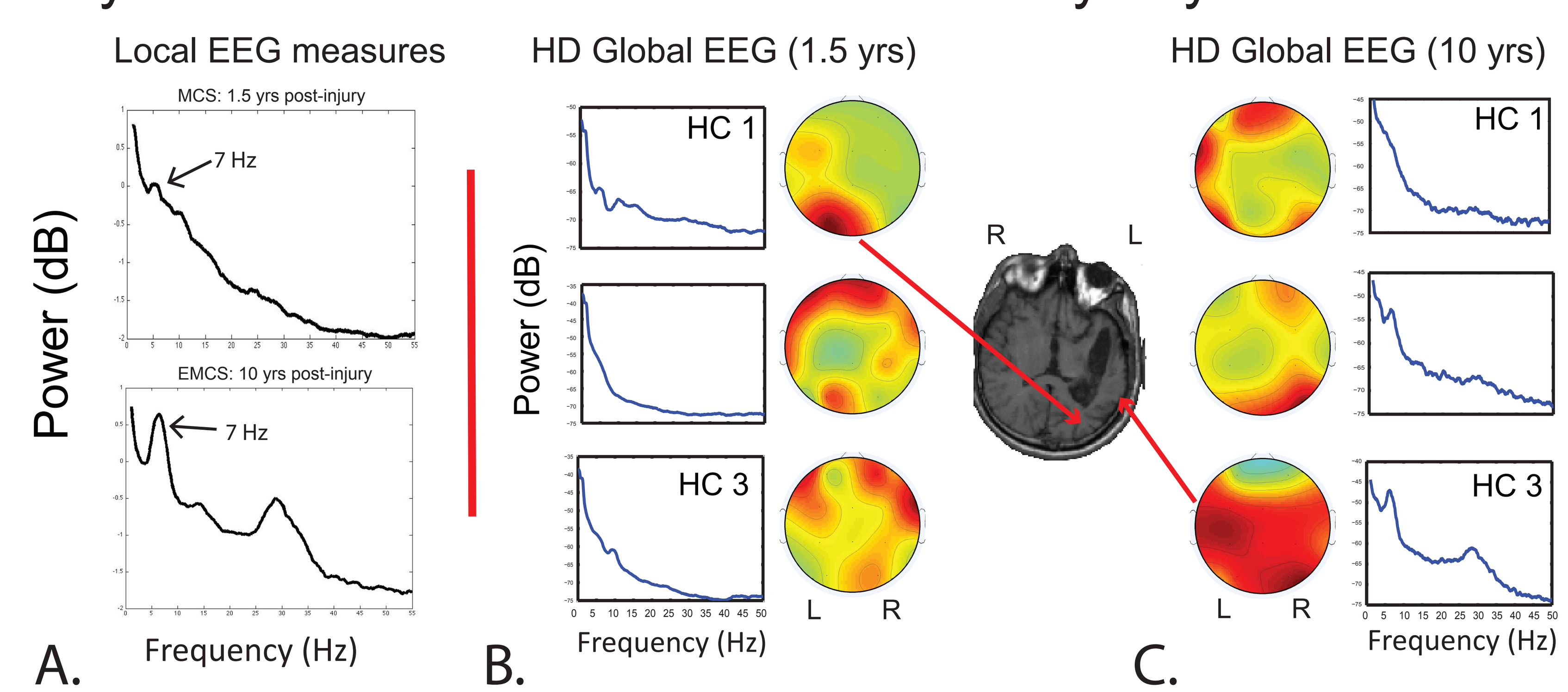
In a patient subject who shows behavioral improvement with zolpidem, the drug leads to a transition from low frequency activity to high (30Hz) frequency activity (spectrogram). This is mirrored in a shift in the power spectrum of HC1.

4. Sensory Stimulation



In another patient subject, sensory stimulation (natural language) shifts the spectrum from low to high frequencies (spectrogram). This is mirrored by a shift in the power spectrum of HC1.

5. Dynamic Isolation of Thalamocortical Dysrhythmia



Longitudinal Recovery from MCS across a 10 year period – Model from "B" to "C"

A. In the local EEG (channel F3 shown), we see a transition from Model type "B" (top; 1.5 yrs post-injury) to a type "C" (bottom; 10 yrs. post-injury) spectral profile. B. At the first time point, HD finds that the component at the origin of the causal hierarchy (HC1) contains the low frequency oscillation (~7Hz) seen in the spectra. C. Following recovery, low-frequency activity is present, but HD finds it is now dynamically isolated and present in the third hierarchical component (HC3), which is localized to a large parietotemporal lesion (red arrows). This component also contains all of the increased 20-30Hz power, demonstrating it is linked to the low frequency activity, as anticipated for a "C" type spectrum (Llinas et al.,1999).

CONCLUSIONS

- In healthy subjects, HD shows a characteristic pattern of resting brain dynamics.
- In patients, normalization of global EEG dynamics is observed during spontaneous recovery, drug induced recovery, and in the setting of salient natural stimuli. These are paralleled by changes in the spectral content of the most causal EEG component, as identified by HD.
- The transitions observed in individual subjects support the mesocircuit hypothesis: recovery is accompanied by reduction in low-frequency oscillations and restoration of higher frequency activity (15-40 Hz) across frontocentral regions.