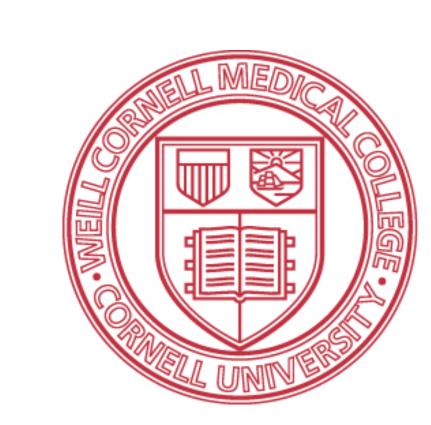
MODULATION OF HIGH FREQUENCY EEG OSCILLATIONS IN RESPONSE TO ZOLPIDEM IN SEVERE HYPOXIC ISCHEMIC ENCEPHALOPATHY



Tanya J. Nauvel^{1,2}, Shawniqua T. Williams³, Mary M. Conte¹, Jonathan D. Victor¹, Nicholas D. Schiff¹

¹Department of Neurology & Neuroscience, Weill Cornell Medical College, New York, NY 10065

²Tri-Institutional Training Program in Computational Biology and Medicine, New York, NY 10065

³Department of Neurology, Johns Hopkins Hospital, Baltimore, MD 21287

553.19/N11 SFN2012

tan2004@med.cornell.edu

MOTIVATION

- The GABA-A alpha 1 selective receptor agonist zolpidem (Ambien) produces paradoxical behavioral facilitation in select patients with severe brain injury. (Whyte et. al., 2009)
- There are characteristic changes in the EEG spectrum of patients who show a paradoxical recovery in response to zolpidem.
- High frequency gamma oscillations are prominent in one subject and raises the question of their biological significance.
- Such narrowly tuned high frequency gamma oscillations are promoted by dopaminergic therapy in patients with Parkinson's Disease (PD), which may provide insight into the physiological nature of this signal.
- Multivariate analysis of the EEG may further elucidate the global dynamical changes involved in the paradoxical response to zolpidem.

Previous Findings	Reference
Upon treatment with levodopa, a new narrowly tuned peak appears at ~70Hz in LFP of STN and GPi in tandem with improved motor performance.	Brown et. al., 2001
A narrowly tuned 70Hz peak in the LFP is present in human thalamus. Activity is modulated by movement and varies over the sleep wake cycle. Reported in patients with Parkinsons (PD), essential tremor, dystonia, myclonic epilepsy.	Kempf et. al., 2009
Coherence in 70-85Hz band between EEG and local potentials in the STN & GPi can only be seen in patients on levodopa. STN and GPi led cortical activity at 70Hz only in treated patients (Fz-Cz).	Williams et. al., 2002
With dopaminergic stimulation, power within STN and coherence between the STN and the EEG is dominated by 70-85Hz activity, which increases with movement.	Cassidy et. al., 2002
Dual ECoG & EEG recordings show high gamma band activity increases during voluntary movement in sensory motor cortex (60-90Hz broadband, C3).	Ball et. al., 2008

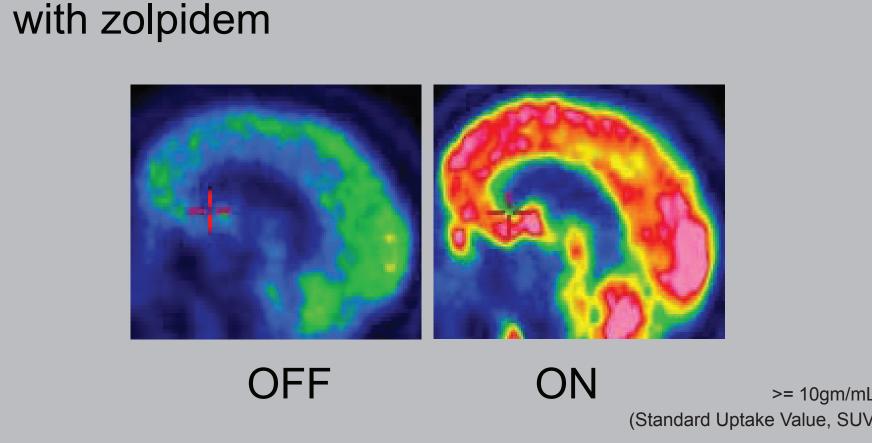
EEG METHODS

electrode placements

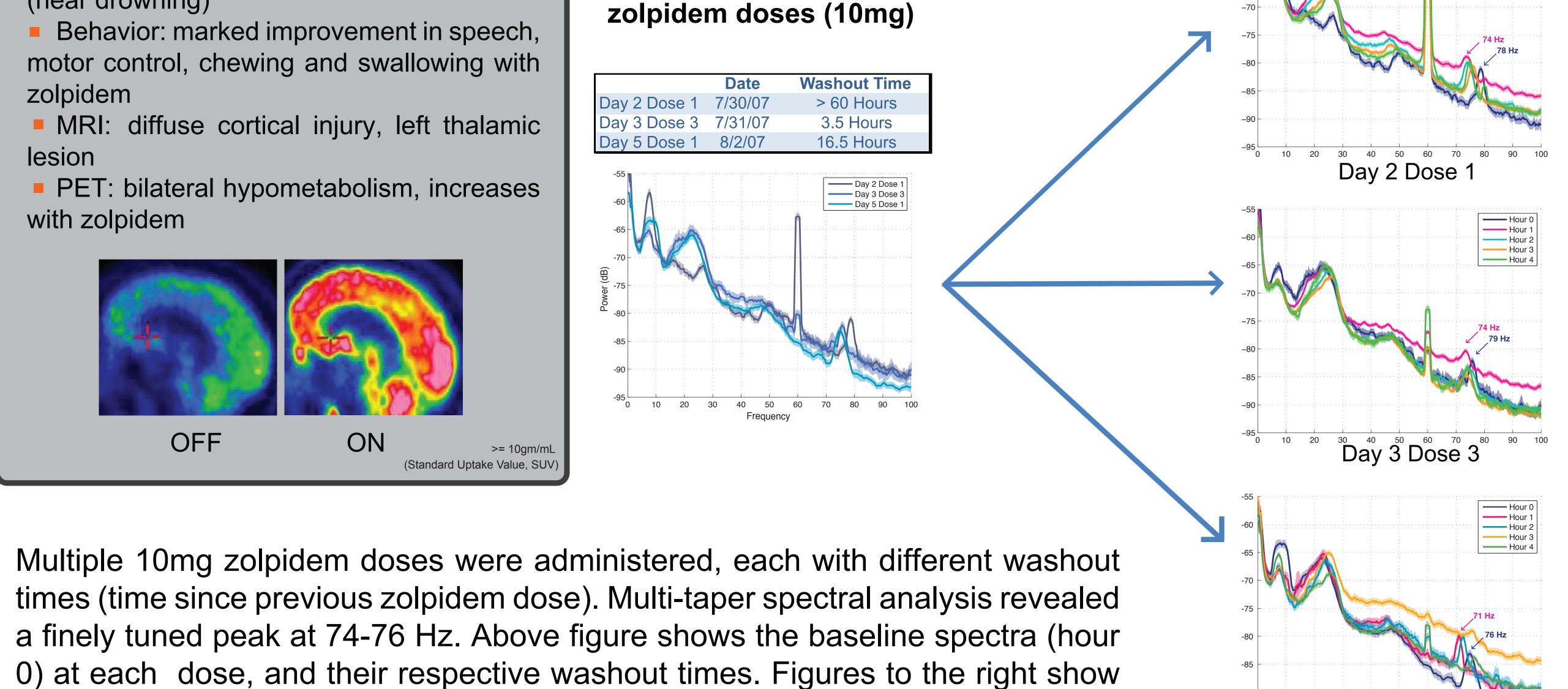
- 100+ hours of recording with 24 hr video
- Longitudinal bipolar recording montage (19 electrodes)
- 200Hz sampling rate via XLTEK (Ontario, CN LH65S1 system).
- 10 mg doses of zolpidem administered up to 3 times a day.
- 3s artifact free EEG segments (~50 150) used for spectra calculations.
- Power spectra and coherence estimated using multitaper methods (MATLAB with Chronux toolbox).
- Functional connectivity network estimated using methods from Kramer et. al, 2009, and Chu et. al, 2012

Subject

- 32 year old male Emerged from minimally conscious state
- (EMCS) Severe hypoxic brain injury at age 23 (near drowning)
- Behavior: marked improvement in speech, motor control, chewing and swallowing with zolpidem
- MRI: diffuse cortical injury, left thalamic lesion
- PET: bilateral hypometabolism, increases

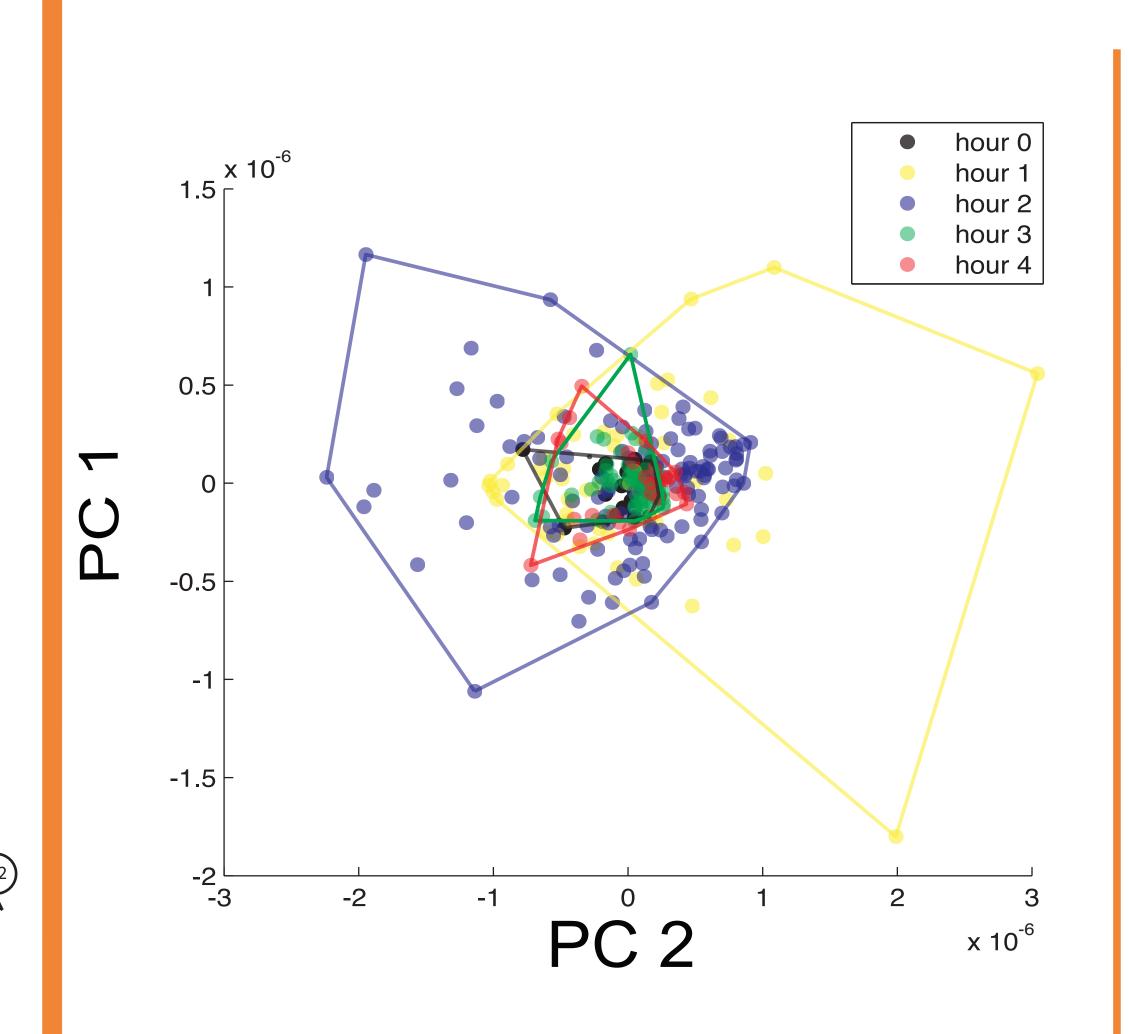


Peak frequency is modulated over time course of zolpidem administration.



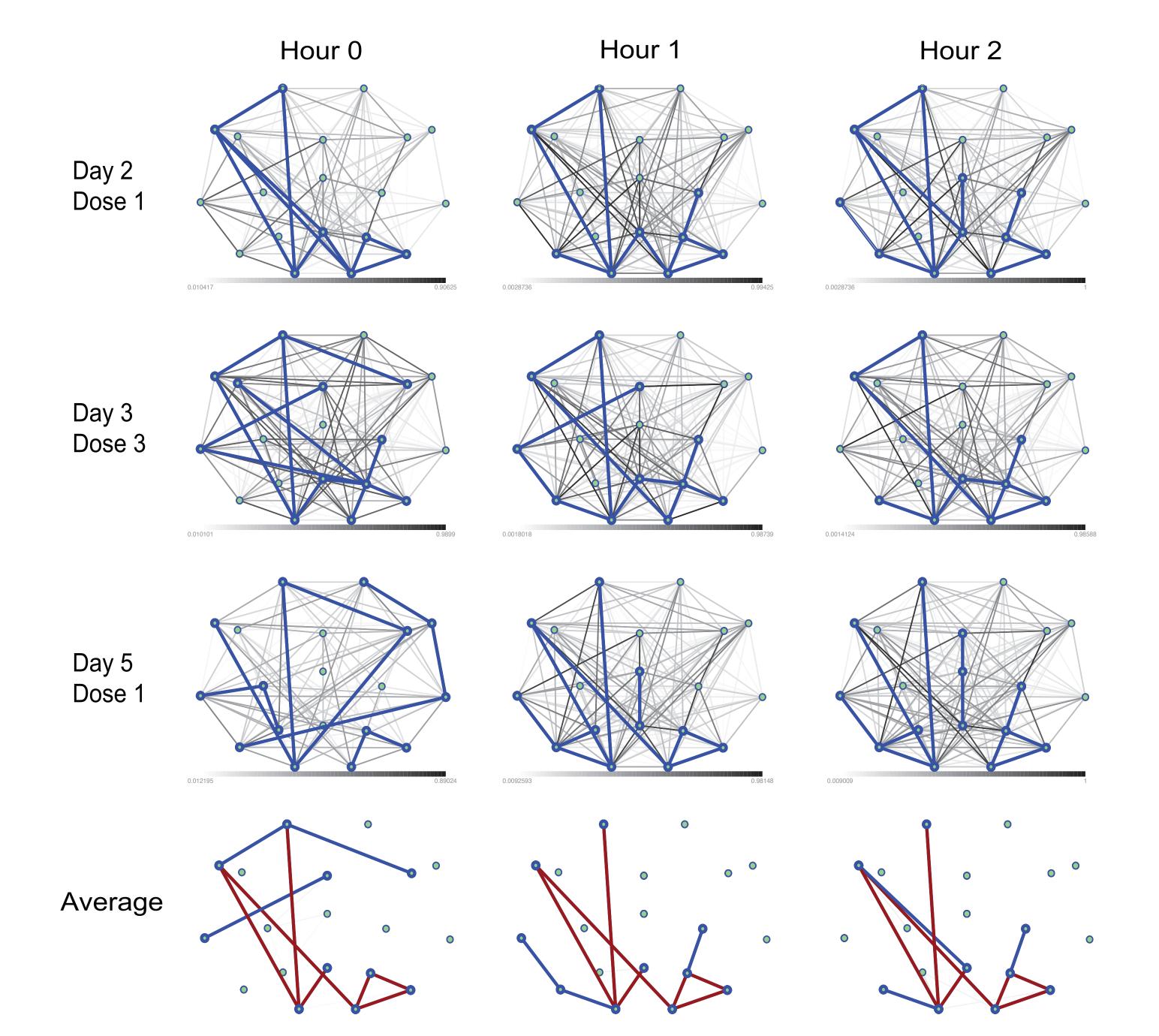
Multivariate Analysis

the peak shifting to the right when ON the drug, and returning to original frequen-



cy over time.

Principal Components calculated using frequency bands of interest from spectrogram (Fz-Cz). Projections of PC 1 vs PC 2 show the cluster spread out when ON zolpidem, and return to original cluster over the time course of the drug. (similar results in 3 doses)



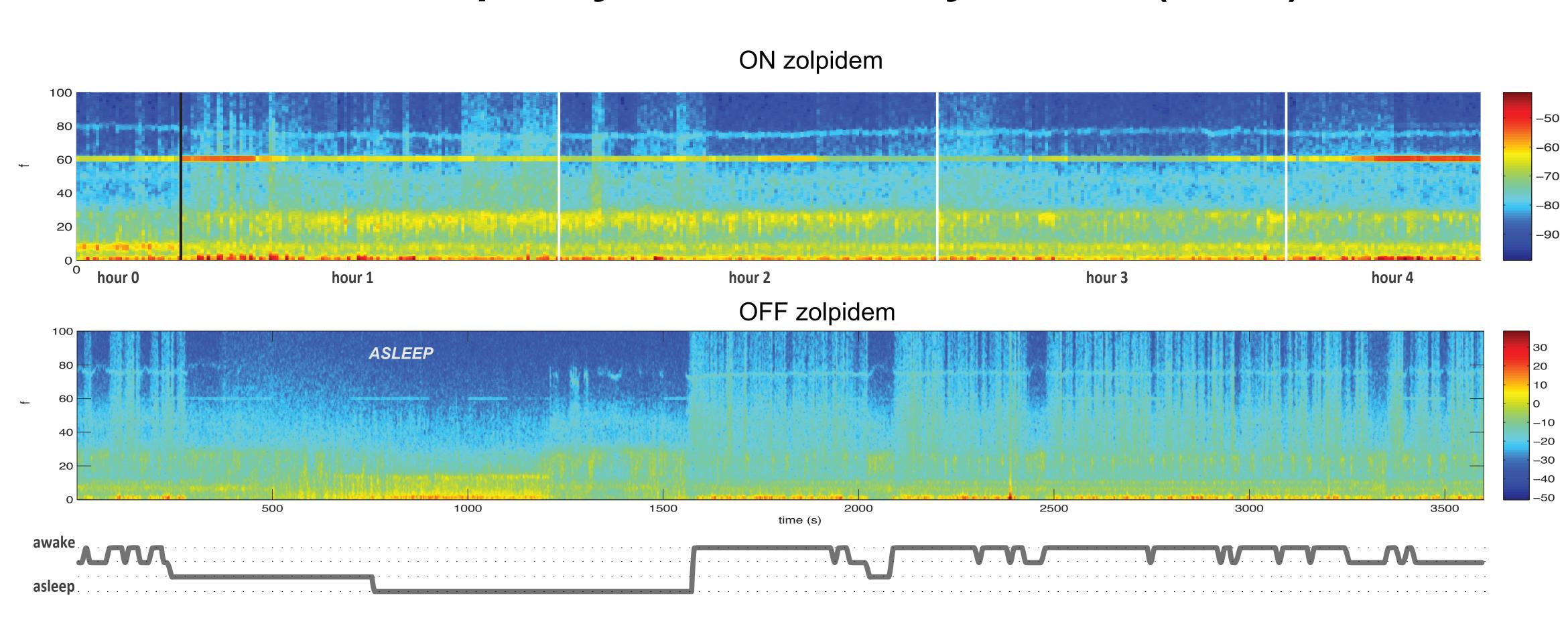
Functional Connectivity network of 3 doses over time. Nodes represent electrodes, edges significant correlation. The blue edges have weights above the 95th percentile. Although there is more variability between networks at hour 0, a core topology does emerge when looking at the average network over all doses.

RESULTS **Spectral Analysis**

Hour 0
Hour 1
Hour 2
Hour 3
Hour 4

Day 5 Dose 1

Peak frequency is modulated by arousal (Fz-Cz)



Spectrogram of activity during the day and at night. ON zolpidem, patient is awake. OFF zolpidem, the high frequency gamma peak disappears as patient becomes drowsy and falls asleep [visual scoring of sleep represented by grey line. 4 states include sleep, "light" sleep (eyes closed for < 10s), drowsy and awake].

Conclusion

- We identify a narrowly tuned high gamma band that is modulated by zolpidem during paradoxical recovery of behavior and brain function in a patient with severe ischemic brain injury.
- This gamma activity is consistent with observations of similar activity in the local field potentials of human basal ganglia, thalamus and motor cortex.
- In our subject the narrowly tuned high gamma activity is linked to improved motor performance and shows a consistent variation across the sleep-wake cycle.
- Zolpidem had a clear effect on the EEG spectrum and on the eigenstructure of the spectrogram, but not on the functional connectivity network.

We would like to acknoledge our funding agencies: The James S. McDonnell Foundation and the Tri-I Training program