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# Novel characterization of an architecturally distinct sleep stage and its implications for recovery from the minimally conscious state

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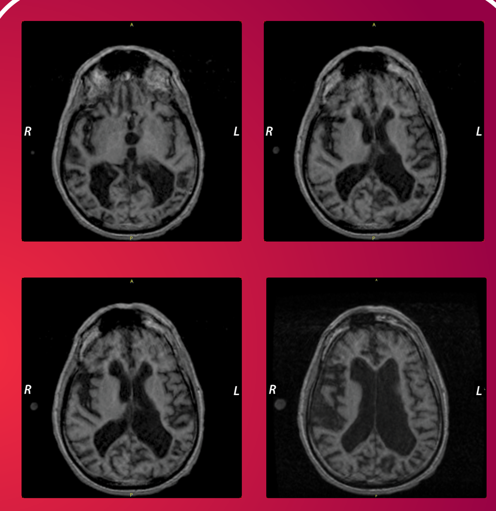
## Motivation

- An estimated 41% of patients with Disorders of Consciousness (DOC) who demonstrate conscious awareness are misdiagnosed as being in the vegetative state (Schnakers *et al.*, 2009)
- The central thalamus has been proposed to play a key role in the maintenance of synaptic activity across frontostriatal systems during wakeful states following severe brain injuries (Schiff, 2012, 2010)
- Central thalamic deep brain stimulation (CT-DBS) may drive frontostriatal activity in the widely deafferented brain to facilitate behavioral recovery (Schiff *et al.*, 2007)
- Cortical firing rates during sleep have been shown to be increased after sustained wakefulness or activity during the day (Vyazovskiy *et al.*, 2009; Adams *et al.*, 2016)

***These considerations motivated examination of longitudinal changes in thalamo-cortically driven elements of sleep electrophysiology in a CT-DBS DOC patient to evaluate the potential impact of daytime driving of fronto-striatal systems.***

## Patient History

- 45 year old man who suffered a severe traumatic brain injury in a motor vehicle accident at the age of 17
- Unable to communicate or respond to spoken commands since the time of injury
- Emotional reactivity to humorous or scatological speech despite no consistent purposeful movements of head, eyes, or limbs
- One of three subjects in a first-in-man study of CT-DBS effects in the minimally conscious state (MCS) (Schiff *et al.*, 2007; Giacino *et al.*, 2012)
- Coma recovery scale-Revised (CRS-R) scores remained consistent with MCS diagnosis across evaluations



Four representative T1 weighted horizontal brain images illustrating left greater than right atrophy secondary to severe diffuse axonal injury

*(For a detailed review, see Adams et al. 2016)*

## Methods

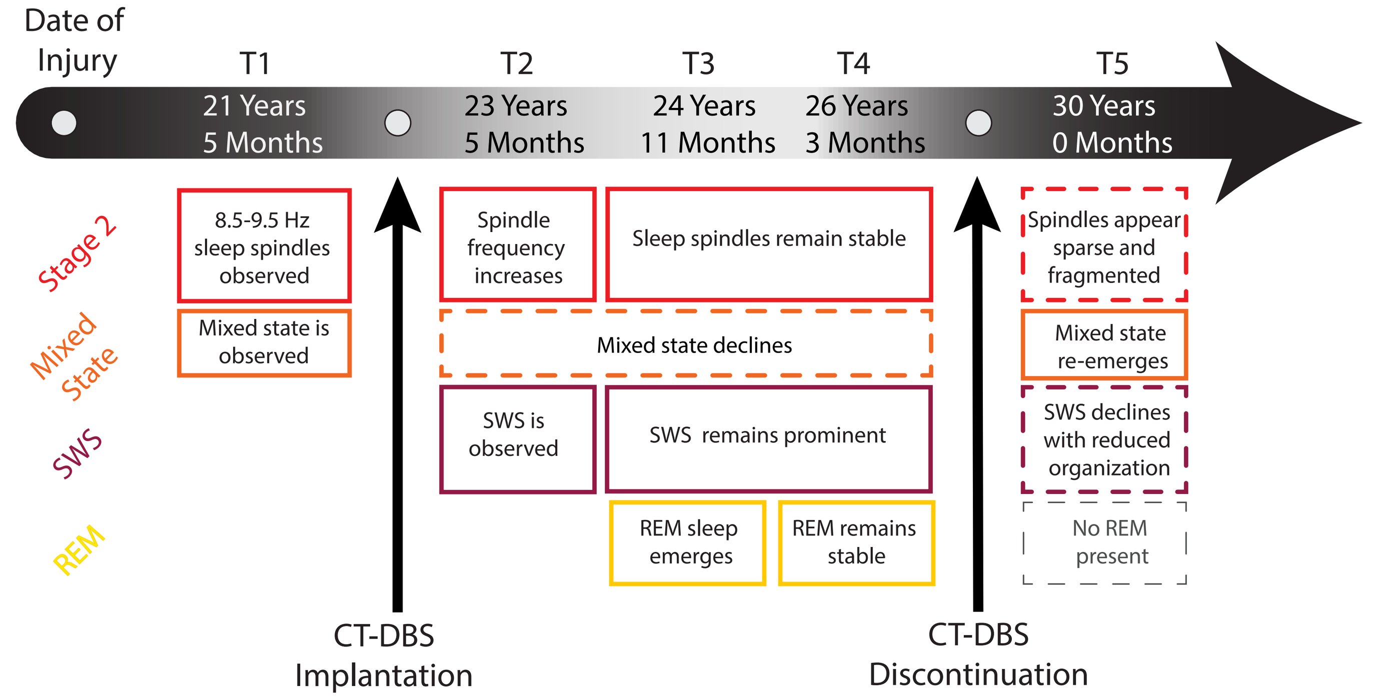
EEG: Overnight video-EEG was collected at five time points (T1-T5) over a course of 8.5 years. Time point 1 occured 21 years and 5 months post severe TBI, immediately prior to CT-DBS implantation. Time points 2-4 occurred during active CT-DBS, and time point 5 occurred post cessation of CT-DBS treatment. EEG was recorded with collodion-pasted electrodes placed according to the International 10-20 system using the Natus XLTEK EEG system (San Carlos, CA).

Power spectra calculation: Multitaper power spectral estimates (5 tapers) were calculated in six fronto-central channels (F3, F4, FC5, FC6, C3, C4) (Thomson, 1982). Hjorth Laplacian montaging was used on 30–35 10-second EEG segments, as implemented by the MATLAB mtspectrumc code in the Chronux toolbox (Bokil *et al.*, 2010).

Comparative analysis of spectral dynamics: Spectral calculations were normalized according to Gottselig *et al.*, 2002. A power law function was fit to each spectrum in the 5-6 and 13-14 Hz frequency range for stage 2, or 5-6 and 17-18 Hz range for SWS. Fitted values were subtracted from the spectrum allowing normalized power values to be compared across visits.

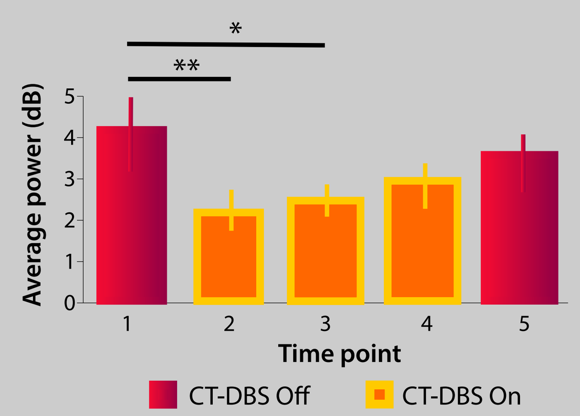
Time-frequency spectrogram calculation: Multitaper spectral estimates were calculated across whole night data (10pm-6am) using non-overlapping 3 second windows. Fast Fourier transform of each tapered data segment was computed using the fftw3 libraries (Frigo and Johnson, 2005) and averaged within each epoch.

## Qualitative sleep architecture timeline



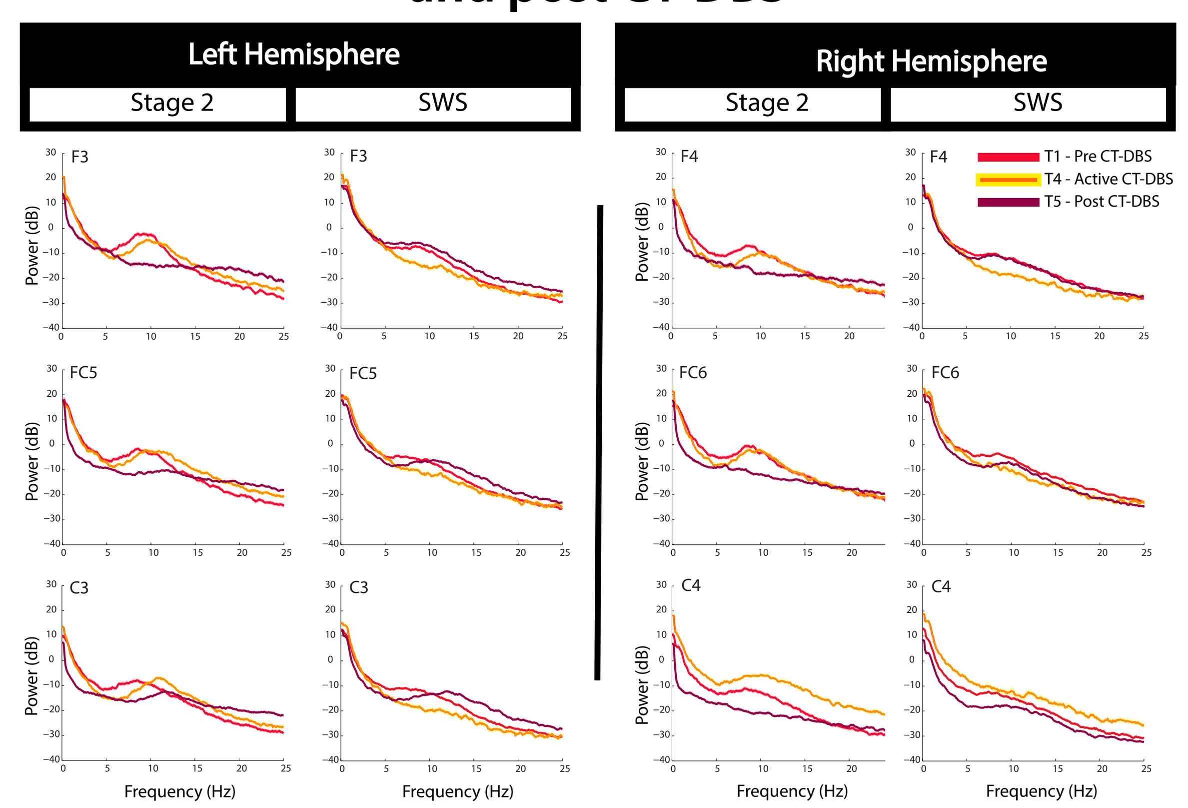

Qualitative EEG analysis revealed dynamic changes across study time points, the most notable being the waning and waxing of an additional sleep stage containing elements of both stage 2 and SWS, referred to here as the "Mixed State."

## SWS power in the spindle frequency range over time



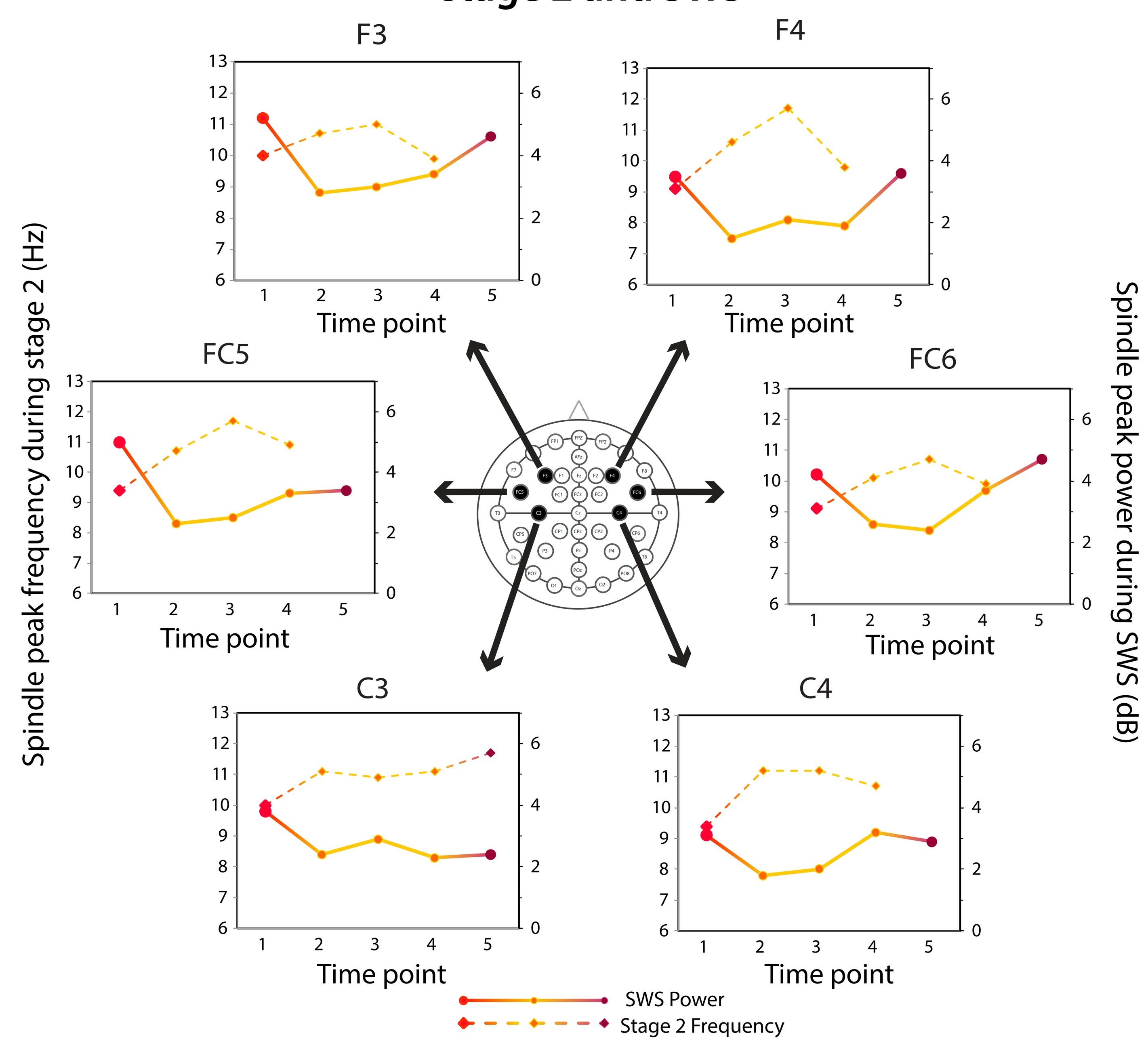

Mean spectral power in the 8.5-16 Hz spindle frequency range during SWS demonstrates a significant reduction from T1 to T2, concurrent with onset of CT-DBS. This reduction remains significant at T3, suggesting continued normalization of SWS architecture with CT-DBS.

## Stage 2 and SWS power spectra pre-, during, and post CT-DBS




Power spectra calculated from stage 2 and SWS at T1, T4, and T5, corresponding to pre-, active, and post CT-DBS conditions. Spectra show a bilateral increase in stage 2 peak frequency in the spindle range from T1 to T4, followed by a complete loss of the spindle peak at T5. During SWS, spectra show an aberrant intrusion of power in the spindle range at T1 that is attentuated at T4 and returns at T5.

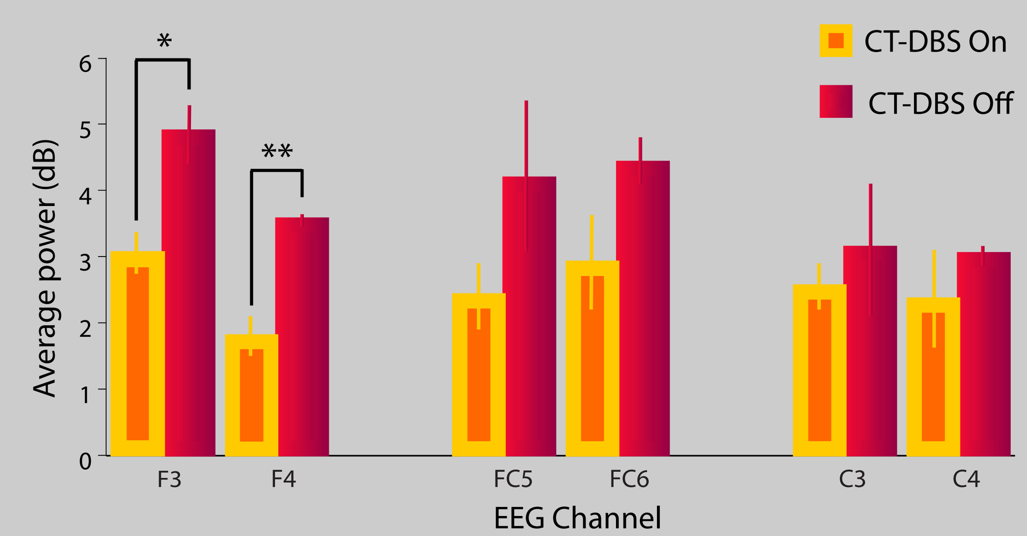
## Power spectral dynamics in the spindle frequency range during stage 2 and SWS



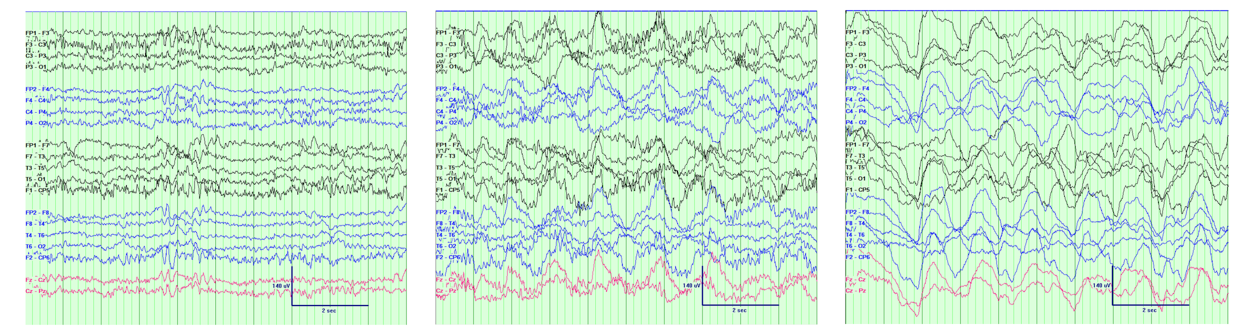

Spindle peak frequency in stage 2 (dotted line) and peak power in the spindle range in SWS (solid line) over time. Stage 2 frequency values increased across all channels from T1 to T2, following onset of CT-DBS. Four fronto-central channels (F3, F4, FC5, FC6) continued to show increasing spindle frequency from T2 to T3, while channels C3 and C4 remained constant. In all channels except for C3, spindle peak frequency slightly decreased at T4, with the spindle peak disappearing entirely at T5 following the cessation of CT-DBS. Notably, C3 is the only channel that retained sleep spindles following CT-DBS cessation, possibly due to resilience and potential strengthening of reflexive language networks (as observed behaviorally). Power in the spindle range during SWS followed the opposite trend, with reductions on all channels from T1 to T2, stabilization from T2 to T3, and increases in the four aforementioned fronto-central channels at T4 and T5. Effects follow a topographical pattern, with the largest changes seen in the most frontal channels and the smallest in the two central channels.

## SWS power in the spindle frequency range according to CT-DBS condition

Power in the 8.5-16 Hz frequency range during SWS by channel. Time points 1 and 5 were averaged and contrasted with time points 2-4 for an analysis of SWS spindle range power according to CT-DBS status. Abberant spindle power during SWS was significantly reduced in both F3 and F4 during the CT-DBS On condition, suggesting a focal frontally-driven effect of CT-DBS in the normalization of sleep architecture.




## Operationalization of the mixed state

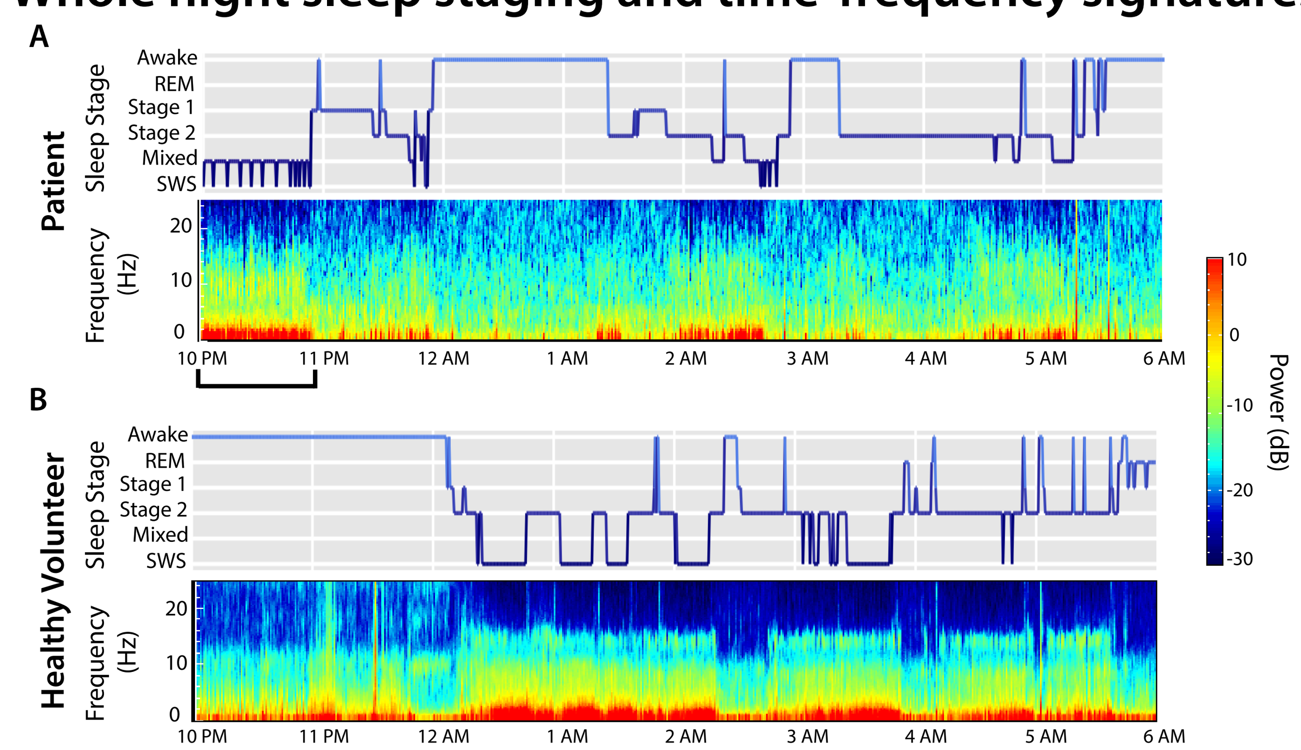


**Stage 2**
K-complexes in addition to 20–100 µV spindle-like formations with 8.5-16 Hz frequency across fronto-central channels

**Mixed State**
>70% of the epoch consists of high voltage, low frequency activity (<2Hz) of which ≥50% displays an overriding mid-frequency (8-14Hz) component

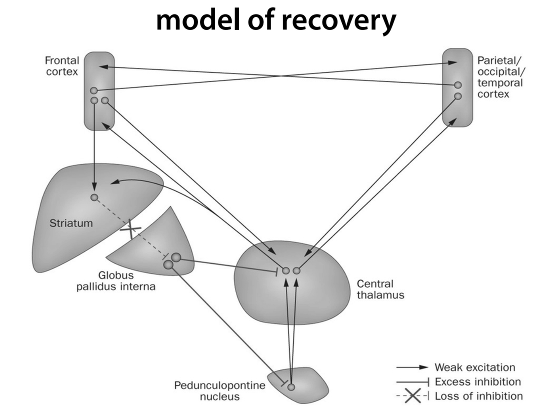
**SWS**
large (>50 µV) polymorphic delta (<4 Hz) waves over 20% of any 30-second epoch

## Whole night sleep staging and time-frequency signatures




Overnight video-EEG was sleep staged for T5 as well as one healthy volunteer with the inclusion of the novel mixed state scoring criterion (Upper panel, A, B). Time-frequency spectrograms calculated from the bipolar Fz-Cz channel reveal a clear frequency signature during mixed state epochs (A, lower panel, bracketed segment) distinct from stage 2 and SWS and not present in normal sleep (B, lower panel).

The anterior forebrain mesocircuit model of recovery



Loss of excitatory thalamic output due to widespread deafferentation may underlie circuit-level dysfunction in patients with DOC. Restoration of thalamocortical input to the anterior forebrain has been proposed to support anterior forebrain excitation needed to maintain consciousness, providing a common mechanism of recovery in DOC (Schiff 2010).

## Conclusions

Daytime CT-DBS may induce consistent, frontally driven changes in sleep electrophysiology during stage 2 and SWS.

A distinct electrophysiological stage during sleep, termed here the "mixed state", may indicate subthreshold forebrain activation.

Specifically, the mixed state may result from an inability of neocortical structures to drive the switch from thalamically-driven stage 2 into cortically-driven SWS.

We hypothesize that:

1) if present, the mixed state is indicative of partial recovery of cortical activation linked to increased daytime arousal and behavioral engagement, and,

2) should consistently yield to normal SWS.

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