Changes in diurnal brain activity of rats with impaired dopaminergic system: Implications to biomarker discovery for the Parkinson's disease

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Abstract

Parkinson's Disease (PD) is one of the most common neurodegenerative diseases, affecting millions of individuals worldwide. Methodologies allowing us to detect this disease at an earlier stage and monitor its progression have been intensively investigated. High-voltage-spindles (HVSs) are spontaneous episodes of brain oscillation (5-13 Hz) which are detected in various brain areas of rodents. Increases in the occurrence and power of HVSs have been reported in rats with impaired dopaminergic neurons. It has thus been proposed that increases in HVS may be considered as an indicator of the disruption of the dopaminergic system in rodents. By utilizing a wireless neural recording system (NeuLive model F, BioPro Scientific), we continuously recorded local field potentials from the primary motor cortex (M1), electrocorticography (ECoG) above the hippocampus and the electromyography (EMG) from the neck (nuchal) for 24 hours during 15-day period. The 15-day period includes 3 days before (day -7, -3, -1) and 3 days after (day +1, +3, +7) compromising the dopaminergic system by systemic reserpine injection. Beta-band oscillation was examined for this Parkinsonian rat model. Our results indicate that sleep/wake status undergoes a shift in the diurnal cycle after disrupting the dopaminergic system. The same set of recording data are also analyzed for the changes of HVS. Together, we demonstrated that by single reserpine administration, it is sufficient to induce long-lasting beta-band oscillation, and observed several PD-related physiological changes reported in human studies, including a shift in sleep/wake proportion and a shift in the sleep spindle dominant frequency. This study introduces the importance of performing continuous brain monitoring for potential biomarkers in PD animal models for early detection, and the potential for HVS as a PD biomarker for early disease detection and for monitoring disease progression.

24-Hour Continuous Recording of Diurnal Brain Signals in Parkinsonian Rats

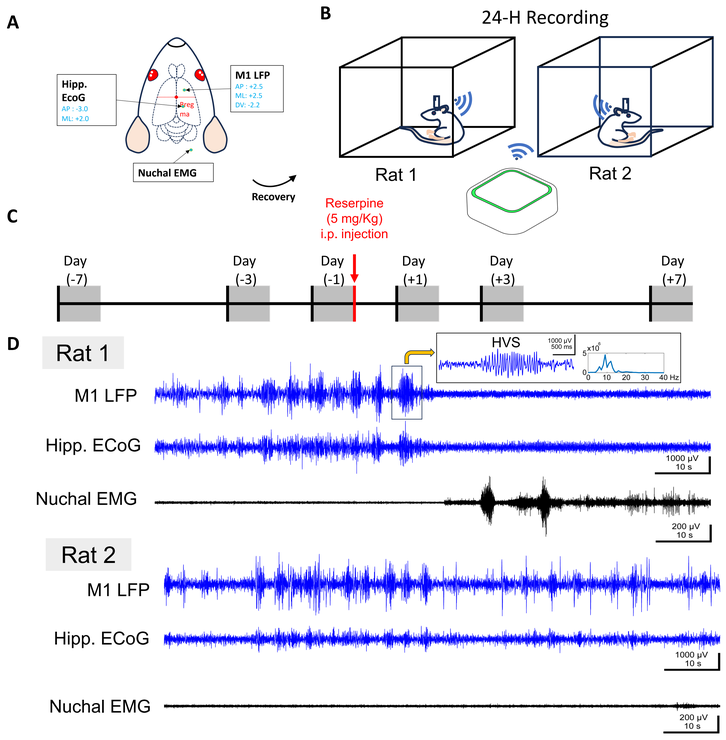

Figure 1. Continuous 24-H recording from Parkinsonian Rats for Changes in Diurnal Brain Activity Monitoring. A, Electrode implantation sites. B, Simultaneous wireless recording from 2 freely behaving rats continuously for 24H. C, Experiment procedure, data were collected on day -7, -3, -1, +1, +3, and +7 of reserpine injection. D, Simultaneously recorded raw data from M1, Hippocampus, and high-pass filtering (>200Hz) data from neck muscle of two rats. These data are subsequently used for sleep stage analysis, HVS detection, and beta-oscillation detection.

Sustained Elevation in Beta-band oscillation after Reserpine Injection

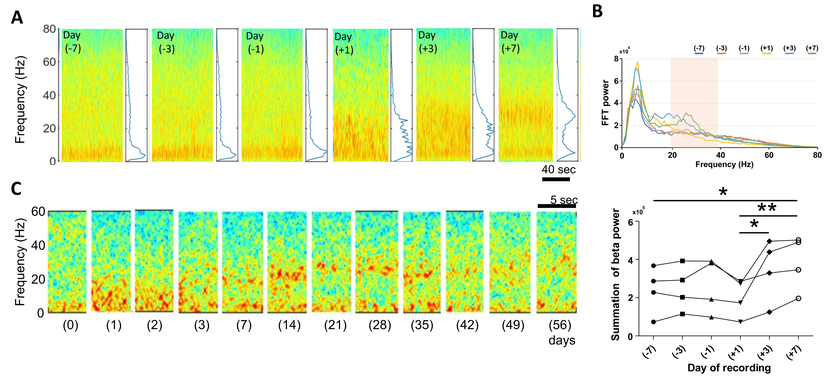

Figure 2. Sustained Elevation in beta-band oscillation after Reserpine Injection. A, Time-frequency analysis showing the elevation in beta-band oscillation (20 – 40 Hz) after reserpine administration. B, Left, average of FFT power-spectrum from 4 animals showing the increase in beta-band oscillation (shaded area) following reserpine administration. Right, statistal analysis showing the change in the beta power on different days. C, Time-frequency analysis reveals a sustained increase in beta-band oscillation for over two months following reserpine administration. One-way ANOVA (repeated measures) with Tukey's multiple comparisons.

Sustained NREM Ratio Elevation After Reserpine Administration

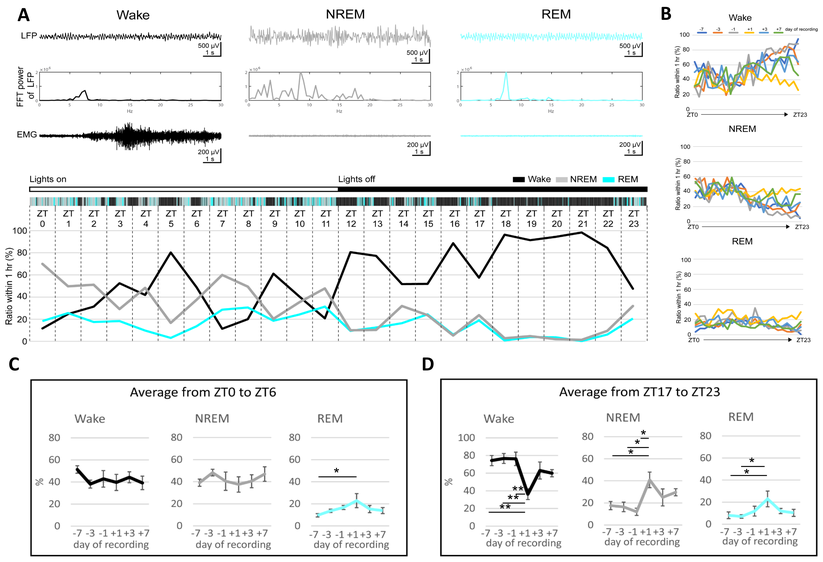

Figure 3. Sustained NREM Ratio Elevation After Reserpine Administration. A, Sleep/wake state analysis over the 24-H timeframe. B, Proportion of wake, NREM, and REM stage over the 24-H timeframe. C-D, Proportion of wake, NREM, and REM stage over the morning and evening periods, respectively (n=4). One-way ANOVA (repeated measures) with Tukey's multiple comparisons. *p < 0.05.

Shift in the HVS Dominant Frequency and Duration after Reserpine Administration

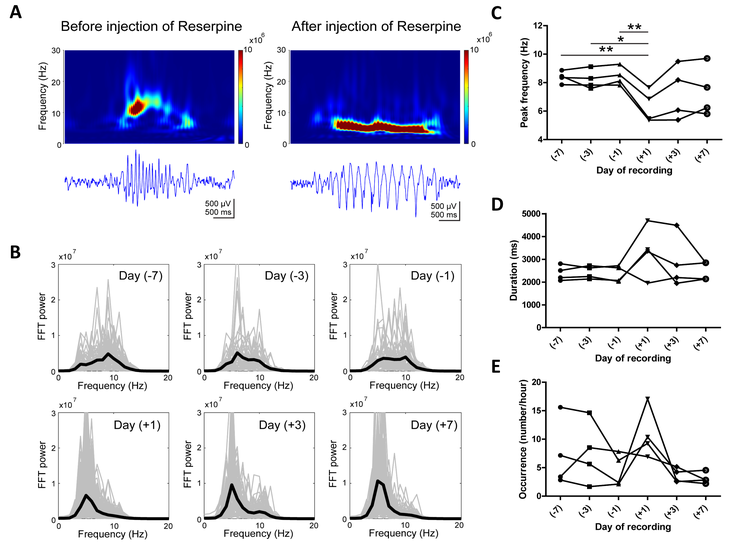

Figure 4. Shift in HVS Dominant Frequency and Duration after Reserpine Administration. A, Representative traces and time-frequency analysis sowing the change in HVS before and after reserpine administration. B, Power spectrum density showing the shift of HVS dominant frequencies before and after reserpine administration. C-E, Line plot showing the change in HVS dominant frequency, duration and occurrence before and after reserpine administration (n=4). One-way ANOVA (repeated measures) with Tukey's multiple comparisons. *p < 0.05, **p < 0.01.

Summary

Parkinson's disease (PD) is a progressive disorder that is associated with the gradual functional loss of the dopaminergic nerve system accompanied by movement deficits such as incontrollable shaking, stiffness, and difficulty with balance, etc. In this study, we first demonstrated that a systemic reserpine administration is sufficient to induce beta-band oscillation, which resembles the pathological brain signals recorded in other Parkinsonian animal models. Secondly, we analyzed the diurnal change of physiological signatures including sleep stages and high-voltage spindles (HVS) in the reserpine-induced Parkinsonian rat model. To collect the brain signals under the most nature behavior, we used a wireless electrophysiology device (NeuLive Model 3, BioPro Scientific Co. Ltd.) to perform recordings throughout the 15-day observation period to overlook the effect upon reserpine administration. Data from 24-hour-lasting electrocorticography (ECoG) and electromyography (EMG) revealed an early onset of sleep disturbance after reserpine administration (day 1), which is consistent with the hypothesis that patients with sleep disorders have a higher risk of developing Parkinson's disease. In addition, a leftward-shift of the HVS dominant frequency was detected among most animals, such a change was reported from sleep spindle analysis in PD patients. The 24-hour continuous multichannel recording is substantial for these observations, that the HVS is predominately detected during the resting stage.

In conclusion, we observed that the sleep/wake proportion is quick affected after reserpine administration, and a sustained effect for up to 7 days after a single injection. On the other hand, we also showed that HVS, a potential biomarker for PD, undergoes a leftward-shift in its dominant frequency, which resembles the shift in sleep spindles detected from PD patients. Suggesting that a continuous HVS monitoring is potentially an ideal biomarker for PD disease progression in Parkinsonian rat models.