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Letter to the Editor

Neural synchronization: Average strength vs. temporal patterning

Excessively strong neural synchrony may contribute to the symptoms of different neurological and neuropsychiatric disorders (Uhlhaas and Singer, 2006). Thus, hypokinetic symptoms of Parkinson's disease are associated with elevated beta-band synchrony (Kühn et al., 2009), however this association is not very consistent (Stein and Bar-Gad, 2013). One possible explanation is that this elevated synchrony is very intermittent (Park et al., 2010).

The temporal variability of synchrony provides an alternative and potentially sensitive way to characterize synchronous activity (e.g., Ahn et al., 2014; Park et al., 2010). Some results (Ahn et al., 2014) suggest that temporal patterning of synchrony may be more sensitive to the changes in the underlying neural circuits (and eventually in behavior) than average synchrony strength.

Here we use parkinsonian beta-band synchronization phenomena to see how the temporal patterning of synchrony may be a more sensitive correlate of behavior than the average synchrony strength. This is not a development of a new marker of parkinsonian beta activity, but an exploration of the relationship of synchrony *patterning* vs. synchrony *strength* with behavior mediated by neural synchrony.

This study includes nine patients (three female) with Parkinson's disease, age: 64.8 ± 7.6 years, disease duration: 9.8 ± 4.4 years, UPDRS motor score: 45.1 ± 8.6 OFF medication and 20.2 ± 3.9 ON medication. It's a small, but relatively homogeneous group; we consider all subjects' data available to us (no special selection bias). Patients had an overall improvement of 56 ± 9% in UPDRS motor score in ON vs. OFF. All patients exhibited hypokinetic symptoms and no or only mild rest tremor. The participants provided a written informed consent and the study was approved by Indiana University IRB.

EEG recordings were performed OFF medication from C3 and C4 scalp electrodes placed according to the 10:20 international system. EEG signals were amplified x5000, digitized at 20 kHz, filtered at 0–200 Hz, and saved for off-line analysis (see Fig. 1A, B). EEG signals were visually examined before analysis to confirm proper signal collection. The average duration of the recorded episodes was 166 ± 35 s.

The data were further filtered with a digital FIR filter to the beta (10–30 Hz) band (zero-phase filtering to avoid phase distortions, see, e.g., Park et al., 2010 for the details). Synchronization strength was quantified with a phase-locking measure

$$\gamma = \left| \frac{1}{N} \sum_{j=1}^{N} e^{i\theta(t_j)} \right|^2,$$

where θ is the difference of the phases of oscillatory activity in the beta band. γ varies from 0 (no synchronization) to 1 (perfect synchronization) (see Park et al., 2010; Ahn et al., 2014 for details).

Temporal patterning of synchronization was characterized by the distribution of desynchronization durations (Park et al., 2010; Ahn et al., 2014). Briefly, this approach considers epochs with overall statistically significant synchrony and extracts intervals, during which the phase difference is close to the preferred value, and intervals, during which the phase difference substantially deviates from the preferred value (desynchronizations). This approach considers the maintenance of the almost fixed phase difference in time and distinguishes between the cases of many short desynchronizations, few long desynchronizations, and possibilities in between even if they all yield the same average synchrony strength.

The distribution of desynchronization durations (as any statistical distribution) may be characterized in different ways. Previously, we showed that the relative frequencies of long vs. short desynchronizations are sensitive to the changes in the network even when the average synchrony stays the same (Ahn et al., 2014). Following Ahn et al. (2014), we use a desynchronization ratio: the ratio of the relative frequencies of the desynchronizations lasting for one cycle and longer than 4 cycles of oscillations (Fig. 1E). A smaller value of the ratio identifies a bias toward longer desynchronizations while a larger value identifies a bias toward short desynchronizations. The distribution of desynchronization durations is dominated by short desynchronizations (many long desynchronizations would lead to virtually no synchrony at all). Therefore, mean or median would not effectively capture the changes in synchrony patterns. But the desynchronization ratio does so, as it is sensitive to the changes in the long desynchronizations. The average synchronization is not necessarily dependent on this ratio. We also performed the statistical analyses with the desynchronization ratios using desynchronizations lasting longer than 3 cycles or longer than 5 cycles. We observed similar outcomes.

The average synchronization strength and desynchronization ratio were correlated with several combinations of UPDRS motor scores (rigidity, bradykinesia, and total motor scores) in OFF state as well as with the improvement in the same combinations of UPDRS motor scores due to dopaminergic medication. Correlations between motor UPDRS score and the synchrony measures (synchronization strength γ and desynchronization ratio) were computed using Spearman's correlation at the significant level of $\alpha = 0.05/6 = 8.33e{-}3$ (Bonferroni correction).

There was no correlation between rigidity and the measures of synchrony strength and pattern ($|r| \leqslant 0.06$, $p > 8.33e{-}3$). However,

Abbreviations: EEG, electroencephalogram; UPDRS, unified Parkinson's disease rating scale

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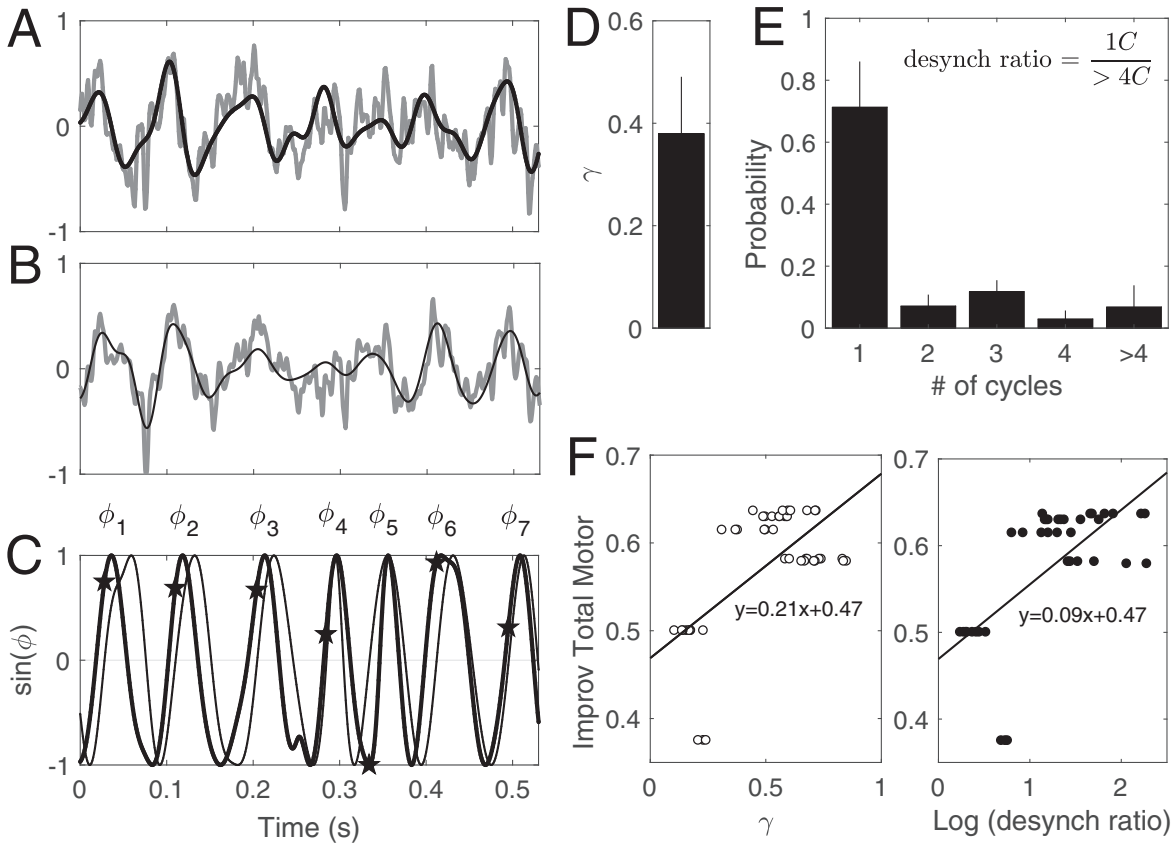

Fig. 1. (A) and (B) are examples of the raw (gray line) and filtered (black line) EEG signals recorded from C3 and C4 electrodes respectively. (C) Phases were reconstructed from the filtered signals using Hilbert transform. The sines of the phases of both filtered signals were plotted. The symbols ϕ_i represent the values of the phase of one signal, when the phase of the other crosses the zero from negative to positive value. The desynchronization (deviation from a preferred phase difference by a large amount) happens at ϕ_5. This yields a desynchronization lasting for one cycle of oscillations (1 cycle). (D) The averaged synchronization index γ with mean ± SEM from all patients. (E) The distributions of desynchronization events with mean ± SEM from all patients. The desynchronization ratio is defined by the ratio of "1 cycle" bin over ">4 cycles" bin. (F) Scatter plots for the improvement of total motor UPDRS scores vs. the synchronization index γ (left panel) and the desynchronization ratio (right panel). Open circles represent a non-significant correlation while closed circles represent a significant correlation. Note that the data do not follow a normal distribution.

there were significant correlations between improvement of rigidity scores and both synchrony measures (r = 0.59, p = 2.17e−5 for synchronization strength; r = 0.63, p = 2.52e−5 for the desynchronization ratio).

There were significant correlations between bradykinesia and both synchrony measures (r = 0.37, p = 4.61e−3 for synchronization strength; r = 0.39, p = 6.80e−3 for the desynchronization ratio). However, there were no correlations between improvement of bradykinesia scores and both synchronization measures ($|r| \leqslant 0.10$, p > 8.33e−3).

There were weak (but not significant) correlations between total motor scores and both synchronization measures. Similarly, there was a weak (but not significant) correlation between improvement of total motor scores and synchronization strength. However, there was a significant correlation between improvement of the total motor scores and the desynchronization ratio (r = 0.65, p = 8.66e−6; Fig. 1F). So, although the improvement of total motor score due to medication was not significantly correlated with the average synchrony strength, it was significantly correlated with temporal patterning of the synchrony.

This situation of weak correlations, some of which may be insignificant, brings up the issue of the temporal structure of the synchronized activity. The relative frequencies of short vs. long desynchronizations may be altered independently of the average synchrony and can be more sensitive than average synchrony (Ahn et al., 2014). The present analysis provides further support for this using different experiments. While the dopaminergic medication-induced improvements are not correlated with the average synchronization strength in EEG, they are correlated with the temporal patterning of neural synchronization, pointing to its potential sensitivity to behaviorally-related changes in the neural circuits.

In conclusion, our observations provide further support to the idea that the temporal patterning of the neural synchrony may potentially be more sensitive to the functionally important and clinically relevant properties of the neural circuits' activity than the synchrony strength. This emphasizes the potential utility of the temporal patterns of neural synchrony.

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References

Ahn S, Rubchinsky LL, Lapish CC. Dynamical reorganization of synchronous activity patterns in prefrontal cortex - hippocampus networks during behavioral sensitization. Cereb Cortex 2014;24:2553–61.

Kühn AA, Tsui A, Aziz T, Ray N, Brücke C, Kupsch A, et al. Pathological synchronisation in the subthalamic nucleus of patients with Parkinson's disease relates to both bradykinesia and rigidity. Exp Neurol 2009;215:380–7.

Park C, Worth RM, Rubchinsky LL. Fine temporal structure of beta oscillations synchronization in subthalamic nucleus in Parkinson's disease. J Neurophysiol 2010;103:2707–16.
Stein E, Bar-Gad I. Beta oscillations in the cortico-basal ganglia loop during parkinsonism. Exp Neurol 2013;245:52–9.
Uhlhaas PJ, Singer W. Neural synchrony in brain disorders: relevance for cognitive dysfunctions and pathophysiology. Neuron 2006;52:155–68.

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