EEG Sample Entropy and Spectral Power: Towards an applicable neuroimaging biomarker in Psychedelic Drug Studies

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What is the Methodological Issue Being Addressed? We use resting-state electroencephalography (EEG) to characterize the effects of a psychedelic drug on brain activity by comparing conventional spectral power endpoints with sample entropy, a nonlinear measure of signal complexity that has been reported across multiple independent studies to be elevated during the psychedelic state.

Introduction There is growing interest in the potential use of psychedelic compounds for the treatment of psychiatric and neurological disorders. As these programs move through early-stage clinical development, objective pharmacodynamic measures can support pharmacokinetic data to inform dose selection and dosing strategy. Resting-state EEG provides a non-invasive approach, with conventional qEEG endpoints such as spectral power offering established measures of frequency-specific effects on the brain. In parallel, the entropic brain hypothesis suggests that psychedelic states may be associated with increased neural signal complexity, making entropy-based measures a potentially relevant EEG endpoint in this context. Here, we compare dose-related and plasma concentration–related changes in conventional spectral power endpoints with changes in entropy to evaluate their relative sensitivity in a psychedelic drug trial.

Methods EEG data were analyzed from a first-in-human study of LPH-5, a novel, next-generation psychedelic compound. Across five sequential cohorts, 38 healthy male participants aged 19–63 years (mean age: 39.9 years) received placebo or ascending doses of LPH-5. Resting-state EEG was recorded at multiple timepoints under eyes-closed and eyes-open conditions (5 minutes each). Raw EEG data was artifact-rejected using independent component analysis, followed by expert review to ensure sufficient data quality for endpoint extraction. Sample entropy and spectral power across IPEG-defined frequency bands were then computed.

Results Dose-dependent attenuation of theta power and elevation of gamma power were observed following LPH-5 administration. Entropy was also elevated in a dose-dependent manner, consistent with previous reports of increased entropy during psychedelic states. Regression analyses using plasma concentration indicated that higher dose levels were associated with a greater number of subjects exhibiting significant concentration-related relationships for entropy, theta and gamma power. At a selected mid-level dose, entropy demonstrated lower mean squared error across subjects than the spectral power endpoints (MSE = 0.007(entropy)<0.021(theta)<0.234(gamma) on average), along with stronger and more consistent positive associations with plasma concentration (Pearson correlation =

0.772(entropy)>0.726(gamma)>0.693(theta) on average). By contrast, theta and gamma power exhibited greater between-subject variability and higher, more variable regression error. We present the supporting figures in the poster.

Conclusion Entropy-based models demonstrated tighter residuals and more consistent relationships with plasma concentration than conventional spectral power measures, suggesting greater stability as an EEG-based pharmacodynamic endpoint in this dataset. These findings support the interpretation that entropy may provide a more reproducible concentration-related measure of psychedelic drug effect and may be a strong candidate for further development as a primary or prioritized endpoint. Spectral power measures remain valuable as secondary or exploratory endpoints, particularly because they may capture frequency-specific, subject-specific, or mechanistic effects that are not fully reflected by entropy. Although these findings are encouraging, cross-validation and population-level modeling in larger datasets will be important to confirm the robustness, sensitivity, and generalizability of these endpoints.

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Keywords

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