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$1/f$ neural noise is a better predictor of schizophrenia than neural oscillations

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Abstract

Schizophrenia has been associated with separate irregularities in several neural oscillatory frequency bands, including theta, alpha, and gamma. Our multivariate classification suggests that instead of irregularities in many frequency bands, schizophrenia-related EEG differences may better be explained by an overall shift in neural noise, reflected by a change in the 1/f slope of the power spectrum.

Introduction

Schizophrenia is characterized by disruptions to multiple cognitive and behavioral domains, including significant working and long-term memory disruptions, impaired attention, and disorganized patterns of thought and language. These cognitive deficits are in addition to the well-established delusions, hallucinations, and affective blunting (Uhlhaas et al, 2010; Crespo-Facorro et al., 2001). Abnormalities in individual brain regions, or cognitive systems, cannot explain the complex and varied schizophrenic symptomatology. Instead, widespread physiological abnormalities leading to reduced and disorganized neural communications are thought to be a better predictor of schizophrenic pathophysiology (Phillips & Silverstein, 2003; Uhlhaas et al, 2010, 2012).

Two specific deficits—increases in neural response variability (i.e., neural noise), and disruptions to oscillatory coupling—are thought to be especially critical for the onset and severity of deficits in schizophrenia (Uhlhaas et al, 2010, 2012). There is ample evidence that disruptions to multiple oscillatory bands are associated with schizophrenia. Disruptions in neural oscillatory activity in schizophrenia may explain deficits in both perceptual processing and disorganized thought patterns (Uhlhaas et al, 2010). Electrophysiological investigations of

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schizophrenia typically report that power in the low frequency delta (1-3 Hz) and theta (4-8 Hz) bands increases, power in the mid-frequency bands of alpha (8-12 Hz) and beta (12-30 Hz) is unchanged, while power in the gamma range (>30 Hz) is decreased (Uhlhaas et al, 2010, Sun et al, 2011). This pattern of activity is typically explained as a series of band specific changes, e.g. theta increases independently of the decrease in gamma.

While these oscillatory results have proved to be robust, there is scarce direct evidence regarding neural noise changes in schizophrenia, as measuring neural noise has proved to be more difficult. Recently, however, it has been proposed that neural noise can be estimated from the EEG power spectrum [REFS]. Specifically, noise in the spectral domain can be clearly identified by its characteristic $1/f^{\chi}$ (power-law) shape. That is, power in a spectrogram decreases exponentially as a function of frequency, where the exponent χ determines the 'slope' of the decline. Of particular interest is that fact that, traditionally, oscillations are measured assuming that this 1/f noise is fixed. Emerging evidence however suggests slope can vary in meaningful ways (El Boustani et al., 2009, Freeman & Zhai, 2009, Podvalny et al., 2015, Voytek & Knight, Voytek, B.). For example, healthy aging is associated with an increase in neural noise (Salthouse & Lichty, 1985) and with changes in the "slope" of the 1/F power spectrum (Voytek, et al, 2015, Wöstmann et al, 2017). This noise perspective is particularly intriguing from an information theoretic perspective, where information theory suggests that increasing noise fundamentally decreases the efficiency of communications (Shannon, 1948). Consistent with this, schizophrenia has been previously linked to decreases in neural signal-to-noise (Winterer & Weinberger, 2003).

Modeling studies suggest neural noise and oscillatory coupling are interdependent. Increasing noise can destabilize neural oscillations (Wang, X.-J., 2010). Likewise, variations in oscillatory power and phase can modulate background excitability (Womelsdorf et al., 2014) and therefore alter noise. Thus, based on prior reports linking schizophrenia symptomatology to abnormal neural noise, we hypothesized that schizophrenic patients should exhibit abnormal power spectrum slopes compared to healthy controls. We further hypothesized that measurements of band-limited oscillatory power may be confounded by changes in background electrophysiological noise. To begin to separate these factors we undertook multivariate analysis of EEG data to identify whether neural noise or oscillatory power was the most reliable predictor of schizophrenic clinical status.

Methods

Participants

EEG and behavioral data were acquired for 65 (1 left-handed) participants recruited from two groups: schizophrenia (SZ) patients (n = 31) or matched control (CO) participants (n = 35). SZ patients were referred by their treating clinician or were recruited from the community alongside the CO participants. Patients met the DSM-IV criteria for schizophrenia-spectrum illness using the SCID interview (First et al, 2002). To reduce long term effects of medication,

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only recent-onset patients were studied, with onset occurring within the last five years. SZ patients were stable and continued treatment plans throughout the course of the study. Study procedures were approved by the Institutional Review Board of the University of North Carolina at Chapel Hill. Participants were compensated for their participation.

Experimental protocol

Data were recorded from a standard 10-20 electrode montage 32-channel EEG cap (Electo-Cap International) using NeuroScan 4.3.1 software and a SynAmps amplifier. Continuous EEG data were sampled at 500Hz with a 0.15-70 Hz band-pass filter and 60 Hz notch filter. Electrode AFz served as ground and the right mastoid as reference. Vertical and horizontal bipolar electroocculogram (EOG) electrodes were placed at the outer canthi of each eye and above and below the right eye. Electrode sites were exfoliated and contacts were affixed with conductive gel. Electrode impedance was kept below 5 kΩ. Recordings were acquired in sound-dampened chamber with participants seated 80 cm from the stimulus presentation monitor.

Task

EEG was recorded while participants completed a selective attention task (see Figure 1). Stimuli consisted of a letter (E, H, L, or P) or number (3, 7, 8, or 9) presented in either red or green typeface on a black background. Each participant was instructed to identify a target stimulus of the correct alphanumeric class and presented in the correct color. Letters were targets (numbers, non-targets) and only one indicated color required attention. Thus, stimuli were binned into four trial conditions: attended targets (letter stimuli of the indicated color), attended non-targets (numeric stimuli of the indicated color), non-attended targets (letter stimuli of the non-indicated color), and non-attended non-targets (numeric stimuli of the non-indicated color). All bins occurred with equal frequency (25%). Stimuli were presented for 200 ms with a jittered inter-stimulus interval of 1500 ± 200 ms, during which a white fixation cross was presented. Participants performed 5 blocks of 100 stimuli each for a total of 500 trials. Overall, 125 trials of each condition were presented in a pseudorandom order. Participants were instructed to respond to attended target stimuli with the left mouse button (index finger) and to all other stimuli with the right mouse button (middle finger). Early analyses showed that the attended non-target, non-attended target, and non-attended non-target conditions exhibited similar behavioral and physiological responses. Therefore, data from these conditions was combined by drawing equal numbers of trials at random from each of the three conditions such that the total count matched the number of attended trials for each participant. In subsequent analyses, the combined non-attended target condition trials were compared to attended trials.

Data analysis

Continuous EEG data were segmented into 500 ms epochs following initial stimulus presentation. Epochs containing artifacts (as determined by a ±100 μV threshold or manual

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inspection) were removed and eye-blink components identified via independent component analysis (ICA) (Makeig et al. 1996; Jung et al. 2000) were removed from further analyses. Artifactual components were selected manually and confirmed by monitoring for reduced correlations between post-ICA EEG and EOG waveforms. All subsequent analyses were performed independently for each EEG channel. Baseline activity was removed by subtracting mean pre-stimulus voltage from each epoch. Participant performance was quantified by computing accuracy and response times (RTs).

Frequency domain analyses were performed by first computing the power spectral density (PSD) of each artifact-free epoch using Welch's method (Welch 1967). For each participant and channel, the PSDs of all epochs of each condition were averaged together. Traditional PSD analysis was performed by dividing the spectra into the following canonical bands: theta (4-8 Hz), alpha (8-12 Hz), beta (12-30 Hz), and gamma (30-50 Hz). In addition, the slope, or exponential decay parameter χ of each average spectrum was estimated using robust linear regression algorithm (i.e. RANSAC; Fischler & Bolles, 1981) across the 4-50 Hz range. In this method, the underlying $1/f$ framework of the spectrum is treated as linear in log-log space (see eq. 1). In this method oscillatory peaks in the spectrum are treated as outlier deviants from this pattern and thus removed using a robust linear model (Fischler and Bolles 1981). The spectral power law is modeled by the log-linear decay coefficient χ, where f is frequency and $S(f)$ is power (Eq. 1).

$$log(S(f)) = \chi * log(f) \quad (1)$$

Statistical analysis

Analysis of the distribution of both behavioral and electrophysiological data revealed the majority of the data was significantly skewed (i.e., behavioral accuracy, as well as all power measurements). We therefore adapted our summary statistics and our statistical methodology to use robust measures, those less susceptible to bias by extreme values. Central tendency is reported using the median, not the customary mean. Variance was likewise measured using the median absolute deviation (MAD; $MAD = median(|x_i - median(X)|)$, where X is represents the complete sample and x_i represents individual samples). Pairwise null hypothesis testing was conducted using Wilcoxon rank sum test. All statistical analysis was done using the R programming language (R Core Team, 2016. R.). Analysis code, and raw data is available at http://voyteklab.com/code-data/ [*available post-publication*].

Multivariate classification

We used multivariate classification to predict patient status (schizophrenia or control) in a selective attention dataset. We compared three different feature sets (behaviour, oscillatory band power, slope) and a range of classifiers (discussed below). To ensure a rigorous test of general model performance, prior to undertaking any multivariate analysis 30% of both neural and behavioral data was randomly selected as a "holdout", or final validation, set. Modeling of

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this set occurred only after model selection (described below) was complete. Additionally, all normalization and rescaling of features used parameters derived separately for holdout or training sets, ensuring independence. That is, the holdout datasets were tested only on a single model per condition. We report only holdout performance here.

An estimate of the precision of classifier accuracy and an estimate of null performance (i.e., shuffled label performance) are useful in assessing overall classifier performance. To estimate both, we conducted two bootstrap procedures. To estimate chance performance we randomized and resampled (with replacement) the group labels (CO or SZ), generating a null distribution (see grey bars in Figure 3). Our second bootstrap procedure left the labels intact but randomly sub-sampled the electrode averaged data (with replacement). This sampling procedure allowed us to better estimate the accuracy variance inherent to the holdout data set. Of course, the single random selection event inherent in creating a holdout set may have been accidentally biased, compared to some true, but unknowable, value. The resampling procedures used here do not remove this potential (and uncontrollable) source of bias. However given that we report the median values of these resampling procedures, the effect of extreme bias events should be minimized. Bootstrapping distributions all consisted of 500 independent samples.

Prior to running the final holdout analysis, we undertook an extensive model and feature selection procedure. Model selection, using 70% of the data, relied on 10-fold cross validation (CV), as well as bootstrapping analysis similar to that outline above. We considered a range of modeling approaches ranging from OLS-based logistic regression to nonlinear models taking advantage of both concurrent strong regularization, and/or boosting (e.g., Bagged AdaBoost, Boosted Logistic Regression, SVM w/ either radial or polynomial kernels, and Ridge Regression). In the end, we selected a linear support vector machine (linear SVM) for behavioral classification, and nonlinear 'Random Forests' for classifying both types of neural data - spectral power and slope. Applying linear models to the neural data tended to reduced performance in the training set by 5-10% (not shown). Likewise, applying a range of nonlinear models (see above) to the behavioral data strongly negatively impacted performance (>10%). We reasoned then that it was better to maximize classification performance on these different data types rather than enforce a consistent (inappropriate) model across both data types. Hyper-parameter optimization for both models was estimated using only training data, see Table 1.

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Features	Model	Hyperparameters
Behavior (accuracy, reaction time)	Linear SVM	C = 0.25
1/f spectral slope	Random Forest	mtry = 9
Oscillatory power (theta, alpha, beta, gamma)	Random Forest	mtry = 2
Oscillatory power (gamma only)	Random Forest	mtry = 6

Table 1. Classifiers, features design, and cross-validation optimized hyperparameters. All spectral features were taken from 10 posterior and midline EEG electrodes (i.e., C3, C4, Cz, FCZ, Fz, O1, O2, P3, P4, Pz).

Results

Task accuracy differs in schizophrenia patients

Schizophrenia patients had significantly lower accuracy (0.91 +/- 0.11 MAD) compared to the control group (0.95 +/- 0.05) (Wilcoxon rank sum test, W = 2896 , *p = 2.3e-5*) (Figure 1**b**). Both groups had worse performance for attention compared to no-attention trials (control W = 1090.5, p = 2.24e-10, Schizophrenia: W = 859.5, p = 9.57e-08). Reaction time was not a significant predictor of group membership (W = 1954, p = 0.4743; 525.51 +/- 95.54 compared to 528.06 +/- 100.68). Within groups, reliable reaction time effects of condition were observed such that, in control subjects, the attention condition had significantly faster reaction time (489.86 +/- 82.97 ms) compared to the no attention condition (578.62 +/- 88.26 ms) (W = 278, p = 0.000163). Similarly, schizophrenia patients were significantly faster for attention (467.55 +\- 83.36) compared to no attention trials (562.5 +/- 77.6 ms) (W = 246, p = 0.0007666) (Figure 1**c**).

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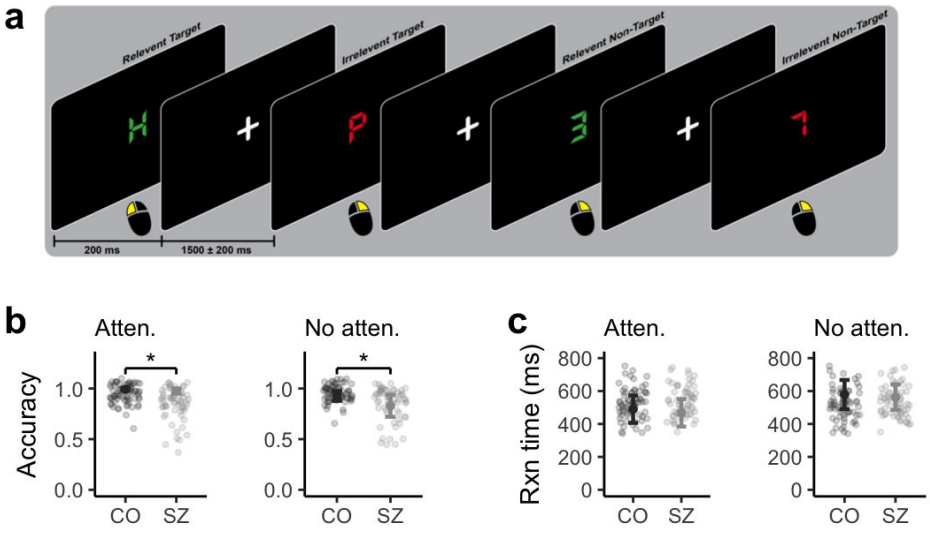

Figure 1. Task and behavior results. **a**) Task diagram. Comparison of median (**b**) accuracy and **c**) reaction time (+/- MAD), between the two groups (control [CO] and schizophrenia [SZ]) and task conditions ([atten]tion and [no atten]tion).

Band-specific increases and decreases in oscillatory power

In the theta band there were no significant there power differences between control and schizophrenia (Wilcoxon rank sum test, W = 17268, p-value = 0.1255), consistent with the small increase in median power difference in (3.49 +/- 2.13) compared to controls (3.19 +/- 1.98) (Figure 2**b**). In the alpha range, SZ had significantly elevated power (2.39 +/- 1.64) compared to CO (1.96 +/- 1.38) (W = 16068, p-value = 0.0090) (Figure 2**c**) while controls had significantly less median power (0.38 +/- 0.18) than patients in the beta range (0.47 +/- 0.26) (W = 15250, p-value = 0.00082) (Figure 2**d**). In the gamma band, however, the trend reversed. Power was significantly reduced in patients (0.11 +/- 0.07) versus controls (0.12 +/- 0.05) (W = 21492, p-value = 0.02346) (Figure 2**e**).

1/f spectral slope decreases in schizophrenia and best predicts schizophrenia status

The slope of the power spectrum in schizophrenia patients was significantly steeper (1.94 +/- 0.48 MAD) compared to controls (1.68 +/- 0.55) (Wilcoxon rank sum test, W = 14104, p = 1.2e-05) (Figure 2**f-h**).

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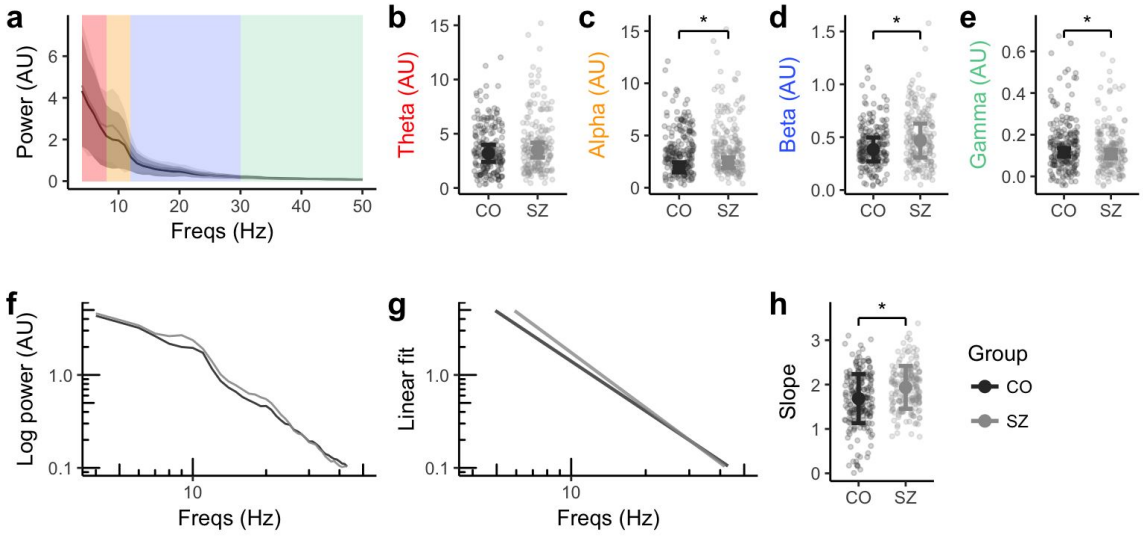

Figure 2. Oscillatory power and spectral slope in Schizophrenia patients (grey) and controls (black). **a**) Median spectral power spectrum (MAD error in represented by shaded areas). Color coded regions represent oscillatory bands - theta (red, 4-8 Hz), alpha (orange, 8-12 Hz), beta (blue, 12-30 Hz), gamma (green, 30-50 Hz). **b-e**) Median power for each band (+/-MAD). **e**) Log transformed spectral power. **f**) Example robust linear fitting of the slope of (e). **g**) Median slope differences between groups (+/- MAD).

Spectral power varies between cortical regions and can be used to identify individual subjects, and tasks (Cox, R. et al., 2016). We therefore employed a spatial multivariate classification approach to predict clinical group (i.e., control or schizophrenia) from either oscillatory band power, spectral slope, or both (see *Methods*). We contrasted these outcomes with predictions made using behavioral data.

The classification model based on spectral slope (Figure 3**b**) achieved the highest median classification accuracy (0.71 +/- 0.11 MAD) compared to a model using all oscillatory band data (0.57 +/- 0.11) (Figure 3**c**). Slope also outperformed gamma power alone (0.57 +/- 0.11) (Figure 3**d**). Further, a joint model relying on slope and all oscillatory bands showed reduced performance (0.64 +/- 0.11) compared to slope alone (median difference of 0.07; Figure 3**e**). Such a reduction is expected if slope and band power are collinear, or otherwise highly covariate. The model based on behavioral response (*i.e.*, reaction time and response accuracy) performed better than either of the oscillatory models (0.67 +/- 0.12; compare Figure 3**a** to **c-e**). Behavioral predictive performance was, however, inferior to spectral slope (0.67 compared to 0.71; Figure 3**a** to **d**).

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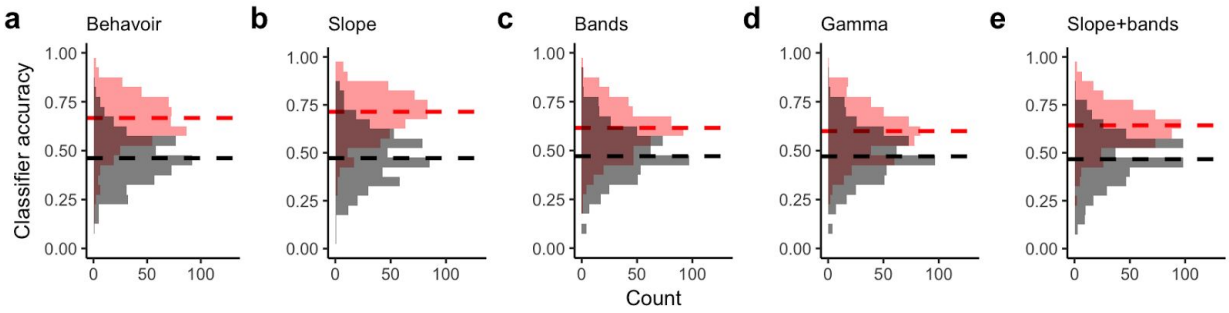

Figure 3. Classifier performance. Classification accuracy was assessed on a hold out data set, comprising 30% of each data set. The effect size, i.e. performance above chance, was estimated by comparing hold out performance to a label-shuffled null distribution (grey). Model precision was estimated by subjecting the holdout set to a bootstrapping procedure (red). Median performance indicated by dashed lines. **a**) Classification accuracy using only behavioral data **b**) Performance using spectral slope **c**) Accuracy for all four canonical oscillatory bands (theta, alpha, beta, gamma, see Figure 2**a**). **d**) Accuracy using only gamma band power **e**) A joint model, including both spectral slope and all oscillatory bands.

Discussion

Our findings reveal that spectral slope, a measure of the neural background noise, is a better predictor of schizophrenia than power measurements derived from specific oscillatory bands or from behavioral responses collected during a selective attention task. The latter is an especially surprising result considering that behavioral measurements remain the gold standard in classifying clinical outcomes in schizophrenia. Given the increasing demand for more objective *biomarkers* to identify and classify clinical pathology, we suggest that spectral slope may serve as an effective biomarker for schizophrenia.

Oscillatory power differences in context

The direction and significance in band-specific differences observed in the current report are broadly consistent with prior work (see Figure 2**a**). The only deviating result is the lack of a group difference in theta power. However all other bands displayed a significant separation based on clinical status.

There is ample evidence that gamma activity is disrupted in schizophrenia. Interpreting these disruptions, however, is difficult. Current results suggest gamma *oscillations* are highly stimulus,

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task, and context dependent (Merker, B., 2013; Ray et al 2010; Hermes et al 2014), though it is important to note that power in the gamma band may not always reflect the presence of a true oscillation in that band. However even when present, the power of gamma oscillations fluctuates strongly in time, and is suppressed by task-irrelevant factors (Merker, B., 2013, Ray et al 2010). We interpret the fact that gamma-alone was a poorer predictor of disease status than slope to be due in part to this variability. We additionally note that there was a strong alpha peak present in the power spectra in our data (Figure 2**f**). Like gamma, this difference was significant, however the strength alpha's predictive capacity using spatial variations in power (a classification accuracy of 0.56 +/- 0.12) was still well below that of spectral slope (0.71 +/- 0.11) and also well below behavior-based predictions (0.65 +/- 0.12).

Slope and oscillatory power may be complementary

In this selective attention dataset we observed that spectral slope, a measure of neural background noise, better predicts schizophrenia compared to band-specific power changes. Combined with previous results in cognitive aging (Voytek et al, 2015), we argue that neural noise, as indexed via spectral slope, can serve as a useful biomarker in clinical populations. The ample literature reporting band specific anomalies in schizophrenia patients complement the range of studies that suggest oscillatory coupling is relevant for healthy cognitive function. However, if our results are representative, future work should consider isolating changes in band-specific power from changes in background noise.

Based on the strength of our classification results, we expect slope to prove a reliable predictor of schizophrenia status outside this single experiment. While we do not expect slope will explain the wealth of band-specific variations across the literature, we believe that measurements of band-limited power and slope may prove to be complementary pieces of information that will improve the utility of electrophysiology as a clinical biomarker. Indeed, both oscillations and noise may be needed to understand, and computationally model, the complex biological interactions that are not doubt involved in generating schizophrenia pathophysiology. For example, an increase in gamma power that occurs inline with a chronic increase in inhibitory conductance (see below) may have an overall suppressive effect on neural excitability (Ray, S et al 2013) whereas in a more homeostatic condition, a gamma can instead act to increase neural gain (Womelsdorf, T. et al., 2014). That is, the functional role of gamma oscillations may change as inhibitory conductance increases. Oscillations with an abnormally strong inhibitory may act to gate or suppress information transmission (Ray & Maunsell, 2013, Börgers & Kopell, 2008), whereas gamma oscillations operating in a more balanced regime may instead amplify information flow (Womelsdorf, T. et al., 2014).

Steeper slope may reflect increased inhibitory conductance

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The slope of the power spectrum is described by a 1/F power law distribution. We focus here on the range from ~4-50 Hz. In this range, slope ({chi}) values vary from to 1-4 (Freeman, W.J. & Zhai, J., 2009, Podvalny, E. et al., 2015). The larger the {chi} the steeper the slope of the power spectrum.

Power laws such as the $1/f^{\chi}$ electrophysiological power spectrum arise from a large number of physical sources (Kendal, W.S., 2013). In neural electrophysiology, aspects of the power spectral slope have been attributed to shot and brownian noise (Mandelbrot, B.B. & Van Ness, J.W., 1968, Milstein, J. et al., 2009), and to network connectivity (Freeman, W.J. & Zhai, J., 2009, El Boustani, S. et al., 2009). Others use the $1/f^{\chi}$ pattern to suggest the brain is operating like a dynamical system tuned to a self-organized "critical point" (Bak, P., Tang, C. & Wiensenfeld, K., 1988,Bédard, C., Kröger, H. & Destexhe,Chaudhuri, R., He, B.J. & Wang, X., 2016). Most obviously relevant to Schizophrenia however are recent modeling results, which link changes in power spectral properties to changes in synaptic activity (Miller, K.J., 2010) and excitatory and inhibitory currents (Destexhe, A. & Rudolph, M., 2004). These efforts, which relate synaptic fluctuations in the membrane voltage to local field potentials (LFP), are supported by recent combined recordings of LFP and single units in human subjects showing that slower inhibitory time constants dominate the LFP (Dehghani, N. et al., 2016)..

In response to these results, we have recently developed a computational model to infer changes in excitatory-inhibitory balance directly from spectral slope in LFP recordings (Gao, et al, 2016). In this model, increasing the inhibitory conductance, or the time constant of inhibitory kinetics, decreases slope. Conversely, decreasing the proportion of inhibitory activity, or increasing excitatory conductance, increases slope. That is, our model suggests the decreases in slope we report here may be a direct consequence of increased inhibitory conductances. This increase is presumably a homeostatic response to the decreased number of inhibitory neurons associated with schizophrenia. Within a limit, increasing the strength of individual synapses can compensate for the overall reduction in inhibitory interneurons, however this may reach a pathological tipping point over time.

If the observed increase in spectral slope is caused by a loss of inhibition and the corresponding homeostatic adjustment, this may explain why slope is the superior predictor of disease status. Loss of inhibition appears as a widespread and chronic phenomenon in schizophrenia. That is while excitatory-inhibitory imbalance ultimately affects oscillatory coupling, oscillatory changes depend on a number of external factors (*e.g.,* attention, stimulus contrast, size, task context, goals). These external factors may act as dynamic "confounds" that are shared between control and schizophrenia subjects undertaking the same cognitive task. Meanwhile slope may reflect a more fundamental physiological index - inhibitory conductance - allowing for the observed improvement in classification performance.

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Drug effects, and other important caveats.

We selected schizophrenia patients diagnosed within the last five years in an effort to minimize drug effects contaminating the electrophysiological results. However both the slope and band specific changes we report here may never the less be due, perhaps in part, to pharmacological confounds. Controlling for this possibility in a chronic condition like schizophrenia is difficult. Ultimately we will need to confirm these results in drug free individuals and in animal models. However more elaborate experiments require an initial robust result, which is what we report here.

We have reported results for a single selective attention task. Despite our relatively large patient pool (n=31), the results require confirmation in other tasks and, ideally, in other laboratories. Concurrent with the line of research outlined here, we are also investigating 1/f noise changes with healthy cognitive aging. The slope *increase* we previously reported with age in ECoG data (Voytek et al 2015) have already been replicated by independent researchers (Waschke et al, 2017). This offers some optimism our schizophrenia related 1/f changes will prove similarly robust.

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