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EEG Biomarkers of reduced inhibition in human cortical microcircuits in depression

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Abstract

Major depressive disorder (depression) is a complex condition that involves multiple physiological mechanisms, spanning a range of spatial scales. Altered cortical inhibition is associated with treatment-resistant depression, and reduced dendritic inhibition by somatostatin-expressing (SST) interneurons has been strongly implicated in this aspect of the pathology. However, whether the effects of reduced SST inhibition on microcircuit activity have signatures detectible in electroencephalography (EEG) signals remains unknown. We used detailed models of human cortical layer 2/3 microcircuits with normal or reduced SST inhibition to simulate resting-state activity together with EEG signals in health and depression. We first show that the healthy microcircuit models exhibit emergent key features of resting-state EEG. We then simulated EEG from depression microcircuits and found a significant power increase in theta, alpha and low beta frequencies (4 – 15 Hz). Following spectral decomposition, we show that the power increase involved a combination of aperiodic broadband component, and a periodic theta and low beta components. Neuronal spiking showed a spike preference for the phase preceding the EEG trough, which did not differ between conditions. Our study thus used detailed computational models to identify EEG biomarkers of reduced SST inhibition in human cortical microcircuits in depression, which may serve to improve the diagnosis and stratification of depression subtypes, and in monitoring the effects of pharmacological modulation of inhibition for treating depression.

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Introduction

Major depressive disorder (depression) is a leading cause of disability worldwide[1] and involves varying mechanisms and symptoms[2,3]. Consequently, a significant proportion of patients remain resistant to antidepressants[4] and second-line treatments[5]. Electro-encephalography (EEG) offers a non-invasive and cost-effective method for brain signal-based biomarkers to improve diagnosis, monitoring and treatment of depression subtypes[6,7]. However, the multi-scale mechanisms of depression and their link to clinically-relevant brain signals remain poorly understood.

There is growing evidence that reduced cortical inhibition plays a critical role in treatment-resistant depression, especially inhibition mediated by somatostatin-expressing (SST) interneurons[8–13]. Recent studies showed a marked reduction in SST expression by SST interneurons in post-mortem tissue of depression patients, across all layers of the prefrontal cortex (PFC), indicating a decrease in SST inhibition[13–16]. In rodent models, silencing SST-mediated inhibition led to depression symptoms[12], and novel therapeutic compounds acting via positive allosteric modulation of alpha-5-gamma-aminobutyric-acid-A (α5-GABA$_A$) receptors targeted by SST interneurons resulted in pro-cognitive and anxiolytic effects[12,17]. Changes in SST-mediated inhibition on circuit activity could have signatures detectible in EEG, due to this cell type's principal role in modulating input to pyramidal (Pyr) neurons, which are the primary contributors to EEG signals[8,18]. SST interneurons provide synaptic and tonic inhibition onto the apical dendrites of Pyr neurons[19,20], and mediate lateral inhibition in the cortex[8,21,22], particularly during periods of quiet, resting wakefulness (resting state) [23]. Accordingly, previous studies indicate that reduced SST inhibition in depression increases baseline activity of Pyr neurons[9,24].

While the contribution of SST interneurons to resting-state cortical oscillations remains largely unknown, studies show a role for this cell type in modulating low-frequency oscillations. SST stimulation entrains network activity in the 5 - 30 Hz range, and SST suppression modulates theta band (4 – 8 Hz) power[25,26]. SST interneurons have also been suggested to govern network synchrony in slow-wave sleep, which is marked by slow oscillations[27]. Thus, reduced SST inhibition in depression may affect EEG low-frequency power[28]. We recently showed that a

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40% reduction in SST inhibition, estimated from post-mortem tissue studies of depression patients[13], significantly increased baseline Pyr spike rate in simulated human microcircuits[24]. However, it is still unknown if this level of reduction in SST inhibition would significantly alter baseline oscillatory dynamics detectable in EEG.

Previous studies have linked neuronal spiking to extracellular signals, although mostly using animal models and local field potential (LFP)[29–32]. Human studies have characterized LFP oscillations in cortical slices and showed phase-amplitude coupling between deep and superficial layers[33]. Others have studied the phase preference of Pyr neuron spikes relative to spindle events in intracranial EEG oscillations[34,35]. However, experimental methods are limited in their ability to characterize the effects of the cellular changes in depression on human brain signals *in vivo*, thus meriting the use of computational models. The increased availability of human neuronal electrical and synaptic connectivity data[22,36,37], provides important constraints on detailed models of human cortical microcircuitry[24] which can be used to simulate microcircuit activity in health and disease, including local circuit-generated EEG signals[38–40].

In this study, we identified EEG biomarkers of microcircuit effects due to reduced SST inhibition, as estimated from gene expression changes in depression. Using biophysically detailed models of human cortical L2/3 microcircuits, we simulated resting-state activity in health and depression together with local EEG signals. We characterized changes in resting-state EEG spectral power, and in relation to spiking activity in different neuron types, to identify biomarkers of reduced SST-mediated inhibition in depression.

Results

Human L2/3 microcircuit models reproduce human EEG features

We used our previous detailed models of human cortical L2/3 microcircuits[24] (Fig 1a) to simulate resting state spiking and EEG signals. The model microcircuits included the four key neuron types: Pyr neurons, SST interneurons, Parvalbumin-expressing interneurons (PV), and Vasoactive intestinal polypeptide-expressing interneurons (VIP). To simulate intrinsic healthy resting-state spiking activity, all neurons received random background excitatory input corresponding to baseline cortical and thalamic drive. The model microcircuits were implemented in a physical volume, enabling simulation of LFP and EEG together with microcircuit spiking (Fig 1a-d).

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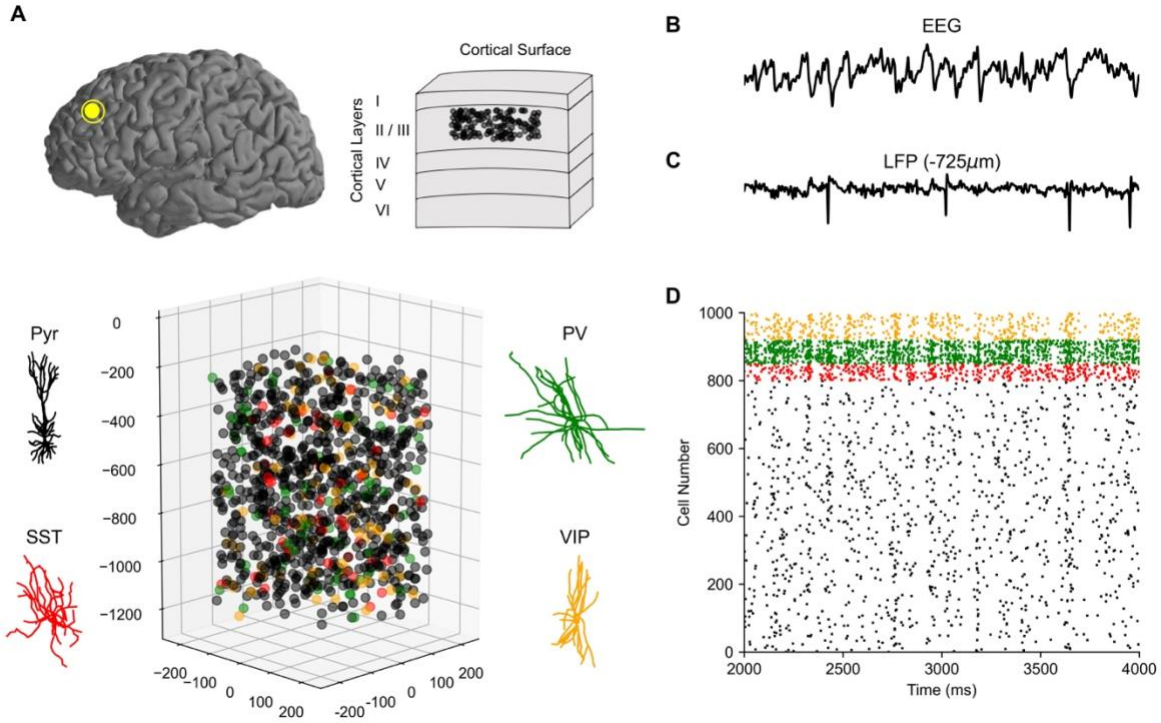

Figure 1. Simulating neuronal spiking and EEG signals from human cortical microcircuits. (a) Detailed models of human cortical microcircuits, showing somatic placement of 1000 neurons in a 500x500x950 μm^3 volume along layer 2/3 (250 - 1200 μm below pia) and reconstructed morphologies used in the neuron models. **(b – d)** Temporally aligned multi-scale simulated signals: EEG (b) from scalp electrode directly above the microcircuit; LFP signal (c) recorded at the middle of L2/3 (depth of -725 μm); Raster plot of spiking in different neurons in the microcircuit (d), color-coded according to neuron type. Neurons received background excitatory inputs to generate intrinsic circuit activity.

Baseline microcircuit activity was oscillatory, marked by synchronous spiking events (Fig 1d) and corresponding fluctuations in LFP and EEG signals (Fig 1b, c). We quantified oscillatory activity in the healthy microcircuits by calculating EEG power spectral density (PSD). The microcircuits EEG exhibited a peak in theta (4 – 8 Hz) and alpha (8 – 12 Hz) bands (n = 60 randomized microcircuits, Fig 2a) and a 1/f background trend (Fig 2a, inset). Peak frequency was 9.9 ± 0.8 Hz. We then calculated spectrograms of circuit activity to analyze the evolution of signal strength in the time-frequency domain. The spectrograms showed 34 ± 5 transient theta-alpha events per 28 s simulation, with average duration of 300 ± 15 ms (Fig 2b). The circuit simulations thus reproduced several key temporal and spectral features of resting-state human EEG. Critically, these oscillatory properties were emergent, and were not explicitly optimized for, which therefore

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constitutes an important validation of the model and demonstration of its ability to capture key properties of human cortical L2/3 microcircuit dynamics.

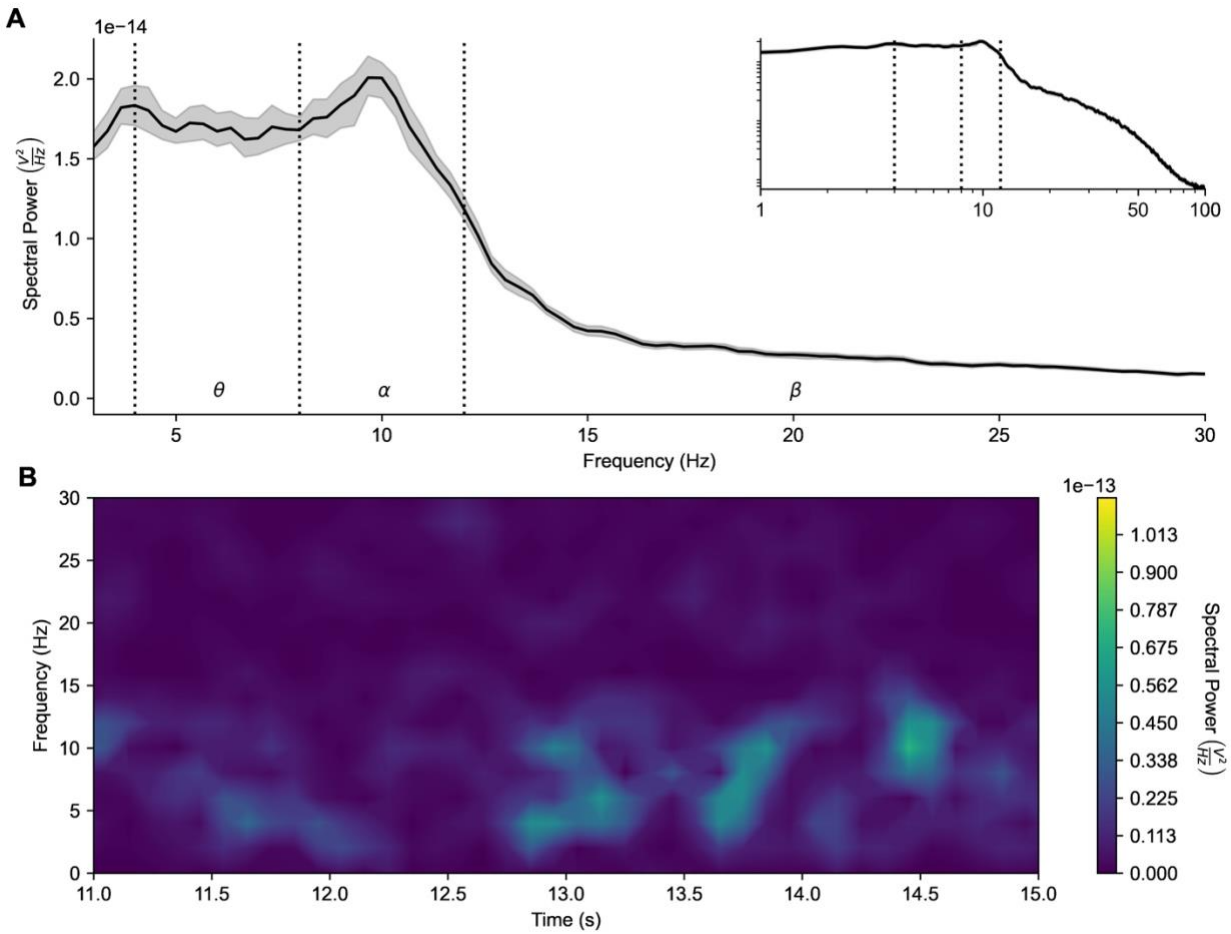

Figure 2. Models of human cortical microcircuits reproduce key features of resting-state EEG. (a) Power spectral density plot of circuit simulations (n = 60 randomized microcircuits, bootstrapped mean and 95% confidence intervals), exhibiting peak power in theta and alpha frequency bands. Inset – same power spectral density plot shown on log-log scale, illustrating the 1/f relationship between power and log frequency, inversely linear between 3-30 Hz with slope -0.98 ± 0.07. Frequency bands are delimited by dotted lines. **(b)** Example spectrogram of simulated microcircuit EEG, exhibiting theta and alpha events.

EEG biomarkers of reduced SST in depression microcircuits

We compared simulated EEG in healthy versus depression microcircuits using our previous depression models, in which SST synaptic and tonic inhibition were reduced (*n* = 60 randomized microcircuits, Fig 3a). The simulated EEG from depression microcircuits exhibited a prominent peak in theta and alpha bands (4 – 12 Hz) similarly to the healthy microcircuits, but there was a significantly increased power in these bands and in low-beta frequencies (5 – 15 Hz, 25% increase

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on average, $p < 0.05$, Cohen's $d = 1.91$, Fig 3b). We decomposed EEG PSDs into aperiodic (Fig 3c) and periodic (Fig 3d) components, to compare the distinct functional components of the absolute PSDs. There was a 43% increase in aperiodic broadband power in depression compared to healthy microcircuits (5 – 30 Hz, $p < 0.05$, Cohen's $d = 5.6$), and a 35% reduction in aperiodic exponent (healthy = 0.98 ± 0.07, depression = 0.64 ± 0.07, $p < 0.05$, Cohen's $d = 4.6$). The periodic component of the PSDs from depression microcircuits showed a 29% increase in theta power (5.6 – 8 Hz, $p < 0.05$, Cohen's $d = 1.5$), and a 63% increase in low-beta power (12 – 15 Hz, $p < 0.05$, Cohen's $d = 2.4$), but no significant change in alpha power compared to healthy microcircuits. Thus, the absolute power increase involved a combination of an aperiodic broadband component, and a periodic theta and low beta component.

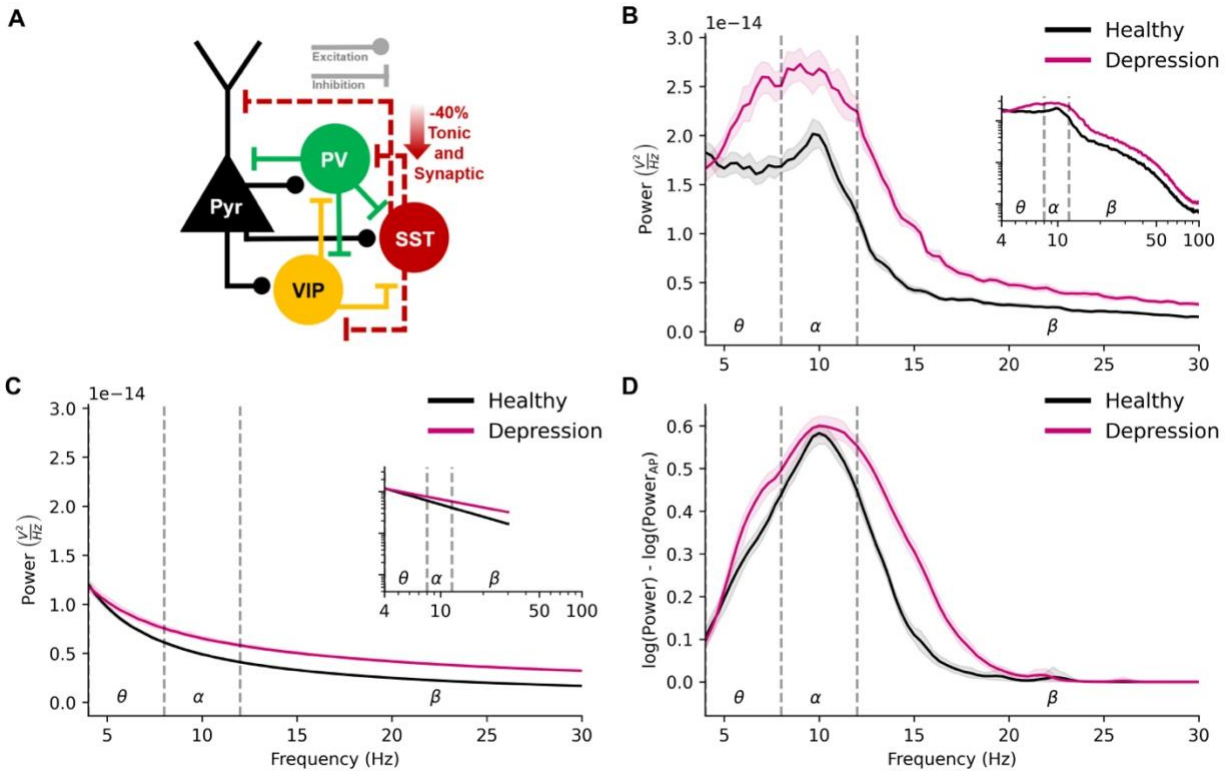

Figure 3. EEG signatures of reduced SST inhibition in depression microcircuit models. (a) Schematic connectivity diagram highlighting the key connections between different neuron types in the microcircuit. In the depression condition, dotted lines from the SST interneurons illustrate reduced synaptic and tonic inhibition onto different neuron types. **(b)** Power spectral density plot of simulated EEG from the healthy (black) and depression (magenta) microcircuit models (n = 60 randomized microcircuits per condition, bootstrapped mean and 95% confidence interval). (**c**) Fitted aperiodic component of the PSD. **(d)** Fitted periodic component of the PSD.

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We identified relationships between neuronal spiking and EEG spectral changes in depression microcircuit models by determining the EEG phase preference of the neuronal populations. The EEG time series were bandpass filtered from 4 – 12 Hz since the periodic component of the PSDs showed equally prominent theta and alpha components (Fig 4d). Spike time was then converted to phase of EEG signal by temporally aligning the bandpass-filtered signal to the angle of its Hilbert transform (Fig 4a-c). In healthy microcircuits, spiking in all neuronal types exhibited preference to the phase preceding the trough of the EEG waveform (Rayleigh's $p < 0.05$; Pyr = 268.2 ± 2.5°, SST = 266.5 ± 4.3°, PV = 282.0 ± 3.2°, VIP = 289.6 ± 2.0°). Depression microcircuits followed a similar phase preference (Rayleigh's $p < 0.05$; Pyr = 281 ± 2.2°, SST = 279.5 ± 5.0°, PV = 293.1 ± 3.0°, VIP = 295.3 ± 2.2°), but there was a decrease in preference selectivity, as quantified by population spike concentrations about the preferred phase (kurtosis, $p < 0.05$ for all; % decrease: Pyr = 12.9%, $d = 2.6$; SST = 19.3%, $d = 2.0$; PV = 21.3%, $d = 3.9$, VIP = 26.3%, $d = 5.5$).

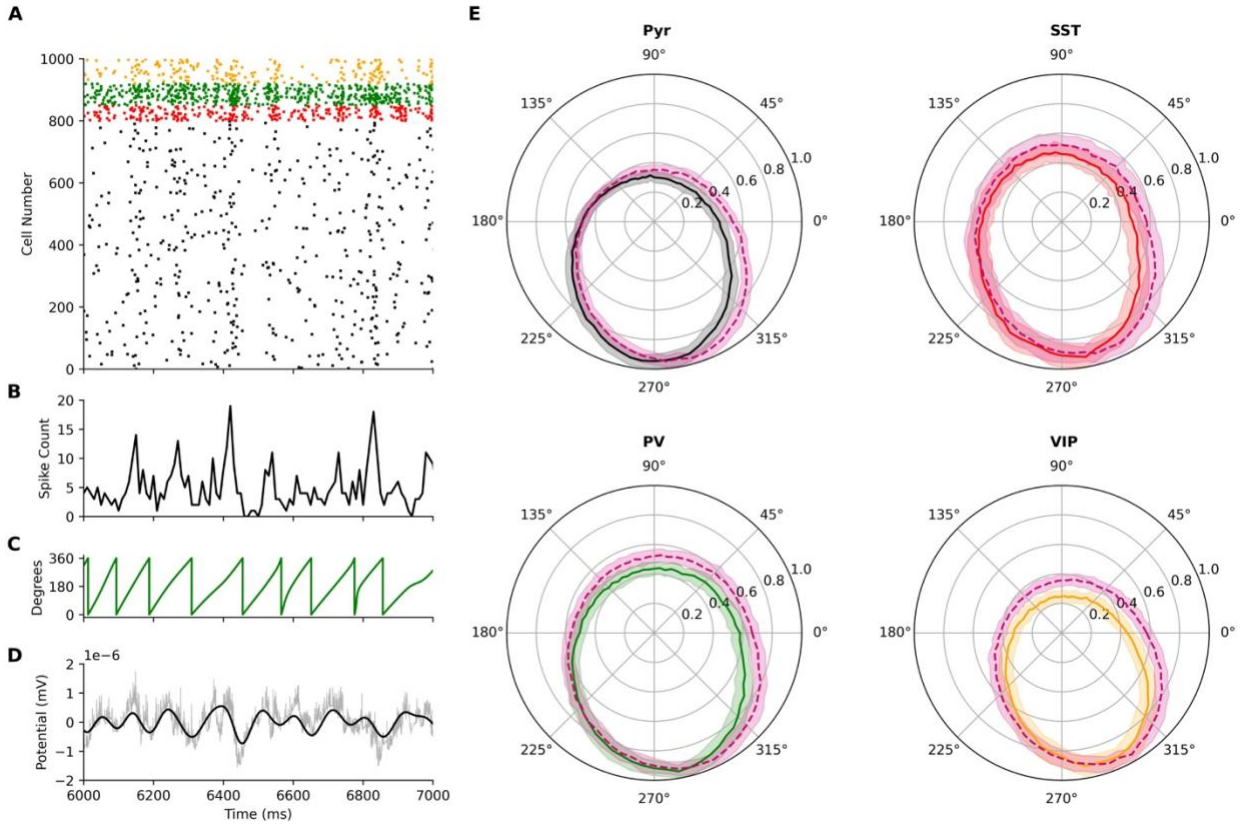

Figure 4. EEG phase preference of neuronal spiking in health and depression microcircuit models. (a-d) Temporally aligned simulated microcircuit signals used in calculating population phase-preference. **(a)** Raster plot of spiking in an example healthy microcircuit model. **(b)** Pyr population spike counts, in 10

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ms bins. **(c)** Instantaneous phase of the theta-alpha bandpass filtered EEG signal, with trough corresponding to 0˚. **(d)** Theta-alpha bandpass filtered EEG signal (black) and unfiltered EEG signal (gray). **(e)** Population spike counts relative to theta-alpha (4 – 12 Hz) bandpass filtered EEG from healthy (non-magenta) and depression microcircuits (magenta). Plots show bootstrapped mean and standard deviation normalized by peak spike count. Neuron type colors for the healthy microcircuits are as in Fig 1.

Lastly, we examined the spatial distribution of scalp-measured EEG signals generated by the microcircuit simulations using a realistic head model, and determined the distance at which it was indistinguishable from noise. We placed the simulated microcircuit dipoles into L2/3 of the dorsolateral PFC, at a location directly underneath 10-20 system electrode AF3 (Fig 5a), and used a forward solution based on a boundary-element model with realistic head geometry and conductivity to compute simulated EEG signals. The resulting time series were obtained at different electrode locations on the scalp (Fig 5b). Difference in theta-alpha power in depression versus healthy microcircuits showed a nonuniform decay over the scalp, which was steeper laterally compared to medially (c.f. contour lines in Fig 5c). A significant difference in power was only seen in electrodes corresponding to the ventral portion of the left dlPFC (AF3, the electrode above source) and the left orbitofrontal cortex (FP1 and FPz - 29mm and 46mm from source, respectively). The EEG biomarkers corresponding to microcircuit changes in depression were therefore mostly localized spatially.

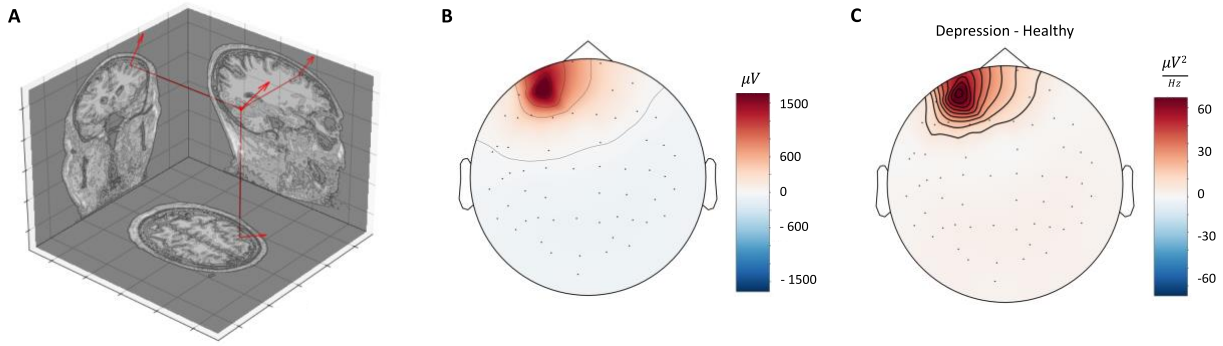

Figure 5: Topographic distribution of microcircuit EEG signal in a realistic head model. (a) Microcircuit dipole placement and orientation in the grey matter of the dlPFC in a head model, perpendicular to the cortical surface and in the middle of L2/3 (depth -725 μm). **(b)** Corresponding average potential spread of the microcircuit EEG signal to the EEG electrodes across the head. **(c)** Distribution of the difference in spectral power for depression versus healthy simulated microcircuit signals for theta-alpha band (4 – 12 Hz).

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Discussion

In this study, we identified the signatures of reduced cortical inhibition in depression on clinically relevant brain signals of resting-state activity using detailed models of human cortical microcircuits. Depression microcircuits with reduced SST interneuron inhibition showed an increase in absolute theta, alpha and low beta power, which involved a broadband increase together with a periodic increase in theta and low-beta activity. These signatures may be used as biomarkers to stratify depression subtypes corresponding to altered inhibition, which are particularly associated with treatment-resistant depression[41]. By simulating both spiking and EEG in detailed microcircuits, we showed that neuronal spiking had a marked preference for the phase preceding the trough of theta-alpha EEG band in both conditions. Our results provide mechanistic links between reduced SST inhibition and candidate biomarkers in EEG signals. These findings have multiple clinical applications, such as improving patient stratification and monitoring the effects of therapeutic compounds targeting SST interneuron inhibition.

Increased theta, alpha, and low beta power in our simulated depression microcircuits are in agreement with several previous depression studies, and are correlated with diagnosis, severity, and treatment response [7,42–47]. Particularly, increased frontal theta power is seen in both the early and late stages of depression, indicating a consistent circuit mechanism underlying the pathology[43–46]. Further, increased frontal theta power is predictive of second line treatment response targeting cortical inhibition in treatment resistant depression [46]. Thus, our results provide support for reduced SST inhibition as a principal mechanism of treatment-resistant depression, and show that it could be detectible in its early stages by increased low frequency power[43,45,48–50]. Future studies relating our simulated EEG biomarkers to experimental EEG and depression features will further establish the link to disease stage, subtype and severity. The increased aperiodic broadband power and decreased aperiodic slope in our depression microcircuits are consistent with the respective effects of increased excitation-inhibition ratio and increased baseline activity[51–53], which in our simulations resulted from reduced SST inhibition. Increased rhythmic theta and low beta activity, but not alpha, may explain a lack of change in relative alpha power seen previously and lend more functional significance to theta and low beta frequencies[54–57]. As previous studies have shown that theta waves modulate network excitability[58], the increased theta activity in depression microcircuits may have further functional consequences via altering cortical dynamics and processing. In summary, our results

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show that altered inhibition in microscale brain circuits in depression is reflected in key features of the EEG spectral density, which can be used to better stratify depression subtype and severity.

Our biophysical models of human cortical microcircuits reproduce the two most ubiquitous features of human resting state EEG: a prominent low-frequency (4 – 12 Hz) peak power and 1/f aperiodic trend [59,60]. In experimental EEG recordings, this low-frequency peak is accentuated when subjects are relaxed with their eyes closed and has the highest test-retest reliability of all spectral features[61]. While recurrent rhythmic activity generated within cortico-thalamic loops is believed to contribute strongly to scalp-measured EEG alpha, cortico-cortical interactions have also been shown to generate alpha activity in top-down processing[62]. Further, it has been shown that cortical Pyr neurons significantly contribute to and sustain theta and alpha-phasic firing due to intrinsic properties and recurrent activity[62–64]. The key features of human EEG reproduced by our microcircuit models were not explicitly constrained for, but rather emerged from the interaction of human neuronal electrical properties, synaptic connectivity, and baseline firing rates. This provides a validation of the models and indicates that they contain circuit motifs responsible for generating realistic microcircuit activity. It will be of interest in future studies to use the models for further elucidating the cellular mechanisms of oscillatory generation, especially in brain states other than rest and during cortical processing, which involve other frequency bands. As our models capture the key spectral EEG features seen *in vivo*, the simulated EEG signal magnitude can also be related to that of the recorded EEG by scaling to account for the difference between the number of neurons in our models compared to the millions of neurons that generate the recorded EEG at a given electrode[40,65].

We simulated surface EEG using cortical L2/3 microcircuits, as these layers are the primary contributors to the EEG signal[66]. As new human cellular data becomes available, future models that also include deeper layers (4 – 6) could further refine the estimated EEG signal and the oscillatory dynamics mediated by interactions between deep and superficial layers[35]. Through coupling the biophysical simulations with a forward solution using a realistic head model we showed that EEG signals would be fairly localized to the source and neighboring electrodes. These computational simulations can serve to further study source localization in interpreting EEG recordings, improve inverse solutions[67], give greater physiological interpretability to statistical decomposition techniques such as independent component analysis[68] and s/eLORETA[69]. This is especially relevant in depression, where distinct brain sub-regions both serve as targets for

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treatment interventions, such as the lateral/medial PFC and lateral orbitofrontal cortex[70–73], and exhibit different spectral power changes in relation to diagnosing depression stage and type[45]. While we modeled and studied a single cortical region at the microcircuit scale, future studies could simulate several microcircuits to examine how the altered circuit inhibition mechanisms affect multi-regional interactions in depression[8].

Using detailed multi-scale models of human cortical microcircuits, we were able to characterize the EEG and spike correlates of reduced SST inhibition in depression. Previous modeling studies have shown that reduced SST inhibition in depression impairs stimulus processing due to increased baseline activity and noise[24]. Our spiking-EEG phase analysis indicates that during the peak of theta-alpha phase, stimulus detection would be further impaired than at the down-phase. Our models can serve to further identify candidate EEG biomarkers of the diverse mechanisms of depression, e.g. the possible altered PV vs. SST inhibition[8], pyramidal cell atrophy and synapses loss[74–78]. Furthermore, the computational models we have developed provide a powerful tool to identify the EEG biomarkers of novel therapeutic compounds and treatments for depression[17,79] via in-silico simulations to improve treatment monitoring. Finally, our models and methodology may further serve to identify EEG biomarkers of altered cellular and circuit mechanism in other neurological diseases, such as epilepsy and schizophrenia[39,80–83].

Methods

Human cortical microcircuit models. We used our previous models of human cortical L2/3 microcircuits[24], consisting of 1000 neurons distributed in a 500x500x950μm^3 volume (250 to 1200μm below pia[84]). The model microcircuits included the four key neuron types in cortical L2/3: Pyramidal (Pyr), Somatostatin-expressing (SST), Parvalbumin-expressing (PV), and Vasoactive Intestinal Peptide-expressing (VIP) neurons. The proportions of the neuron types were: 80% Pyr, 5% SST, 7% PV, and 8% VIP in accordance with relative L2/3 neuron densities[85,86] and RNA-seq data[87,88]. The models were simulated using *NEURON*[89] and *LFPy*[38].

Resting-state activity simulations. We simulated eyes-closed resting-state by injecting the microcircuit models with background excitatory input representing cortical and thalamic drive, as

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used previously[24]. The background input was generated by random Orstein-Uhlenbeck (OU) point processes[90] placed on all neurons at the halfway point of each dendritic arbor, and 5 additional OU processes placed along the apical trunk of Pyr neurons in equal intervals, from 10% to 90% apical dendritic length. This enabled the circuit to generate recurrent activity with neuronal firing rates as measured *in vivo*[23,24,91,92]. For both healthy and depression microcircuit models (see below) we simulated 60 randomized microcircuits, for 28 seconds each.

Depression models. We used previous models of depression microcircuits[24], with 40% reduced synaptic and tonic inhibition from SST interneurons onto all other neurons, in accordance with gene expression studies in SST interneurons in post-mortem brains from depression patients[13]. For Pyr neurons, we decreased apical tonic inhibition by 40%. For each interneuron, we decreased the relative SST contribution to tonic inhibition by 40%.

Simulated microcircuit EEG. We simulated layer-averaged dipole moments together with neuronal activity using *LFPy*. Corresponding EEG time series was generated using a four-sphere volume conductor model that assumes homogeneous, isotropic, and linear (frequency independent) conductivity. The radii of the four spheres representing grey matter, cerebrospinal fluid, skull, and scalp were 79 mm, 80 mm, 85 mm, and 90 mm, respectively. The conductivity for each sphere was 0.047 S/m, 1.71 S/m, 0.02 S/m, and 0.41 S/m, respectively[93]. A fixed dipole origin was placed at the midpoint of L2/3 (-725 μm), and the EEG signal was obtained via forward solution for an EEG electrode placed on the scalp surface. EEG time series were lowpass filtered at 130 Hz. EEG power spectral density (PSD) and spectrograms were calculated using Welch's method[94], with a 3s second Hanning window for PSD, and 0.5s Hanning window for spectrograms. Both analyses used 80% window overlap.

EEG periodic and aperiodic components. We decomposed EEG PSDs into periodic and aperiodic (broadband) components using tools from the FOOOF library[51]. The aperiodic component of the PSD was a 1/f function, defined by a vertical offset and exponent parameter. Periodic components representing putative oscillations were derived using up to 4 Gaussians, defined by center frequency (mean), bandwidth (variance), and power (height).

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Population spiking phase preference. We calculated the instantaneous phase of EEG using tools from the *SciPy*[95] and *NumPy*[96] Python libraries. The EEG time series was bandpass filtered from 4 – 12 Hz, with 2 Hz padding on either end to avoid edge effects. A second order Butterworth filter was used to acquire filter coefficients, which were then passed to a linear digital filter applied forward and backwards to eliminate phase lag. The angle of the bandpass-filtered Hilbert transform was calculated and shifted by 180° to obtain the instantaneous phase of the signal with trough and peak corresponding to 0° and 180°, respectively. For each of the four neuron populations (Pyr, SST, PV, VIP), spike times were aggregated into a population spike vector and converted to corresponding phase of EEG. Spike phases were binned into 5° bins and the counts were summated over all circuits in each condition. To compare spike preference between conditions, bin counts were normalized by the maximal count.

Realistic head source modelling. The x-y-z components of microcircuit dipole moments generated from *LFPy* were imported into *MNE*[97] and downsampled to a 400 Hz sampling rate. The dipole was placed within L2/3 of the left dorsolateral PFC (MNI 30, -36, -42)[98], which has been implicated in depression[99]. We solved the forward solution using a three-layer boundary element model, as implemented in LFPy, corresponding to the inner skull, outer skull, and scalp with conductivities of 0.3 S/m, 0.006 S/m and 0.3 S/m, respectively. The resulting potential was calculated for a standard 60-channel simulated EEG electrode array.

Statistical tests. We used two-sample t-test to determine statistical significance where appropriate. We calculated Cohen's *d* to show effect size. We used Raileigh's test of non-uniformity to determine if populations had a non-uniform phase preference, and kurtosis to quantify variance around the preferred mean angle.

Data availability statement. All models and code will be available online upon publication.

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