

RESEARCH ARTICLE

Linking reduced prefrontal microcircuit inhibition in schizophrenia to EEG biomarkers in silico

Sana Rosanally^{1,2}, Frank Mazza^{1,2,3}, Heng Kang Yao^{1,2}, Faraz Moghbel^{1,2}, Hannah Seo^{1,2}, Etay Hay^{1,2,4*}

1 Krembil Centre for Neuroinformatics, Centre for Addiction and Mental Health, Toronto, Ontario, Canada, **2** Department of Physiology, University of Toronto, Toronto, Ontario, Canada, **3** Schulich School of Medicine, University of Western Ontario, London, Ontario, Canada, **4** Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada

✉ These authors contributed equally to this work.
* etay.hay@camh.ca



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Abstract

Reduced cortical inhibition by parvalbumin-expressing (PV) interneurons in schizophrenia is thought to be associated with impaired processing in the prefrontal cortex and altered EEG signals such as oddball mismatch negativity (MMN). Recent studies also suggest loss of somatostatin (SST) interneuron inhibition. However, establishing the link between reduced interneuron inhibition and reduced MMN experimentally in humans is currently not possible. To overcome these challenges, we simulated spiking activity and EEG during baseline and oddball response in detailed models of human prefrontal microcircuits in health and schizophrenia, with reduced PV and SST interneuron inhibition as constrained by postmortem patient data. We showed that reduced PV interneuron inhibition can account for the decreased MMN amplitude seen in schizophrenia, with a threshold below which the amplitude effect was low as seen in at-risk patients. In contrast, reduced SST interneuron inhibition did not affect the MMN amplitude. We further showed that both types of inhibition loss were necessary to account for changes in resting EEG in schizophrenia, with reduced SST interneuron inhibition increasing broadband power, and reduced PV and SST interneuron inhibition both leading to a right shift from alpha to beta frequencies. Our study thus links reduced PV and SST interneuron inhibition in schizophrenia to distinct EEG biomarkers that can serve to improve stratification and early detection using non-invasive brain signals.

Author summary

Reduced cortical interneuron inhibition in schizophrenia is implicated in impaired processing in prefrontal cortex and altered EEG signal mismatch

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negativity (MMN) during oddball task. However, establishing the link between reduced interneuron inhibition and reduced MMN experimentally in humans is currently not possible. To overcome these challenges, we simulated spiking activity and EEG during baseline and oddball response in detailed models of human prefrontal microcircuits in health and schizophrenia, with reduced parvalbumin (PV) and somatostatin (SST) interneuron inhibition constrained by postmortem patient data. We showed that reduced PV interneuron inhibition can account for the decreased MMN amplitude in schizophrenia, whereas reduced SST interneuron inhibition did not affect the MMN, but both types of inhibition loss contributed to changes in resting EEG in schizophrenia. Our study links reduced PV and SST interneuron inhibition in schizophrenia to distinct EEG biomarkers that can serve to improve stratification and early detection using non-invasive brain signals.

Introduction

Cortical dysfunction in schizophrenia involves changes in processing across brain areas [1] and at the cellular and microcircuit level [2–5]. Altered brain activity underlying impairments in schizophrenia may also have signatures in brain signals obtained by electroencephalography (EEG) [1,6], which offer a promising source of objective and quantitative biomarkers [7] to improve patient stratification and early diagnosis, especially when symptoms are mild [8]. However, the link between cellular and microcircuit mechanisms of schizophrenia to altered cortical activity and EEG biomarkers remains to be established.

Previous studies indicate that changes in the microcircuitry of the prefrontal cortex (PFC) may underly impaired cognitive functions in schizophrenia [9–11]. Reduced inhibition has been implicated as a key mechanism, whereby post-mortem studies in schizophrenia patients found a reduced expression of parvalbumin (PV) and GAD67 in PV interneurons in PFC [2,5,12,13]. PV interneurons provide important and timely inhibition of pyramidal (Pyr) neurons [14], and modulate brain oscillations in high frequencies (gamma band, 20 – 80 Hz) [15,16] which support cognitive functions in PFC [17]. Accordingly, reduced GABA neurotransmission in the PFC has been associated with impaired function [18], and with altered brain oscillations and impaired cognition in schizophrenia [19,20]. Reduced PV expression in PV interneurons indicates a loss of functionality in these neurons, supported by the accompanying decreased GAD67 expression that directly influence synaptic inhibition, as GAD67 knock-out in PFC PV interneurons in rodents resulted in loss of inhibition from PV to Pyr neurons and consequently overexcitability of Pyr neurons [21]. Overall, reduced PV and GAD67 expression in PV interneurons in schizophrenia thus indicates a reduced synaptic inhibition from these interneurons to other neurons in the microcircuit.

Another altered mechanism of PV interneurons implicated in schizophrenia is reduced excitatory innervation via NMDA receptors. Post-mortem studies found

that NMDA subunit NR2A expression was mostly absent in more than half of PV interneurons in PFC in schizophrenia [22–24], whereas there was no significant change found in other NMDA subunits NR2B-D [25]. NR2A directly affects the potency of glutamate and thus mediates excitatory activity in NMDA receptors [26]. Furthermore, rodent studies found that working memory depended on NR2A in the PFC as they mediate the majority of evoked NMDA receptor currents in layer 2/3 Pyr neurons [27]. The role of NMDA dysfunction in PV interneurons in schizophrenia is further supported by studies showing that administration of NMDA antagonists induced schizophrenia-like symptoms [28] and reduced GAD67 and PV expression in cortex [29].

In addition to changes in PV interneurons, recent studies also showed reduced somatostatin (SST) expression in SST interneurons in schizophrenia [5], indicating a loss of inhibition from these interneurons as well. SST interneurons mediate baseline activity [30,31] through lateral inhibition [32,33], modulate brain oscillations in low frequencies (theta and alpha band, 4–12 Hz) [34,35], and modulate cortical response [36]. However, reduced SST interneuron inhibition is implicated in a variety of other conditions such as aging and depression [37] and its role in schizophrenia remains unknown, whereas reduced PV interneuron inhibition has been indicated as a more specific mechanism of schizophrenia.

Altered PFC microcircuitry in schizophrenia may also underlie the respective changes seen in EEG signals [38]. In particular during auditory oddball task, which involves the presentation of a series of same-frequency tones followed by a different tone (the deviant tone or “oddball”), schizophrenia patients show a reduced performance and a smaller difference between the PFC EEG signal response to the standard and deviant tones ~100–160 ms post-stimulus, referred to as mismatch negativity (MMN) [6,39]. Recordings of spike activity in monkey auditory cortex and PFC show that microcircuits in PFC process the difference between the expected and actual subsequent stimulus and generate a larger spike response to oddball stimuli, which is associated with MMN in the EEG [40]. Changes in PV or SST interneuron inhibition can lead to detectable signatures in EEG signals since these interneurons closely modulate inputs to Pyr neurons, which are the main contributors to EEG signals [41]. In addition to altered EEG during oddball response, studies found changes in resting-state EEG in schizophrenia such as increased theta and beta power vs decreased alpha power [42–46], but the underlying mechanisms remain unknown.

Whereas experimental studies either implicated cellular mechanisms of schizophrenia post-mortem or characterized changes in EEG features in living patients, the link between the two remains to be established in humans due to technical and ethical limitations in probing microcircuitry in the living human brain. Computational models offer a powerful tool for overcoming the challenges, and have been previously used to link altered ion channel mechanisms in schizophrenia to their EEG biomarkers [47]. Previous studies mainly used rodent microcircuit models to study mechanisms of EEG in health and disease [47,48], but modeling human cortical microcircuits to identify these links is motivated by several reasons. Although there are many circuit and cellular similarities between rodents and humans such as intrinsic firing properties and connectivity patterns between different cell types [49,50], there remain some important differences. Inhibitory synapses from SST and PV interneurons onto Pyr neurons are stronger in humans, have lower synaptic failures and larger postsynaptic potential (PSP) amplitudes [33,51,52]. Furthermore, there is a higher connection probability between Pyr neurons in human cortical layer 2/3 [53]. Pyr neurons are larger in humans and have longer and more complex dendrites which affect input integration [54,55]. The increased availability of human neuronal and synaptic connectivity data [33,53,56] has enabled the generation of detailed models of human cortical microcircuits [57,58], which were used to simulate microcircuit activity in health and disease as well as local microcircuit-generated EEG signals, and link changes in microcircuit mechanisms to EEG biomarkers [59].

In this study, we identified EEG biomarkers of reduced PV and SST interneuron inhibition in detailed models of human PFC microcircuits in schizophrenia, which implemented two key altered PV interneuron mechanisms and reduced SST interneuron inhibition as estimated from gene expression changes in schizophrenia. We modeled oddball response as constrained by spike recordings in monkeys in previous studies and linked reduced PV vs SST interneuron inhibition to altered PFC activity, MMN and resting EEG in schizophrenia.

Results

We simulated baseline and oddball response activity in models of human PFC microcircuits in health and schizophrenia. We first modeled healthy PFC microcircuits by adapting our previous detailed models of human cortical L2/3 microcircuits (Fig 1A–B) using the proportions of Pyr neurons and PV/SST/VIP interneurons in human PFC as seen experimentally (Fig 1C). To simulate the healthy baseline activity of the PFC microcircuit, all neurons received background random excitatory input corresponding to baseline cortical and thalamic inputs. The baseline firing rates of Pyr neurons and PV interneurons in the PFC microcircuit models (Fig 1D) were within the range measured *in vivo* in humans, Pyr: 0.94 ± 0.05 Hz (experimental: 0.66 ± 0.51 Hz), PV: 7.44 ± 0.42 Hz (experimental: 2.63 ± 2.55 Hz). Baseline firing rates of SST and VIP interneurons were on the order of magnitude seen in rodents, SST: 3.28 ± 0.16 Hz (experimental: 6.3 ± 0.6 Hz), VIP: 2.22 ± 0.25 Hz (experimental: 3.7 ± 0.7 Hz). We therefore left the rest of the microcircuit parameters unaltered from the previous models. The power spectral density (PSD) of the simulated EEG from the microcircuit models during baseline activity exhibited a peak in the alpha (8–12 Hz) frequency band (Fig 1E), as well as a 1/f relationship, all of which were in line with spectral properties of human prefrontal resting-state EEG activity.

We modelled microcircuit changes in schizophrenia by implementing two key mechanisms involving PV interneuron inhibition (Fig 2A) according to human PFC post-mortem studies. The first mechanism (referred to as the output

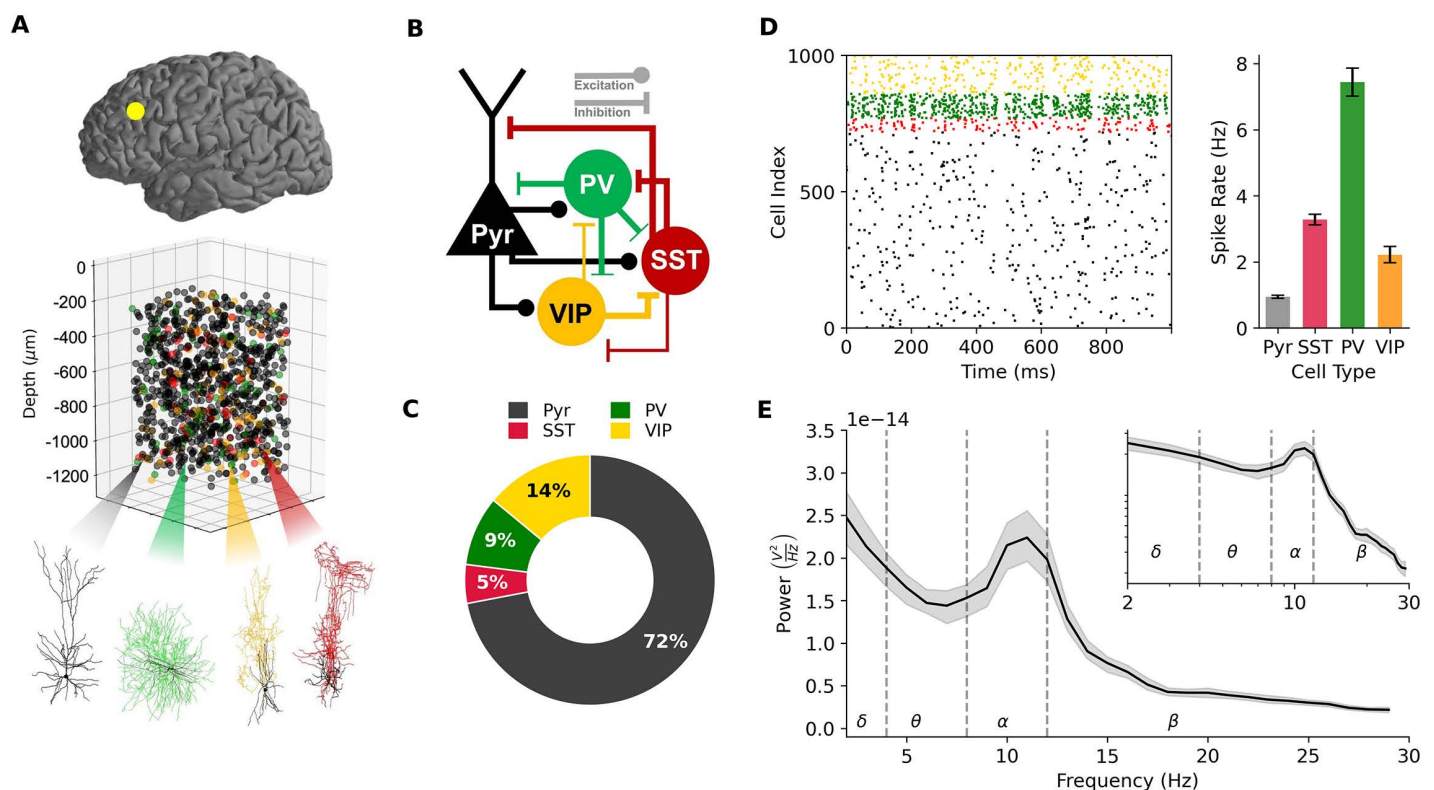


Fig 1. Detailed models of human prefrontal microcircuit baseline spiking activity and EEG. **A.** Detailed models of human PFC microcircuits showing placement of 1000 connected neurons, human neuronal morphologies of the four key neuron types (green: PV, red: SST, black: Pyr, yellow: VIP). **B.** Connectivity diagram between neuron types in the microcircuit. **C.** Cellular proportions of each neuron type: Pyr (72%), SST (5%), PV (9%), VIP (14%). **D.** Left - raster plot of neuronal spiking in the microcircuit at baseline, color-coded according to each neuron type. Right - baseline firing rates of all neurons (mean and SD, $n=30$ random microcircuits). **E.** PSD plot of simulated EEG at baseline (mean across $n=30$ random microcircuits, showing bootstrap mean and 95% confidence interval). Canonical frequency bands are shown by vertical dotted lines. Inset: the same plot in log-log scale, showing 1/f relationship.

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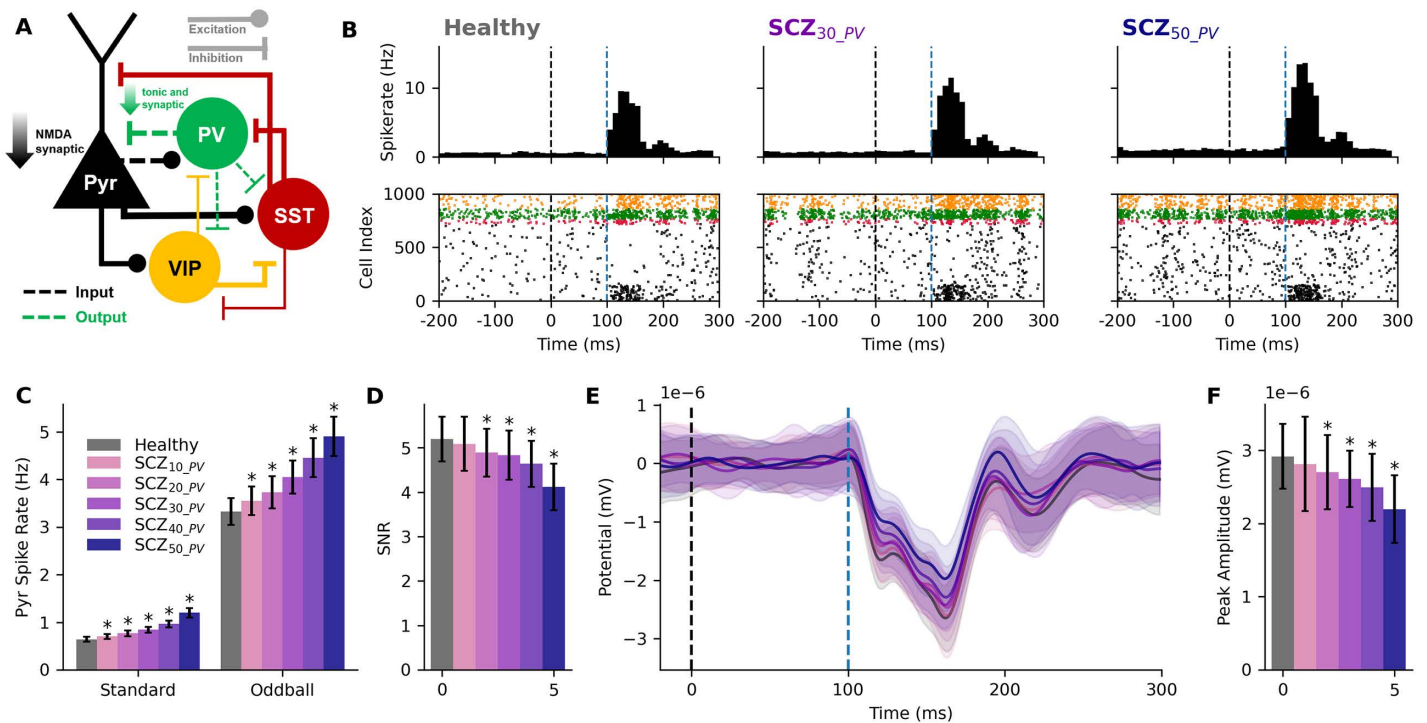


Fig 2. Simulated oddball response and MMN in healthy and schizophrenia microcircuits. **A.** Connectivity diagram of the schizophrenia microcircuit models showing the altered PV output and input mechanisms (green and black dashed lines). **B.** Peristimulus time histogram (top, $n = 50$ randomized microcircuits) and raster plot (bottom) of simulated oddball response in a healthy microcircuit (left) and schizophrenia microcircuits with 30% (middle) or 50% (right) reduced PV interneuron inhibition. Healthy models reproduced response firing rates and profiles from previous experimental studies in primates. Black dashed line denotes the external stimulus time and blue dashed line denotes PFC activation time. **C.** Average Pyr spike rate during simulated standard (baseline) and oddball response in healthy and schizophrenia microcircuits with 10–50% reduced inhibition (mean and SD). **D.** SNR in healthy and schizophrenia microcircuits. **E.** Difference between simulated ERP during oddball vs standard response in healthy and schizophrenia microcircuit models (oddball - standard response, mean and SD, $n = 50$ randomized microcircuits). **F.** Peak amplitude of MMN response in healthy and schizophrenia microcircuits. Asterisks in parts C, D, F indicate significance $p < 0.05$.

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mechanism) was a reduced PV interneuron synaptic and tonic inhibition conductance, and the second mechanism (referred to as the input mechanism) was a reduction in NMDA synaptic conductance from Pyr neurons to PV interneurons. We simulated the firing rates during response to standard tones and deviant tones (oddball) in the healthy and schizophrenia microcircuits.

We modeled healthy oddball response as recorded in primates, reproducing the firing rate profile of Pyr neurons along the period 100–160 ms post-stimulus by stimulating a population of Pyr neurons and PV and SST interneurons (Fig 2B). We used our model baseline activity as approximation of the response to standard tones, since in PFC primate recordings it did not differ significantly from baseline activity. We then applied the same stimulus paradigm to schizophrenia microcircuit models with 10–50% reduced PV interneuron inhibition, while also applying the respective reduced NMDA mechanism effect on the stimulus synapses onto PV interneurons.

Both baseline and oddball response firing rates increased linearly and moderately with reduced PV interneuron inhibition for most levels of reduction, but there was a supralinear jump in effect for higher reductions (Fig 2C). There was a steady 10% increase in baseline firing per 10% reduced inhibition, but the increase became 15% when going from 30% to 40% reduction, and 25% (> 2-fold) when going from 40% to 50% reduction. For response firing, there was a steady increase of 6% per 10% reduced inhibition, with a supralinear jump in effect of 10% (2-fold) when going from 30% to 40%

reduction, or from 40% to 50%. The effect of inhibition reduction was larger for baseline activity (healthy: 0.61 ± 0.05 Hz; SCZ₃₀: 0.80 ± 0.05 Hz, +31%, $p < 0.0005$, $d = 3.68$; SCZ₅₀: 1.14 ± 0.09 Hz, +86%, $p < 0.0005$, $d = 7.03$) compared to oddball response (healthy: 3.32 ± 0.29 Hz; SCZ₃₀: 4.05 ± 0.35 Hz, +22%, $p < 0.0005$, $d = 2.25$; SCZ₅₀: 4.90 ± 0.42 Hz, +47%, $p < 0.0005$, $d = 4.42$). Consequently, the signal-to-noise ratio (SNR) of firing rates during oddball response (signal) vs standard response (noise) decreased with inhibition reduction (Fig 2D, healthy: 5.46 ± 0.52 ; SCZ₃₀: 5.07 ± 0.58 , -7%, $p < 0.005$, $d = -0.71$; SCZ₅₀: 4.33 ± 0.54 , -21%, $p < 0.0005$, $d = -2.11$).

We determined the individual contributions of the NMDA or synaptic output mechanisms by simulating SCZ_{40_NMDA} microcircuits with only the NMDA mechanism reduced, or SCZ_{40_output} microcircuits with only reduced PV interneuron synaptic weight ($n = 50$ randomized microcircuits per condition). We found that the decrease in PV interneuron synaptic inhibition contributed to most of the effect on baseline firing rate, where SCZ_{50_output} microcircuits had a 54% increase from healthy (0.94 ± 0.06 Hz, $p < 0.0005$, $d = 5.78$), compared to 86% increase in SCZ₅₀ microcircuits (that included both mechanisms) and only a 16% increase in SCZ_{50_NMDA} microcircuits (0.71 ± 0.06 Hz, $p < 0.0005$, $d = 1.81$). Similarly, SCZ_{50_output} microcircuits had a larger effect on the response rate, leading to a 41% increase (4.69 ± 0.47 Hz, $p < 0.0005$, $d = 3.48$), compared to 47% increase in SCZ₅₀ microcircuits and only a 9% increase in SCZ_{50_NMDA} microcircuits (3.62 ± 0.34 Hz, $p < 0.0005$, $d = 0.95$). SCZ_{50_output} microcircuits accounted for about half of the effect on SNR, with a -8% decrease (5.00 ± 0.55 , $p < 0.0005$, $d = -0.85$), compared to -21% decrease in SCZ₅₀ microcircuits.

To determine the effect of reduced PV interneuron inhibition on the MMN amplitude of the event related potential (ERP) during oddball response, we simulated the EEG from the microcircuits during baseline and oddball response and plotted the difference (Fig 2E). The MMN amplitude in schizophrenia microcircuits decreased linearly and moderately with inhibition reduction, involving a -5% decrease in amplitude per 10% reduced inhibition, but there was a supralinear jump in effect to a -11% (2-fold) decrease in amplitude when going from 40% to 50% reduction (Fig 2E and 2F; healthy: 2.92 ± 0.45 nV; SCZ₃₀: 2.61 ± 0.39 nV, -10%, $p < 0.05$, $d = -0.72$; SCZ₄₀: 2.50 ± 0.46 nV, -14%, $p < 0.05$, $d = -0.93$; SCZ₅₀: 2.2 ± 0.47 nV, -25%, $p < 0.05$, $d = -1.58$). The PV interneuron synaptic inhibition mechanism contributed more to the ERP effect, with a decrease of -11.7% in SCZ_{50_output} microcircuits (2.58 ± 0.5 nV, $p < 0.05$, $d = -0.71$), compared to -5.9% in SCZ_{40_NMDA} microcircuits (2.75 ± 0.50 nV, $p > 0.05$, $d = -0.36$), and -25% in SCZ₅₀ microcircuits.

We next compared the effects of reduced PV and SST interneuron inhibition, by simulating schizophrenia microcircuits with either 50% reduced PV or SST interneuron inhibition (SCZ_{50_PV} or SCZ_{50_SST}, respectively) or both PV and SST interneurons (SCZ_{50_PV+SST}). Baseline Pyr neuron firing rates (Fig 3A) increased to a similar extent in microcircuits with reduced

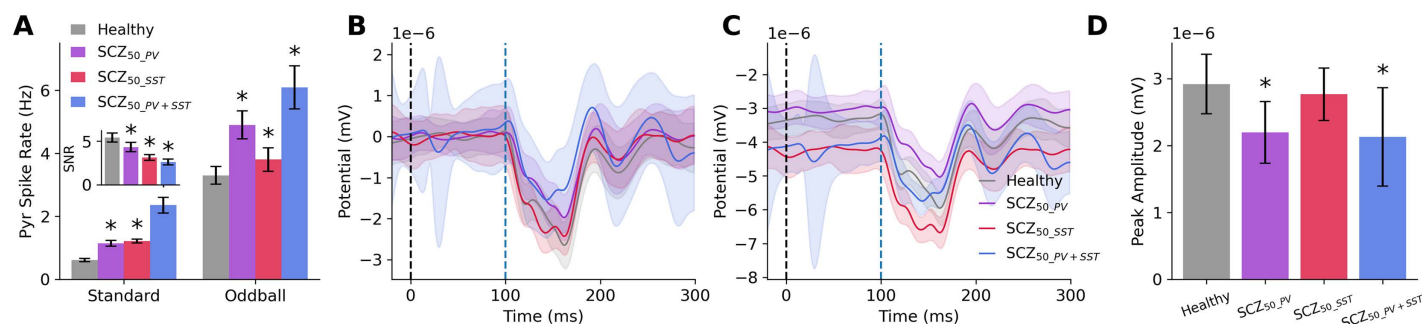


Fig 3. Effects of PV vs SST interneuron inhibition on oddball response and MMN. **A.** Pyr neuron spike rate during simulated standard and oddball response in healthy and schizophrenia microcircuits with either 50% reduced PV (purple) or SST (red) interneuron inhibition or both (blue; $n = 50$ randomized microcircuits per condition). Inset: SNR of Pyr neurons in the different conditions. **B.** Difference between simulated ERP during oddball vs standard response in healthy and the different schizophrenia microcircuit models (oddball - standard response). Black and blue dashed lines denote stimulus and PFC activation times, respectively. **C.** Simulated ERP during response to oddball alone. **D.** Peak amplitude of MMN response in healthy and schizophrenia. All plots show mean and SD. Asterisks indicate significance $p < 0.05$.

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PV or SST interneuron inhibition (SCZ_{50_PV} : 1.14 ± 0.09 Hz, +86%, $p < 0.0005$, $d = 7.03$; SCZ_{50_SST} : 1.22 ± 0.06 Hz, +99%, $p < 0.0005$, $d = 11.14$). The effect in SCZ_{50_PV+SST} was larger than the sum of the separate effects (2.35 ± 0.25 Hz, +285%, $p < 0.0005$, $d = 9.54$). Oddball response increased in SCZ_{50_PV} (4.90 ± 0.42 Hz, +47%, $p < 0.0005$, $d = 4.42$), with a minor effect in SCZ_{50_SST} (3.79 ± 0.37 Hz, +14%, $p < 0.0005$, $d = 1.40$). The combined effect in SCZ_{50_PV+SST} was larger than the sum of the separate effects (6.06 ± 0.68 Hz, +82%, $p < 0.0005$, $d = 5.27$). The SNR decreased in all schizophrenia microcircuits, with a larger effect for SCZ_{50_SST} (3.12 ± 0.32 , -43%, $p < 0.0005$, $d = -5.40$, Fig 3A) compared to SCZ_{50_PV} (4.33 ± 0.54 , -21%, $p < 0.0005$, $d = -2.11$), and the combined effect in SCZ_{50_PV+SST} was approximately the sum of the separate effects (2.60 ± 0.33 , -52%, $p < 0.0005$, $d = -6.51$).

Interestingly, schizophrenia microcircuits with reduced SST interneuron inhibition did not have an altered MMN compared to healthy (SCZ_{50_SST} : 2.98 ± 0.44 nV, $p = 0.54$, Cohen's $d = -0.12$, Fig 3B and 3D). Even when combined with reduced PV interneuron inhibition, the effect did not differ ($p = 0.32$) from that seen in microcircuit with reduced PV interneuron inhibition alone (SCZ_{50_PV+SST} : -27.1%, 2.13 ± 0.74 nV, $p < 0.001$, $d = -1.29$; SCZ_{50_PV} : -24.7%, 2.20 ± 0.47 nV, $p < 0.001$, $d = -1.58$). The reason for this was because reduced SST interneuron inhibition affected both baseline (-14%, $p < 0.0005$, Cohen's $d = 0.9$, Fig 3C) and oddball ERP (-9%, $p < 0.0005$, Cohen's $d = 0.8$), and the changes were cancelled out in the difference waveform used to measure MMN amplitude. This was seen also when examining different combinations of reduced SST (20, 50%) and PV (20, 50%) interneuron inhibition. Reducing SST inhibition by 20% or 50% together with reducing PV inhibition by 50% resulted in a decrease of -27.7% and -27.1% in oddball ERP amplitude, respectively, a similar effect to reducing PV inhibition alone (-24.7%, $p > 0.05$). Similarly, reducing SST inhibition by 20% or 50% together with reducing PV inhibition by 20% resulted in -5.2% and -8.7%, respectively, similarly to when reducing PV inhibition by 20% alone (-7.4%, $p > 0.05$).

We next characterized signatures of the altered inhibition effects on simulated resting-state EEG by comparing the PSD in healthy and schizophrenia microcircuit models (Fig 4). Simulated EEG from schizophrenia microcircuits with reduced PV interneuron inhibition showed a prominent peak in the alpha band (8–12 Hz) as the healthy microcircuit models but exhibited a rightward shift (Fig 4A). We decomposed the EEG PSD into aperiodic (Fig 4B) and periodic (Fig 4C) components to compare the distinct functional components of PSD. There were no major changes in aperiodic broadband power (Fig 4B), but there was a large rightward shift in periodic peak alpha frequency from 11.2 to 12.7 Hz in SCZ_{40_PV} compared to healthy (+13%, $p < 0.05$, $d = 0.34$, Fig 4C), evident also in a large increase in low beta (12 – 20 Hz) power compared to healthy (+41%, $p < 0.0005$, $d = 1.39$). There was only a minor change in peak frequency in SCZ_{20_PV} ($p = 0.24$).

SCZ_{40_SST} microcircuits with reduced SST interneuron inhibition showed a similar shift in peak frequency to 12.6 Hz (+13%, $p < 0.0005$, $d = 0.7$, Fig 4D and 4F) but also increased power in multiple bands (Fig 4D, alpha: +11%, $p = 0.035$, $d = 0.43$; beta: +125%, $p < 0.0005$, $d = 3.5$). Correspondingly, unlike SCZ_{40_PV} microcircuits which showed no change in aperiodic features, SCZ_{40_SST} microcircuits showed a decrease in aperiodic exponent (-17%, $p < 0.0005$, $d = -1.03$, Fig 4E) and an increase in broadband power (+36%, $p < 0.0005$, $d = 21.62$).

SCZ_{40_PV+SST} microcircuits had altered PSD that combined the effects of PV and SST interneuron inhibition reduction, with a larger right shift in peak frequency from alpha to beta (11.2 to 14.4 Hz, +28%, $p < 0.0005$, $d = 1.75$, Fig 4D and 4F), though also a decrease in absolute power in delta (-27%, $p < 0.0005$, $d = -1.08$). SCZ_{40_PV+SST} microcircuits exhibited a similar decrease in aperiodic exponent (-23%, $p < 0.0005$, $d = -1.51$, Fig 4E) and increase in broadband power (+21%, $p < 0.0005$, $d = 1.09$), but also showed a decrease in offset (-21%, $p < 0.01$, $d = -0.52$).

Discussion

Our study mechanistically links altered cell-specific inhibition with clinically relevant EEG changes in schizophrenia. Using detailed simulations of baseline activity and oddball response of human prefrontal microcircuits constrained by human cellular, circuit and gene-expression data in health and schizophrenia, we showed that reduced PV interneuron inhibition in schizophrenia can account for the decrease in MMN amplitude seen in patients, whereas reduced SST interneuron

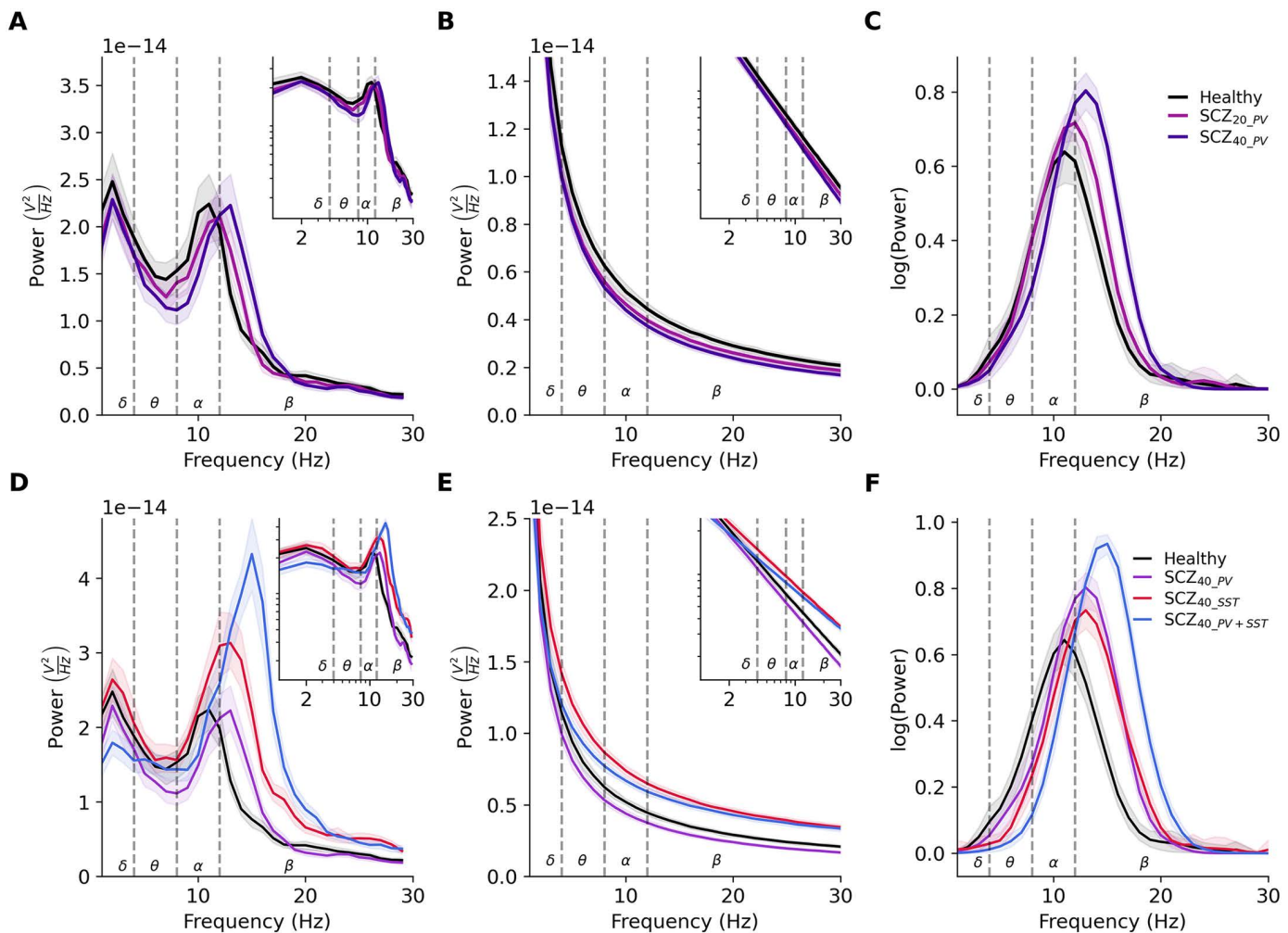


Fig 4. Resting-state EEG signatures of reduced PV vs SST interneuron inhibition in schizophrenia microcircuit models. **A.** PSD of simulated EEG from the healthy (black) and schizophrenia microcircuit models with 20% (light purple) and 40% (dark purple) reduced PV interneuron inhibition ($n=30$ randomized microcircuits per condition, bootstrapped mean and 95% confidence interval). Insets show the same PSD on the log-log scale. Dashed lines delimit the frequency bands. **B-C.** Aperiodic (B) and periodic (C) components of the PSD in healthy and schizophrenia microcircuits with reduced PV interneuron inhibition. **D.** PSD of simulated resting-state EEG from healthy (black) and schizophrenia microcircuit models with either 40% reduced PV (purple) or SST (red) interneuron inhibition or both (blue; $n=25$ randomized microcircuits per condition, bootstrapped mean). **E-F.** Aperiodic (E) and periodic (F) components of the PSD in the healthy and schizophrenia microcircuits with reduced PV vs SST interneuron inhibition.

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inhibition effects were limited to resting EEG. Our results thus establish PV and SST interneuron inhibition as target mechanisms for new treatments and indicate a primary role of PV interneuron inhibition as an underlying mechanism in schizophrenia. Moreover, our results show a threshold effect of reduced inhibition and make testable quantitative predictions about the degree of reduced inhibition that underlies decreased MMN amplitude in different severities, which may improve the subtyping of schizophrenia and early detection of the disorder when it is still largely asymptomatic.

Our results establish a primary role of reduced PV interneuron inhibition as an underlying mechanism of the decreased MMN amplitude seen in patients [60,61], and thus validate previous hypotheses [62]. The lack of effect of reduced SST interneuron inhibition on MMN is supported by the role of these interneurons in maintaining baseline activity [30,31], which in our simulations led to changes in both baseline ERP and oddball ERP that cancelled each other. Interestingly,

the reduction in MMN amplitude had a threshold effect, with a 50% inhibition reduction leading to 25% decrease in MMN, within the range seen in schizophrenia patients [60,61]. Smaller levels of reduced inhibition (10–40%) led to a milder effect on MMN which correspond well with the 15% decrease seen on average in individuals at clinically high risk for schizophrenia [8,63]. Our results thus suggest that the at-risk population may already have a reduced PV interneuron inhibition, which may underlie the milder symptoms that later develop into more severe symptoms in schizophrenia [63]. Thus, our models of schizophrenia PFC microcircuits characterize the implications of different levels of reduced PV interneuron inhibition on the MMN response, which enable a mechanistic stratification and improved early detection and outcome prediction in at-risk population [61].

Although reduced SST interneuron inhibition on its own did not affect the MMN amplitude, the decreased MMN amplitude in schizophrenia microcircuits was mediated by the reduced PV interneuron inhibition disinhibiting SST interneurons, consequently enhancing their inhibition of the distal apical dendrites of Pyr neurons [32]. The apical dendrites generally act as a negative current source by receiving a large number of excitatory inputs, and as the distance between the apical dendrites source and the soma and basal dendrites sink is large, their difference in potential is the major contributor of the dipole from the neuron. Increased SST interneuron inhibition of the apical dendrites due to the reduced PV interneuron inhibition makes the apical dendrites less positively charged, which consequently reduces the electric dipole of the neuron and thus the MMN amplitude measured by EEG [64].

Reduced inhibition also accounted well for changes seen in resting state EEG in schizophrenia. The rightward shift in the peak frequency from high-alpha band to low-beta band due to reduced PV or SST interneuron inhibition in our simulated schizophrenia microcircuits is a key change seen in schizophrenia patients [42–46]. Reduced power in alpha frequency band has been associated with schizophrenia positive and negative symptoms and with chronicity [65], whereas increased beta power is associated with increased distraction [66,67] and is a symptom of schizophrenia. Reduced SST interneuron inhibition was necessary to reproduce the increased broadband power seen in schizophrenia patients [46], in agreement with previous studies that showed the role of SST interneurons in modulating low frequencies [35].

Our MMN and resting-state EEG biomarkers can be applied on patient data, with simulation of additional levels of PV and SST interneuron inhibition reduction, to better stratify schizophrenia patients and facilitate early detection in at-risk population. As the simulated EEG and ERP are smaller in amplitude compared to experimental, due to the model microcircuits encompassing only L2/3 and also involving a down-sampled population by a factor of ~ 7 [68], machine learning methods can be trained to estimate the mechanisms from in-silico data using normalized biomarkers [69] that can be applied to patient data, or the simulated EEG can be scaled to account for the difference between the number of neurons in our models compared to the amount of neurons that generate the recorded EEG at a given electrode, which would be about a factor of 10,000–100,000 [70,71].

The reduced SNR of cortical processing in our schizophrenia microcircuit models was mainly driven by increased baseline firing rates resulting from the reduced PV and SST interneuron inhibition. The increase in baseline rates is in agreement with previous fMRI and EEG studies that showed increased baseline activity in schizophrenia, associated with positive symptoms [72,73].

The link between gene expression and inhibitory interneuron synaptic function that we implemented in our models is not trivial, but a few factors support our framework. The reduced PV expression was accompanied by reduced GAD67, an enzyme that synthesizes GABA and directly affects synaptic inhibition [74]. In living rodents, a reduction of cortical PV interneurons elicited deficits in social behaviour and cognition relevant to schizophrenia symptoms [75]. The change in gene expression could alternatively correspond to a reduced number of synapses [76], however the net decrease in inhibition would be mostly similar. We also simplified the implementation of the 50% reduction in NMDA NR2A subunit, which is expressed in 40% of the PV interneurons in PFC [24], as an overall 20% reduction in synaptic NMDA conductance across all connections between Pyr and PV interneurons in the microcircuit, assuming that the net decrease in inhibition would be mostly similar in either case. We found that the reduction in MMN amplitude seen experimentally in

schizophrenia corresponded to a larger inhibition reduction as suggested by the percent change in expression, suggesting that the percent change in gene expression may translate to a larger physiological effect in terms of NMDA and synaptic conductance. Relatedly, bulk-tissue expression studies indicate that some layers (3 and 4) may involve a larger reduction of PV expression than the average expression across L2/3 [2] that we implemented and thus could underlie the larger physiological effect.

The PV interneuron synaptic output mechanism contributed more to the effects on spike rate and ERP, likely due to the NMDA mechanism relying on depolarized potentials due to the magnesium block at lower potentials [77], and also due to the lower ratio of NMDA to AMPA on PV interneurons. Nevertheless, the NMDA mechanism contributed to a third of the effect on ERP, a quarter of the effect on baseline firing rates and half of the effect on SNR. This was due to the sufficiently depolarized membrane potentials in all conditions, and importantly also because the reduced NMDA input directly impacted the rate/probability of spiking in PV interneurons. The different effect on rate vs ERP are a common occurrence of the dissociation between neuronal population spiking and EEG [64], indicating different effects of the two mechanisms on pyramidal synchrony and soma/apical sink/source underlying the EEG dipole.

Our models were constrained with microcircuit data taken from PFC where possible, and various other brain regions due to limited availability of human neuronal and microcircuit data, thus the models aimed to primarily represent canonical cortical microcircuits. While different brain regions such as the PFC and sensory regions have some differences in wiring and function when taking into account all six layers of the cortex, layers 2 and 3 microcircuitry (which was the focus of our models) is similar across regions [78]. Future studies should investigate the effect of reduced SST and PV interneuron inhibition in other layers, where the proportions of the interneuron types may be different [79,80]. For example, some studies in cingulate cortex measured smaller PV interneuron proportion in layer 6 and larger SST interneuron proportion in layer 5–6 [80]. As the proportions are highly dependent also on the brain area, e.g., somatosensory and motor areas have smaller proportions of PV interneuron relative to other interneurons [80] compared to the proportions reported for PFC or cingulate cortex which we have used, more data for PFC in different layers will be needed to refine our models and results. In addition, once human cortical multilayer models become available, they will enable studying the effects across multiple layers to refine the accuracy of the model prediction. Finally, for this study we modelled oddball processing in a single region (PFC microcircuit) rather than the interaction between multiple brain regions. While oddball processing may involve ongoing interactions between PFC and other brain regions such as the primary and secondary auditory cortex [81], the main computation of the MMN signal is performed in the PFC [40,81], thus supporting modeling and studying it in isolation. However, future studies can simulate multiple microcircuits to study the multi-regional aspects of oddball processing in health and schizophrenia. While we modeled oddball activity during presentation of standard and oddball tones as approximately all-or-none firing as seen in monkey recordings [40], future models could try to apply a more explicit approach of engineering the detailed microcircuit to detect the oddball stimulus, e.g., with recent machine learning methods for biophysical models [82] and when more data becomes available.

Methods

PFC microcircuit models. We modeled detailed human PFC microcircuit models by adapting our previous models of human cortical layer 2/3 microcircuits [57], which consisted of 1000 connected neurons distributed randomly in a $500 \times 500 \times 950 \mu\text{m}^3$ volume, situated $250 \mu\text{m}$ - $1200 \mu\text{m}$ below the pia (corresponding to human L2/3) [55]. The model included four key neuron types: Pyr neurons, SST interneurons, PV interneurons, and VIP interneurons, with detailed reconstructed human morphologies. To adapt the models to the human PFC, we increased the proportion of interneurons relative to Pyr neurons, as measured in human PFC tissue, to have 72% Pyr neurons and 28% interneurons [83]. For the relative proportion of particular interneuron types, postmortem studies reported the relative proportion of PV interneurons out of total interneurons to be 33% in L2/3 of Brodmann areas 9 and 46, which form the dorsolateral PFC [79]. A similar proportion was reported in L2/3 cingulate cortex by another dataset, which also reported the relative proportion of SST

and VIP to be 16% and 50%, respectively (ultra high-depth human neocortex single-nucleus RNA-seq from the Allen Institute for Brain Sciences “Multiple Cortical Areas - Smart-seq (2019)” dataset [80], with methodology described in [49]). Given a proportion of 28% interneurons out of all neurons, we thus used: 9% PV, 5% SST and 14% VIP interneurons. Other parameters were unchanged from the previous models.

The neuron models included sodium, potassium and calcium channels in the axon and soma, and h-current in the dendrites, and reproduced the axosomatic firing pattern and gain, dendritic sag current, and synaptic properties (amplitude and short-term dynamics) measured in human neurons (see supplementary tables in Yao et al 2022 [57] for the ion channel density parameters, which differed between each of the four neuron type models). Connection probability between Pyr neurons was 0.15, as measured in humans [53], and other connection probabilities were constrained using rodent data for connections between the different neuron types. PV interneurons targeted the basal dendrites of Pyr neurons, whereas SST interneurons targeted the apical dendrites of Pyr neurons. Excitatory synapses included AMPA and NMDA ($\tau_{rise,NMDA} = 2$ ms; $\tau_{decay,NMDA} = 65$ ms; $\tau_{rise,AMPA} = 0.3$ ms; $\tau_{decay,AMPA} = 3$ ms), whereas inhibitory synapses were GABA_A ($\tau_{rise,GABA} = 1$ ms; $\tau_{decay,GABA} = 10$ ms). AMPA/NMDA ratios for all excitatory synapses were 1:1, except for synapses onto PV interneurons which had lower ratios, whereby Pyr-PV synapses used a ratio of 1:0.2, and activation inputs onto PV interneuron during stimulus response used a ratio of 1:0.5, according to intralaminar and extralaminar experimentally reported values, respectively [84]. The synaptic reversal potentials were $E_{exc} = 0$ mV and $E_{inh} = -80$ mV. We modelled tonic inhibition using a model for outward rectifying tonic inhibition [85], with $G_{tonic} = 0.938$ mS/cm² for all neurons. The synaptic conductance and number of contacts of excitatory and inhibitory connections were constrained using human and rodent data for each type of connection between specific neuron types (see supplementary tables in Yao et al 2022 [57]). The models were simulated using NEURON [86], LFPy [87] and parallel computing in high-performance grids (SciNet) [88,89].

PFC baseline activity simulations. The microcircuit was injected with background excitatory input, simulated using Ornstein-Uhlenbeck (OU) processes [90] at each dendritic midpoint, to ensure similar levels of inputs along the dendritic path to the soma. We placed 5 additional OU processes along the apical trunk of the Pyr neuron models at 10%, 30%, 50%, 70% and 90% of the apical dendrite length. The base excitatory OU conductance was 28 pS, 280 pS, 30 pS and 66 pS for Pyr, PV, SST and VIP neurons respectively. We did not use inhibitory OU because the model microcircuit provided sufficient inhibition. We scaled the OU conductance values to increase with distance from the soma by multiplying them with the exponent of the relative distance from the soma (ranging from 0 to 1): $\bar{g}_{OU} = \bar{g} \cdot \exp(X_{relative})$. We compared the baseline firing rates to *in-vivo* data recorded in humans (Pyr: 0.66 ± 0.51 Hz, PV: 2.63 ± 2.55 Hz) [91] or rodents (SST: 6.3 ± 0.6 Hz, VIP: 3.7 ± 0.7 Hz) [31].

Schizophrenia microcircuit models. Schizophrenia microcircuits were modelled by altering two types of mechanisms affecting the output and input of PV interneurons. The output mechanism corresponded to a 22% reduction in PV expression in schizophrenia [2], which was modelled by a 22% reduction in synaptic and tonic inhibition from PV interneurons onto other neurons in the microcircuit. The input mechanism corresponded to a 20% decrease in NMDA subunit expression (NR2A) [24], and was modelled by a 20% reduction in NMDA synaptic conductance from Pyr neurons onto PV interneurons. We referred to these schizophrenia microcircuit models as SCZ₂₀, and in addition simulated other levels of the effect (10, 30, 40, 50%). We additionally modeled reduced SST interneuron synaptic and tonic inhibition, in line with a similar reduced expression in schizophrenia measured postmortem [5].

Oddball response models. We simulated PFC activity during presentation of standard and deviant tones in oddball auditory task, by reproducing the approximately all-or-nothing response seen in single neuron recordings in monkeys performing the task [40], whereby the response to standard tones did not differ from baseline, and the response to oddball tones exhibited increased firing rate 100 – 160 ms post-stimulus. The firing response profile had three phases: an increase in firing rate to 6 Hz over 100–120 ms, a further increase to 11 Hz over 120 – 140 ms, and a decrease to 7 Hz over 140 – 160 ms. To reproduce the experimental response, we stimulated a population 150 Pyr neurons, according to the experimental estimate of 20% responsive neurons [40]. Adapting our previous method [57], we used three activation

phases of varying stimulus strength of 5 synapses in the basal dendrites (representing bottom-up input), applied at a uniformly random time within the activation period to each Pyr neuron (1.3 nS during $t=97-117$ ms, 2.75 nS during $117-137$ ms, and 1.4 nS during $137-152$ ms). We also stimulated 40 PV interneurons, each with 5 synapses of 2.5 nS every 10 ms between $t=95-155$ ms, thus starting 2 ms before the Pyr neuron activation. In addition, we stimulated 30 SST interneurons, each with 5 synapses of 2.5 nS every 10 ms between $t=110-130$ ms. This balanced excitation/inhibition activation was necessary to achieve the target firing rates, whereas activating Pyr neurons alone resulted in either too low or too high firing rates. For the PFC activity during standard tones we used the baseline activity, since the experimental firing rate during standard tones was not significantly different from baseline [40].

Simulated microcircuit EEG. We simulated dipole moments together with neuronal spiking activity using LFPy. EEG time series was generated by the microcircuit models using the same methodologies as in previous work [59]. Specifically, we used a four-sphere volume conductor model corresponding to the brain (grey and white matter), cerebrospinal fluid, skull, and scalp with radii of 79 mm, 80 mm, 85 mm, and 90 mm, respectively, that assumes a homogeneous, isotropic, and linear (frequency-independent) conductivity. The conductivity for each sphere was 0.47 S/m, 1.71 S/m, 0.02 S/m, and 0.41 S/m, respectively [92]. The EEG power spectral density was calculated using Welch's method [93] for 3–30 Hz using the SciPy python package.

Simulated EEG event related potentials (ERP). To analyze ERP during the oddball MMN response, simulated EEG timeseries were first lowpass filtered to 40 Hz and downsampled to 100 Hz. They were then baseline corrected using the period 0 ms - 500 ms before the stimulus. ERP potential amplitude was identified as the largest negative peak from 100 ms – 200 ms post stimulus.

EEG periodic and aperiodic components. We decomposed EEG PSDs into periodic and aperiodic (broadband) components using tools from the FOOOF library [94]. The aperiodic component of the PSD was a $1/f$ function, defined by a vertical offset and exponent parameter. The periodic components were derived using up to four Gaussians, defined by center frequency (mean), bandwidth (variance) and power (height).

Statistical tests. Although simulation data, even from detailed models, does not contain the full variability of brain microcircuits, there were several significant sources of variability including different levels of PV and/or SST interneuron inhibition reductions, corresponding to different levels of severity that would be seen in different subjects. In addition, microcircuits were randomized in terms of the particular connections and synapse locations, and the background inputs affecting the activity state (within the statistics defined by the respective probability parameters). As such, simulated EEG data and even firing rates exhibited a fair degree of variability on the order of magnitude seen experimentally between trials and subjects. Therefore, statistical significance was determined wherever appropriate using two-sample t-tests. Cohen's d was calculated to determine effect size.

Author contributions

Conceptualization: Sana Rosanally, Etay Hay.

Data curation: Sana Rosanally, Frank Mazza, Heng Kang Yao, Hannah Seo.

Formal analysis: Sana Rosanally, Frank Mazza, Heng Kang Yao, Faraz Moghbel, Hannah Seo, Etay Hay.

Funding acquisition: Etay Hay.

Investigation: Sana Rosanally, Frank Mazza, Heng Kang Yao, Faraz Moghbel, Hannah Seo, Etay Hay.

Methodology: Sana Rosanally, Frank Mazza, Heng Kang Yao, Faraz Moghbel, Hannah Seo, Etay Hay.

Project administration: Etay Hay.

Resources: Etay Hay.

Software: Sana Rosanally, Frank Mazza, Heng Kang Yao, Faraz Moghbel, Hannah Seo, Etay Hay.

Supervision: Etay Hay.

Validation: Sana Rosanally, Frank Mazza, Heng Kang Yao, Faraz Moghbel, Hannah Seo, Etay Hay.

Visualization: Sana Rosanally, Frank Mazza, Heng Kang Yao, Hannah Seo, Etay Hay.

Writing – original draft: Sana Rosanally, Frank Mazza, Heng Kang Yao, Hannah Seo, Etay Hay.

Writing – review & editing: Sana Rosanally, Frank Mazza, Heng Kang Yao, Etay Hay.

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