Synaptic Variability and Cortical Gamma Oscillation Power in Schizophrenia

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Objective: Cognitive impairments in schizophrenia are associated with lower gamma oscillation power in the prefrontal cortex (PFC). Gamma power depends in part on excitatory drive to fast-spiking parvalbumin interneurons (PVIs). Excitatory drive to cortical neurons varies in strength, which could affect how these neurons regulate network oscillations. The authors investigated whether variability in excitatory synaptic strength across PVIs could contribute to lower prefrontal gamma power in schizophrenia.

Methods: In postmortem PFC from 20 matched pairs of comparison and schizophrenia subjects, levels of vesicular glutamate transporter 1 (VGlut1) and postsynaptic density 95 (PSD95) proteins were quantified to assess variability in excitatory synaptic strength across PVIs. A computational model network was then used to simulate how variability in excitatory synaptic strength across fast-spiking (a defining feature of PVIs) interneurons (FSIs) regulates gamma power.

Results: The variability of VGlut1 and PSD95 levels at excitatory inputs across PVIs was larger in schizophrenia relative to comparison subjects. This alteration was not influenced by schizophrenia-associated comorbid factors, was not present in monkeys chronically exposed to antipsychotic medications, and was not present in calretinin interneurons. In the model network, variability in excitatory synaptic strength across FSIs regulated gamma power by affecting network synchrony. Finally, greater synaptic variability interacted synergistically with other synaptic alterations in schizophrenia (i.e., fewer excitatory inputs to FSIs and lower inhibitory strength from FSIs) to robustly reduce gamma power.

Conclusions: The study findings suggest that greater variability in excitatory synaptic strength across PVIs, in combination with other modest synaptic alterations in these neurons, can markedly lower PFC gamma power in schizophrenia.

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Impairments in certain cognitive processes, such as working memory, are a core clinical feature of schizophrenia (1). Working memory is associated with synchronized neural oscillatory activity at gamma band frequency (~30–80 Hz) in the prefrontal cortex (PFC) (2–4), and the power of these oscillations during the performance of cognitive tasks is lower in individuals with schizophrenia (5–7). Thus, alterations in PFC neural circuitry are thought to contribute to impaired gamma oscillations and working memory performance in schizophrenia (8, 9).

The generation of cortical gamma oscillations appears to depend, at least in part, on the activity of a local neural circuit that includes regular-spiking excitatory pyramidal neurons and fast-spiking GABAergic parvalbumin-expressing interneurons (PVIs) (10). PVIs receive excitatory synaptic inputs from neighboring pyramidal neurons (11) and provide phasic inhibition that synchronizes the firing of those pyramidal neurons at gamma frequency (10, 12). For example, in animal models, driving excitatory inputs to PVIs generates local field potentials at gamma frequency (13, 14), whereas the loss of excitatory drive to PVIs impairs gamma oscillations (15–17). Thus, the generation of gamma oscillations in the PFC is thought to be dependent on excitatory synaptic inputs to PVIs.

Excitatory synaptic inputs to cortical neurons vary in their strength (18, 19). Furthermore, introducing variability to anatomical and physiological properties that determine synaptic strength disrupts network behaviors in computational models (20–27). These findings suggest that shifts in the normal levels of variability in excitatory synaptic strength across cortical neurons could influence how these neurons participate in the generation of network oscillations. Thus, disease-driven alterations in the variability of excitatory synaptic strength across PVIs may contribute to lower prefrontal gamma oscillation power in schizophrenia.

To explore this idea, we first examined variability in excitatory synaptic strength across PVIs by quantifying pre- and postsynaptic markers of synaptic strength to individual PVIs in postmortem human PFC from matched pairs of schizophrenia and unaffected comparison subjects. Then, we utilized a computational model network of regular-spiking excitatory and fast-spiking (a defining feature of PVIs)

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inhibitory neurons to simulate how variability in excitatory synaptic strength across PVIs might regulate gamma band power. Finally, we used the model network to simulate how variability in excitatory synaptic strength interacts with other synaptic parameters of PVIs that are altered in schizophrenia. Our findings suggest that greater variability in excitatory synaptic strength across PVIs is characteristic of the disease process of schizophrenia, regulates network oscillations by affecting synchronous neuronal firing, and can interact synergistically with other synaptic alterations in PVIs to robustly reduce prefrontal gamma power.

METHODS

Quantifying Variability in Excitatory Synaptic Strength Across PVIs in the PFC

To quantify variability in excitatory synaptic strength across individual PVIs in the PFC of persons with schizophrenia, we reanalyzed our immunohistochemical data set from a previous study (28). This data set contains the relative protein levels of vesicular glutamate transporter 1 (VGlut1) and postsynaptic density 95 (PSD95) in excitatory inputs to PVIs (see Figure S1 and the Supplemental Methods section in the online supplement for detailed information) in the PFC (Brodmann area 9) of unaffected comparison and schizophrenia subjects (N=20 matched pairs; see Table S1 in the online supplement for summary characteristics of study subjects) and monkeys that had received oral haloperidol, olanzapine, or sham treatment for 17–27 months (N=6 matched triads). In the present analysis, given that both VGlut1 and PSD95 protein levels are correlated with the amplitude of AMPA-mediated excitatory postsynaptic currents (29, 30), the relative levels of VGlut1 protein and of PSD95 protein in all excitatory inputs to each PVI were averaged to index the mean strength of excitatory synaptic inputs to each PVI. Then the variability in mean excitatory synaptic strength across individual PVIs for each subject in both the human and monkey cohorts was computed as the coefficient of variation (CV) of either VGlut1 or PSD95 levels or the combined levels of VGlut1 and PSD95 levels (VGlut1 + PSD95 levels). The same method was used to compute the variability in excitatory synaptic strength across calretinin interneurons, which are not thought to contribute directly to the generation of gamma oscillations (31, 32).

Statistical Tests for Empirical Immunohistochemical Data

Two analysis of covariance (ANCOVA) models were used to compare the dependent variables between schizophrenia and unaffected comparison subject groups. The paired ANCOVA model included subject pair as a blocking factor and postmortem interval and tissue storage time as covariates. This model accounts for the matching of subject pairs for sex and age and for the parallel tissue processing of subject pairs but is not a true statistical paired design. Thus, we also used an unpaired ANCOVA model, which included age, sex, race, postmortem interval, and tissue storage time as covariates. Nonsignificant covariates were excluded in the final reported analyses. The paired and unpaired ANCOVA analyses produced comparable levels of statistical significance on all dependent variables. Thus, the results from the paired ANCOVA analysis are reported in the main text, and the results from the unpaired ANCOVA analysis are provided in Table S2 in the online supplement. For the antipsychotic-exposed monkeys, an ANCOVA was used to assess the main effect of antipsychotic treatment with triad as a blocking factor. The effect size was calculated by Cohen's d (33) to assess the magnitude of difference in all dependent measures between subject groups.

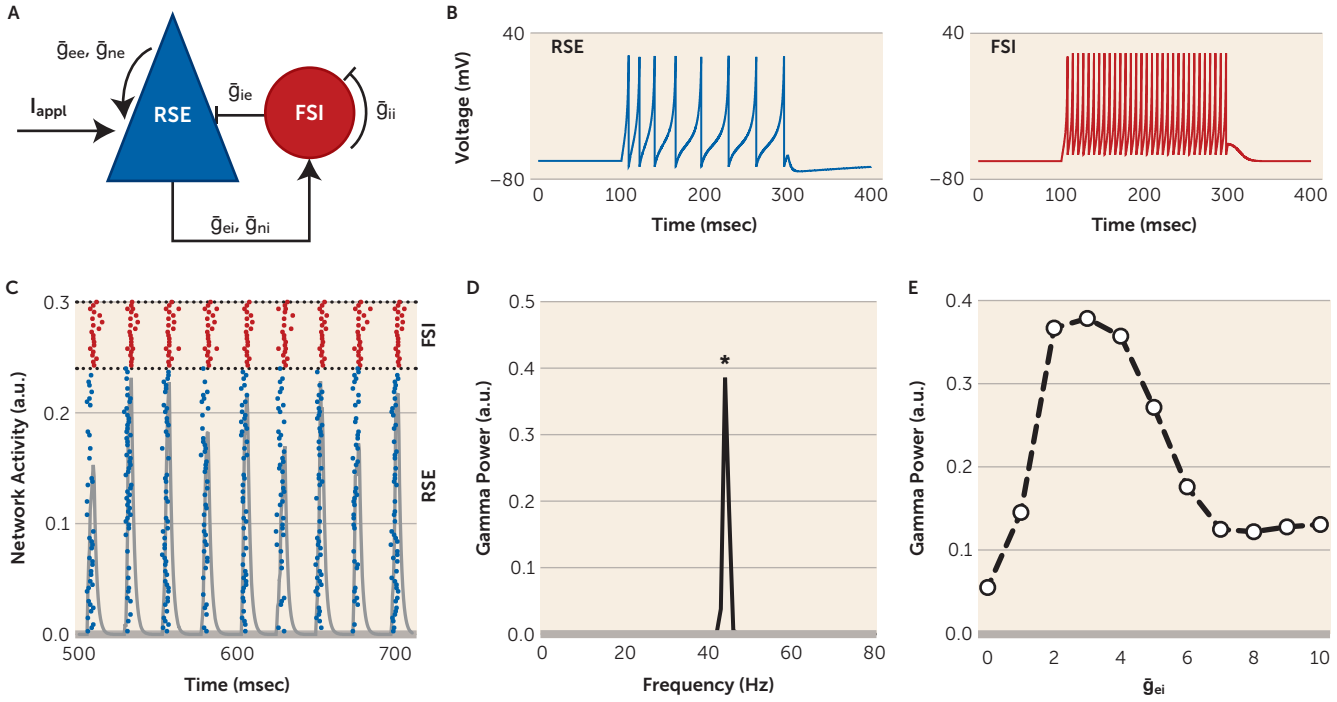
Computational Model Network of Excitatory and Fast-Spiking Inhibitory Cells

We simulated gamma oscillations using a pyramidal interneuron gamma (PING) network that can model the effect of various properties of excitatory and inhibitory synapses on gamma band power (34, 35) (see the Supplemental Methods section in the online supplement for detailed information). In brief, the PING network consisted of 80 regular-spiking excitatory (RSEs) and 20 fast-spiking inhibitory (FSIs) quadratic integrate-and-fire cells (36). Cells were connected to every other cell in the network (all-to-all connection). Each excitatory synaptic connection contained AMPA and NMDA conductance, and each inhibitory synaptic connection contained GABA conductance (Figure 1A). Parameters used to model the regular-spiking property of RSEs (Figure 1B, left panel), the fast-spiking property of FSIs (Figure 1B, right panel), and synaptic conductance between these cells are described in the Supplemental Methods of the online supplement. External excitatory synaptic currents were applied to RSEs to initiate network activity. For each simulation trial, power spectral density was taken on the network activity (i.e., the sum of all excitatory synaptic currents into RSEs) to compute peak gamma power and frequency (Figure 1C, D) (35). Results of each experiment are the average of 200 trials.

Simulating Synaptic Parameters of FSIs in the Model Network

Previous studies demonstrated that 1) excitatory postsynaptic currents in PVIs are predominantly mediated by AMPA receptors (34, 37–40); 2) loss of excitatory synaptic inputs to PVIs primarily reduces AMPA receptor–mediated excitatory postsynaptic currents (15); 3) knockout of AMPA receptor subunit in PVIs reduces gamma power (17); and 4) NMDA receptors in PVIs regulate PVI-mediated inhibition via presynaptic mechanisms (41) but minimally contribute to excitatory postsynaptic currents in these neurons (34, 37–40). Thus, excitatory synaptic strength across PVIs was modeled by AMPA conductance onto individual FSIs from their presynaptic RSEs (g_{ei}). To simulate variability in excitatory synaptic strength across PVIs, we computed the CV of g_{ei}, which we termed CV_g, by assigning g_{ei} randomly drawn from a normal distribution with a mean of $\bar{g}_{ei}=2$ and varying

FIGURE 1. Properties of pyramidal interneuron gamma (PING) model network[a]



[a] Panel A is a schematic diagram of the network architecture illustrating recurrent connectivity among regular-spiking excitatory cells (RSEs) and fast-spiking inhibitory cells (FSIs). $\bar{g}_{ee}$ and $\bar{g}_{ne}$ indicate mean AMPA and NMDA conductance to RSEs, respectively. $\bar{g}_{ei}$ and $\bar{g}_{ni}$ indicate mean AMPA and NMDA conductance to FSIs, respectively. $\bar{g}_{ie}$ and $\bar{g}_{ii}$ indicate mean GABA conductance to RSEs and FSIs, respectively. I_{appl} indicates current applied to RSEs to initiate network activity. Panel B shows membrane properties of an RSE (left) and an FSI (right) under current injection. Panel C is an example of a raster plot (blue dots indicate RSEs, N=80; red dots indicate FSIs, N=20) and network activity (gray) across time during gamma oscillations. a.u.=arbitrary units. Panel D shows a power spectral density analysis from the network behavior shown in panel C. Asterisk indicates the frequency with peak power for this trial. Panel E is a plot showing the effect of $\bar{g}_{ei}$ on gamma power computed as an average over 200 trials. $\bar{g}_{ei}$ and gamma power form an inverted U curve with a peak at $\bar{g}_{ei}$=2–4.

standard deviations. The normal distribution had a lower limit of 0 to avoid assigning negative values to g_{ei}. To simulate the effect of fewer excitatory inputs to PVIs on gamma power, the probability of excitatory synapse connectivity on FSIs ($Conn_{ei}$) was lowered from 1. Finally, to simulate the effect of lower strength of inhibitory outputs from PVIs, the GABA conductance from FSIs to RSEs ($\bar{g}_{ie}$) was reduced from 0.8. For all experiments, the number of FSIs in the model network was kept constant based on findings that the relative density of PVIs (as assessed by both mRNA and protein measures) is not altered in the PFC of subjects with schizophrenia (28, 42, 43).

RESULTS

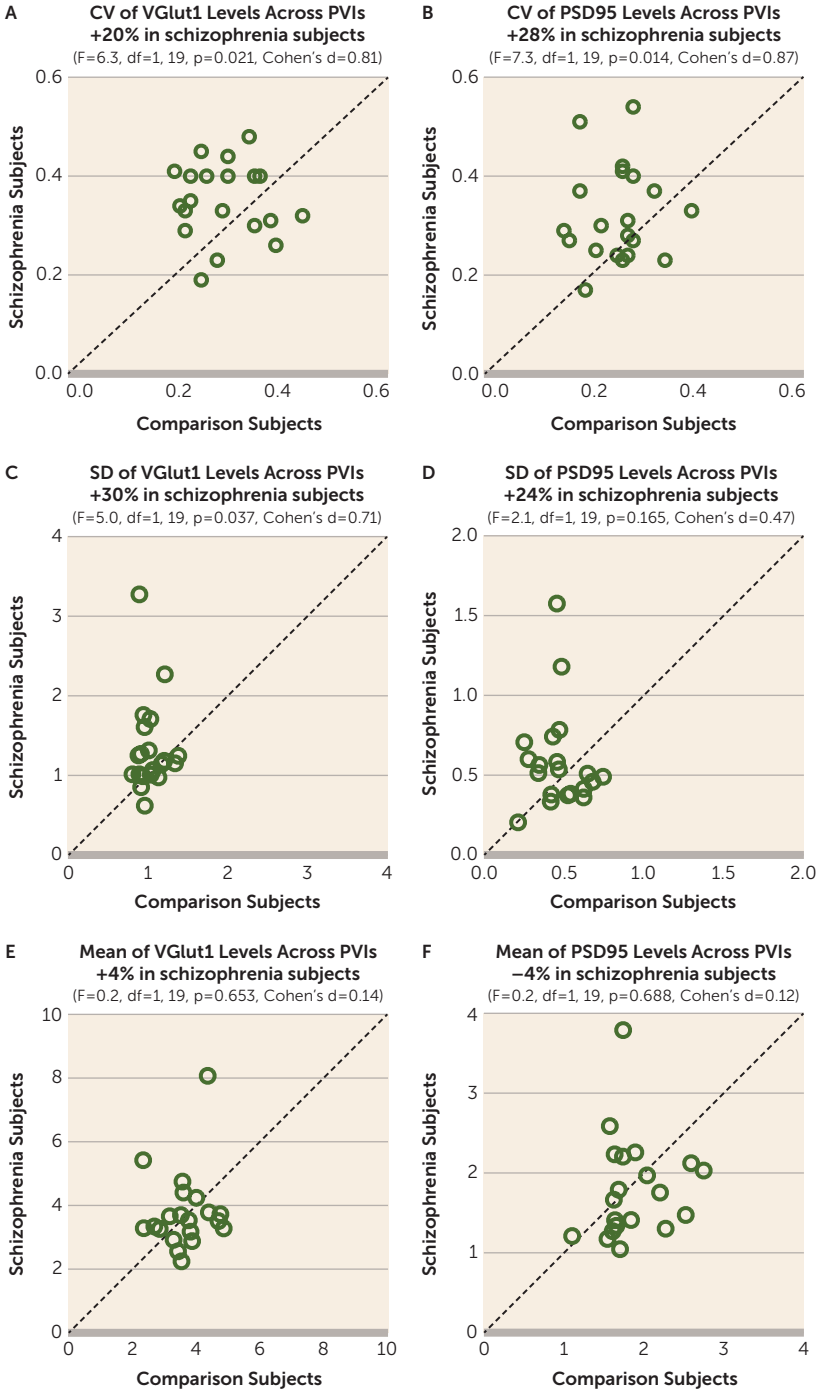
Greater Variability of Excitatory Input Strength Across PVIs in Schizophrenia

The CV of VGlut1 or PSD95 levels across PVIs was significantly higher by 20% (Figure 2A) or 28% (Figure 2B), respectively, in the PFC of schizophrenia relative to unaffected comparison subjects. The greater CV in schizophrenia was due to a higher standard deviation of VGlut1 and PSD95 levels (Figure 2C,D), and not to differences in their mean values (Figure 2E,F). These findings support the idea that schizophrenia is associated with greater variability in excitatory synaptic strength across PVIs in the PFC.

Next, we investigated whether greater synaptic variability across PVIs in schizophrenia might be due to other factors commonly associated with the illness. Neither diagnosis of schizoaffective disorder; nor history of substance abuse or nicotine use at the time of death; nor use of antidepressants, benzodiazepines, or valproic acid at the time of death; nor death by suicide had a significant effect on the CV of VGlut1 or PSD95 levels across PVIs among schizophrenia subjects (see Figure S2 in the online supplement). Moreover, the CV of VGlut1 or PSD95 levels across PVIs did not differ between monkeys chronically exposed to olanzapine or sham treatment, although the CV of VGlut1 appeared to be lower in monkeys exposed to haloperidol, perhaps suggesting a normalizing effect of this medication on the variability of excitatory synaptic strength onto PVIs (see Figure S3 in the online supplement). These findings suggest the absence of effects from comorbid factors or antipsychotic medications on greater synaptic variability across PVIs in schizophrenia.

Finally, we assessed variability in excitatory synaptic strength across calretinin neurons, a subclass of inhibitory neurons that do not share local excitatory inputs with PVIs (11, 44) and do not directly contribute to the generation of gamma oscillations (31, 32). The CV of VGlut1 or PSD95 levels across calretinin neurons did not significantly differ between subject groups (see Figure S4A,B in the online supplement).

FIGURE 2. Greater variability in excitatory synaptic strength across parvalbumin interneurons (PVIs) in the PFC of schizophrenia subjects[a]



[a] Presented here are scatterplots for coefficient of variation (CV) (panels A and B), standard deviation (panels C and D), and mean (panels E and F) of VGlut1 and PSD95 levels within excitatory inputs across PVIs for each unaffected comparison subject (x-axis) and schizophrenia subject (y-axis) in a pair. Data points above the diagonal unity line indicate a higher level in the schizophrenia subject relative to the matched unaffected comparison subject. The greater CV in schizophrenia subjects was evident in both VGlut1 and PSD95 levels, and this difference was due to higher standard deviations and not differences in mean values.

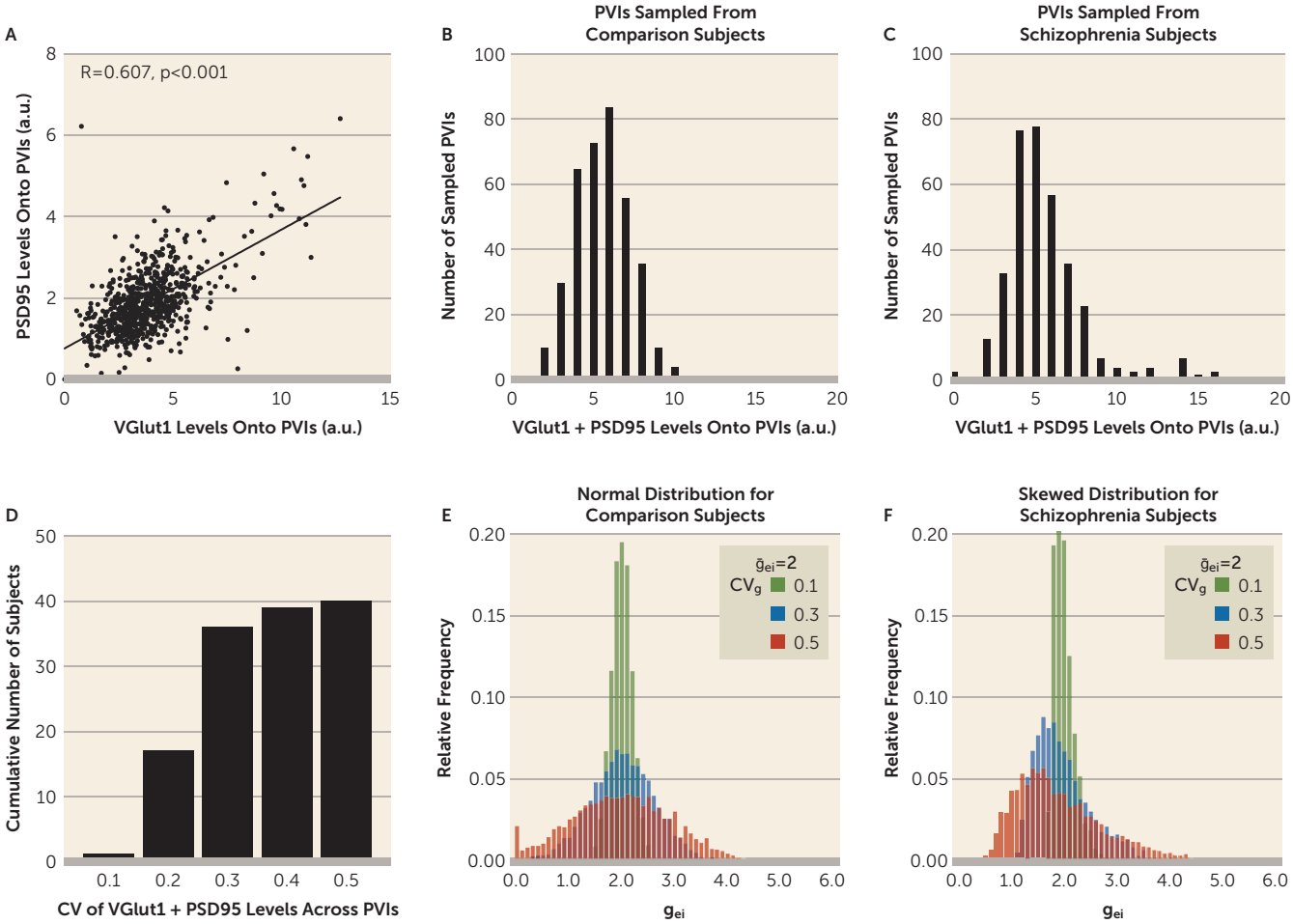
These findings suggest that variability in excitatory synaptic strength is not altered across calretinin neurons in schizophrenia, consistent with previous studies demonstrating that these neurons are relatively unaffected in the illness (28, 42, 45–47).

Simulated Effect of Greater Synaptic Variability Across PVIs on Prefrontal Gamma Power

Based on these findings of greater variability in excitatory synaptic strength across PVIs in schizophrenia, we explored how synaptic variability affects the generation of gamma oscillations in a computational model network of regular-spiking excitatory (RSEs) and fast-spiking inhibitory (FSIs) neurons that can robustly generate network gamma oscillations (Figure 1A–D). We first characterized how changes in mean excitatory synaptic strength from RSEs to FSIs ($\bar{g}_{ei}$) influence gamma power in our model network when variability in excitatory synaptic strength across individual FSIs (CV_g) is 0. Gamma power sharply increased as $\bar{g}_{ei}$ increased from 0 and reached a peak at $\bar{g}_{ei}=2$, which was maintained as $\bar{g}_{ei}$ was further increased from 2 to 4 (Figure 1E). Gamma power sharply decreased with $\bar{g}_{ei}>4$ and reached a stable nadir at $\bar{g}_{ei}\geq 7$. Thus, our model network replicated the inverted U relationship between $\bar{g}_{ei}$ and gamma power observed in a previous study (48).

Next, we assessed how shifts in CV_g regulate gamma power in the model network. To simulate biologically relevant shifts in CV_g, we utilized the VGlut1 and PSD95 levels within excitatory inputs to PVIs in our 20-pair human cohort. To obtain a single molecular index to model excitatory synaptic strength onto each FSI (g_{ei}), the mean VGlut1 and the mean PSD95 levels, measures of synaptic strength in pre- and postsynaptic compartments (29, 30), respectively, at excitatory inputs onto each PVI were summed (VGlut1 + PSD95 levels). The mean VGlut1 levels and the mean PSD95 levels within excitatory inputs onto PVIs (N=723) sampled from all 40 subjects were significantly positively correlated (Figure 3A), supporting the use of a single index to simulate g_{ei}. Further analyses showed that the VGlut1 + PSD95 levels onto each PVI sampled from comparison subjects conformed to a normal distribution (Figure 3B) (Shapiro-Wilk test: W=4.7, p=0.062), whereas those sampled from schizophrenia subjects had a distribution with skewness of 1.58 and

FIGURE 3. Modeling variability in excitatory synaptic strength across FSIs (CV_g) using empirical data[a]



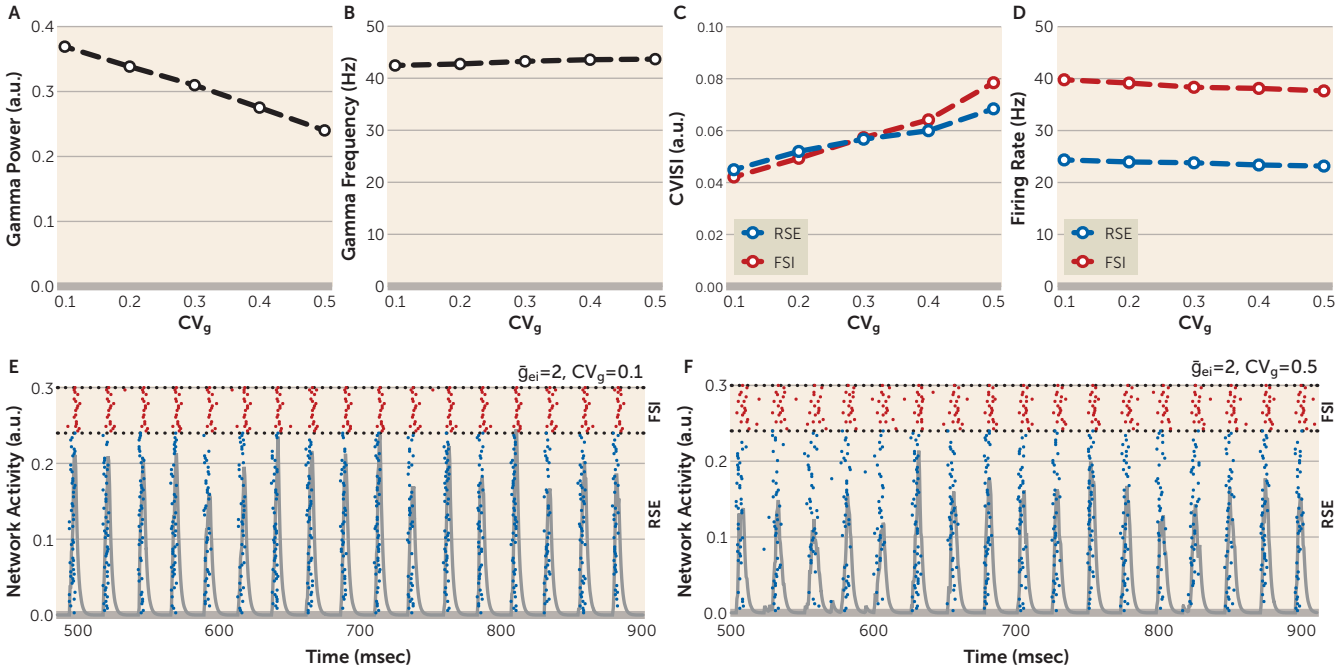
[a] Panel A is a correlation graph plotting mean VGlut1 and mean PSD95 levels within excitatory inputs to PVIs. a.u.=arbitrary units; PVIs=parvalbumin interneurons. The regression line represents the significant positive association of these measures across all sampled PVIs (N=723). Given the strength of this correlation, the mean VGlut1 and mean PSD95 levels were summed (VGlut1 + PSD95 levels) to index excitatory synaptic strength for each PVI. Panels B and C show frequency distributions (bars) of VGlut1 + PSD95 levels onto each PVI sampled from comparison subjects (panel B) and schizophrenia subjects (panel C). VGlut1 + PSD95 levels onto each PVI sampled from comparison subjects conformed to a normal distribution, whereas those sampled from schizophrenia subjects conformed to a distribution with skewness of 1.58 and kurtosis of 7.57. Panel D shows the cumulative frequency distribution of the coefficient of variation (CV) of VGlut1 + PSD95 levels across PVIs for all subjects (N=40). Panels E and F show relative frequency distributions of excitatory synaptic strength for individual FSIs (g_{ei}) in the model network with CV_g=0.1, CV_g=0.3, and CV_g=0.5 generated from either the normal distribution (panel E) or the skewed distribution (panel F) based on empirical data. $\bar{g}_{ei}$=2 for all conditions.

kurtosis of 7.57 (Figure 3C) (Shapiro-Wilk test: W=0.8, p<0.001). Also, the mean for the CV of VGlut1 + PSD95 levels across PVIs was 0.24 (SD=0.05) in unaffected comparison subjects and 0.30 (SD=0.07) in schizophrenia subjects. Finally, the CV of VGlut1 + PSD95 levels across PVIs ranged from 0.1 to 0.5 across all subjects (Figure 3D). Based on these empirical findings, we generated values for g_{ei} from either a normal distribution for comparison subjects (Figure 3E) or a skewed distribution for schizophrenia subjects (Figure 3F). In each distribution, we varied the standard deviation without changing the mean value to introduce shifts in CV_g from 0.1 to 0.5 in the model network.

We first assessed how CV_g generated from the normal distribution regulates gamma power and frequency. Shifting CV_g from 0.1 to 0.5 progressively reduced peak gamma power (Figure 4A) but had a minimal effect on peak gamma frequency (Figure 4B). The effect of CV_g on gamma power was observed over a wide range of background noise levels (see Figure S5 in the online supplement), demonstrating that the effect of CV_g on gamma power is robust to noise in the model network. Furthermore, CV_g generated from the skewed distribution showed differences of similar magnitudes in peak gamma power and frequency (see Figure S6 in the online supplement), suggesting that the effect of CV_g is comparable between the distributions found in the comparison and schizophrenia subject groups. Based on these findings, CV_g generated from the normal distribution was used for subsequent analyses.

Finally, to investigate the network properties affected by CV_g, we assessed the effect of CV_g on network synchrony and activity, measured by the coefficient of variation of the interspike interval (CVISI) and the firing rates, respectively,

FIGURE 4. Effect of greater CV_g on network behavior in pyramidal interneuron gamma (PING) model network[a]



[a] In panels A and B, increasing CV_g from 0.1 to 0.5 progressively reduces peak gamma power (panel A) without affecting peak gamma frequency (panel B). a.u.=arbitrary units. In panels C and D, increasing CV_g from 0.1 to 0.5 increases the coefficient of variation of the interspike interval (CVISI) of regular-spiking excitatory cells (RSEs) and fast-spiking inhibitory cells (FSIs) (panel C) without affecting the firing rates of these cells (panel D), suggesting that greater CV_g lowers gamma power by disrupting the synchrony but not the activity of the model network. All data were computed as an average over 200 trials. Panels E and F are representative raster plots (blue dots indicate RSEs, N=80; red dots indicate FSIs, N=20) and network activity (gray) over time for CV_g=0.1 (panel E) or 0.5 (panel F). Relative to CV_g=0.1, desynchronization (greater horizontal scatter of blue and red dots) is seen at CV_g=0.5.

of RSEs and FSIs. Shifting CV_g from 0.1 to 0.5 increased the CVISI of RSEs and FSIs (Figure 4C) but had minimal effect on the firing rates of RSEs and FSIs (Figure 4D). Together, these findings demonstrate that CV_g regulates gamma power by affecting the synchrony, while minimally affecting the activity, of the model network.

Simulated Interaction Between Greater Synaptic Variability and Other Synaptic Alterations in PVIs

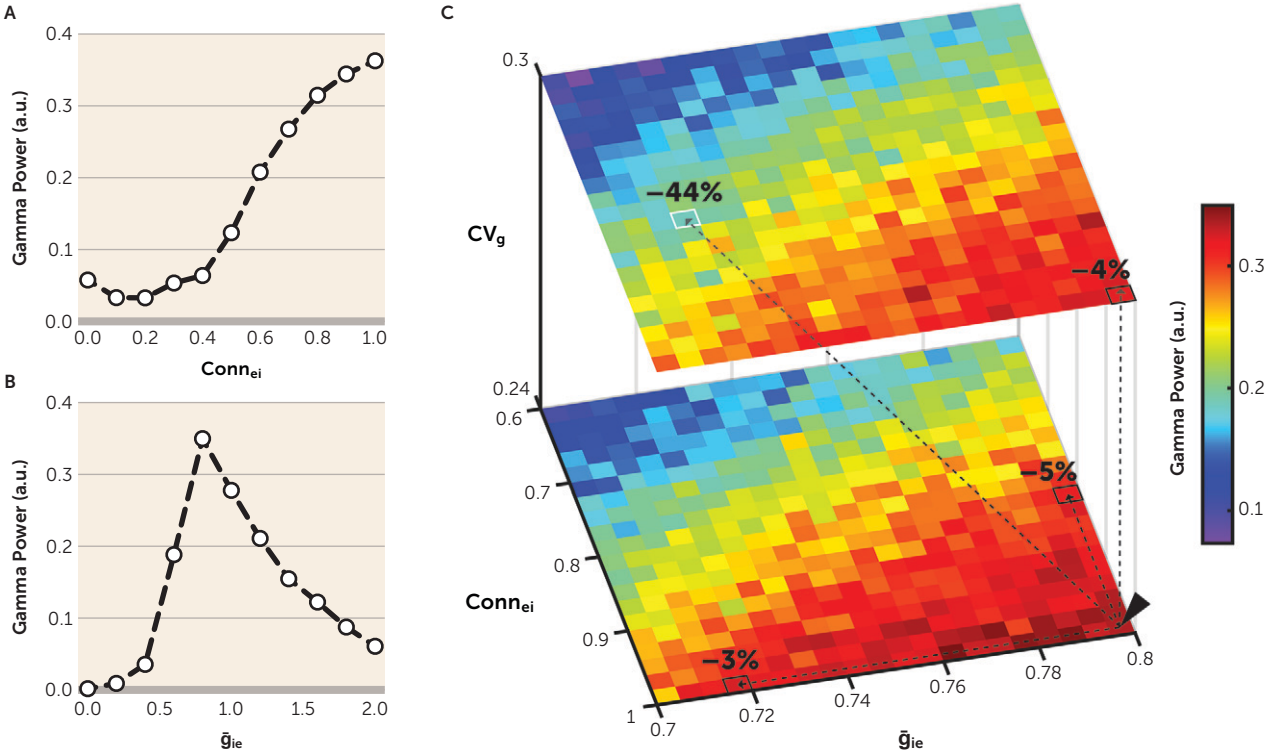
These simulations suggested that lower prefrontal gamma power in schizophrenia could be due in part to greater synaptic variability across PVIs. Previous studies have shown alterations in other synaptic parameters of PVIs that may also contribute to lower prefrontal gamma power in schizophrenia. Thus, we utilized the model network to explore the impact of alterations in these synaptic parameters on gamma power and the interaction of these parameters with synaptic variability in the regulation of gamma power.

We first assessed how our model network simulated the effect of two synaptic alterations in PVIs previously reported in the PFC of subjects with schizophrenia. For example, the mean density of excitatory inputs onto PVIs in the PFC was reported to be 18% lower in schizophrenia (28). Also, decreasing excitatory drive to PVIs was shown to lower cortical gamma power in animal models (17, 49). Thus, we assessed how a lower mean probability of excitatory synapse connectivity on FSIs ($Conn_{ei}$) affects gamma power in the model network (Figure 5A). At CV_g=0, maximal gamma power occurred at $Conn_{ei}$=1. Gamma power progressively declined to very low levels as $Conn_{ei}$ decreased from 1 to 0.4 and reached a stable nadir at $Conn_{ei} \leq 0.4$. Thus, decreasing $Conn_{ei}$ in the model network provided proof-of-concept evidence that fewer excitatory inputs to PVIs in schizophrenia could result in lower prefrontal gamma power.

Previous studies had reported that mean protein and mRNA levels of the GABA-synthesizing enzyme glutamic acid decarboxylase 67 (GAD67), a marker for GABA conductance, were 10% to 30% lower in the PFC of subjects with schizophrenia (50–53). Also, decreasing GABA conductance to pyramidal neurons was shown to lower cortical gamma power in animal models (54, 55). Thus, we assessed in the model network the effect of lower mean GABA conductance ($\bar{g}_{ie}$) from FSIs to RSEs on gamma power. At CV_g=0, maximal gamma power occurred at $\bar{g}_{ie}$=0.8, with $\bar{g}_{ie}$ and gamma power forming an inverted U relationship (Figure 5B). Thus, decreasing $\bar{g}_{ie}$ from 0.8 (i.e., shift from the peak to the left side of the inverted U) in the model network provided proof-of-concept evidence that lower GABA conductance from PVIs to pyramidal neurons, secondary to less GABA synthesis due to lower GAD67 levels, could result in lower prefrontal gamma power in schizophrenia.

Finally, we assessed whether greater CV_g, lower $Conn_{ei}$, and lower $\bar{g}_{ie}$ interact to regulate gamma power in the model network. In this simulation, we utilized empirical findings from the previous and present postmortem studies of

FIGURE 5. Synergistic effect of greater synaptic variability and other synaptic parameters of FSIs on gamma power in the pyramidal interneuron gamma (PING) model network[a]



[a] FSIs=fast-spiking inhibitory cells. Panel A is a plot showing the effect of $Conn_{ei}$ on gamma power. Decreasing $Conn_{ei}$ from 1 to 0.4 progressively reduces gamma power to very low levels. a.u.=arbitrary units. Panel B is a plot showing the effect of $\bar{g}_{ie}$ on gamma power. Peak gamma power is present at $\bar{g}_{ie}$=0.8, with lower and higher levels of $\bar{g}_{ie}$ producing lower gamma power. Panel C presents three-dimensional heat maps showing the effects of CV_g (z-axis), $Conn_{ei}$ (y-axis), and $\bar{g}_{ie}$ (x-axis) on gamma power. Relative to their initial values at CV_g=0.24, $Conn_{ei}$=1, and $\bar{g}_{ie}$=0.8 (black arrowhead), increasing CV_g to 0.3, decreasing $Conn_{ei}$ to 0.82, or decreasing $\bar{g}_{ie}$ to 0.72 individually (see text for the rationale for each difference) reduces gamma power by 4%, 5%, or 3% (black squares), respectively. Thus, the additive effect of these shifts in these three parameters would be expected to be a 12% reduction in gamma power. However, the model network revealed a 44% reduction in gamma power (white square), demonstrating a synergistic effect of greater CV_g, lower $Conn_{ei}$, and lower $\bar{g}_{ie}$ on gamma power.

schizophrenia to simulate disease-relevant alterations in each parameter as follows: 1) CV_g was increased from 0.24 to 0.30 to reflect the observed greater value of CV of VGlut1 + PSD95 levels across PVIs in schizophrenia relative to unaffected comparison subjects (see Results above); 2) $Conn_{ei}$ was decreased from 1 to 0.82 to reflect the 18% lower mean density of excitatory inputs to PVIs in schizophrenia (28); and 3) $\bar{g}_{ie}$ was decreased from 0.8 to 0.72 to reflect a 10% lower mean level of GAD67 in schizophrenia, which represents the smallest mean difference reported in previous studies (50–53). Simulations showed that these changes in CV_g, $Conn_{ei}$, and $\bar{g}_{ie}$ individually reduced gamma power by 4%, 5%, and 3%, respectively (Figure 5C). Consequently, the additive effect of all these parameter changes would be expected to be a 12% reduction in gamma power. However, when combined in the model network, these differences in CV_g, $Conn_{ei}$, and $\bar{g}_{ie}$ reduced gamma power by 44% (Figure 5C), demonstrating a synergistic interaction among these synaptic parameters. Thus, these simulations suggest that modest alterations in multiple synaptic parameters of PVIs might interact synergistically to produce a substantial reduction in prefrontal gamma power in schizophrenia.

DISCUSSION

The neurobiology of schizophrenia has been conventionally studied by assessing the difference in mean values of isolated components of neural circuits. Here, we combined findings from postmortem human brain studies and computational modeling to demonstrate that the disease process of schizophrenia also involves alterations in the variability of synaptic strength, and that these alterations can interact synergistically with other modest alterations in synaptic parameters to produce marked impairments in physiological properties of neural circuits that are critical for working memory.

Greater Variability in Excitatory Synaptic Strength Across PVIs in Schizophrenia: Empirical Evidence

In this study, we report that variability in a molecular index of excitatory synaptic strength across PVIs is greater in the PFC of individuals with schizophrenia relative to unaffected comparison subjects. Greater variability in schizophrenia was evident in both pre- and postsynaptic markers and was solely due to a higher standard deviation without alterations

in the mean values of these markers. Furthermore, greater synaptic variability across PVIs was not attributable to factors commonly associated with schizophrenia and was not influenced by long-term exposure to antipsychotic medications in nonhuman primates. Thus, our findings support the idea that the disease process of schizophrenia includes a greater variability in excitatory synaptic strength across PVIs.

In the primate PFC, PVIs are a major target of excitatory synaptic inputs from neighboring pyramidal neurons in layer 3 (11), where gamma oscillations are most prominent during working memory tasks (56). In contrast, calretinin neurons are much less frequent targets of axons from neighboring pyramidal neurons and are thought to receive excitatory inputs primarily from long-range cortico-cortical projections (11, 44). Furthermore, calretinin neurons appear to be unaffected in schizophrenia (28, 42, 45–47). Consistent with these findings, we did not find evidence of altered variability in excitatory synaptic strength across calretinin neurons in subjects with schizophrenia. Thus, greater synaptic variability across PVIs in schizophrenia may be due to disturbances in their inputs from PFC layer 3 pyramidal neurons, which are known to exhibit both transcriptional and morphological alterations in the illness (57).

Variability in the strength of excitatory inputs to PVIs could arise during development via intrinsic and/or experience-dependent mechanisms. For example, in mouse cortex, the strength of excitatory drive to PVIs differs substantially depending on the timing of their neurogenesis (58, 59), demonstrating an intrinsic mechanism that determines synaptic variability across PVIs during prenatal development. The strength of excitatory drive to distinct subsets of PVIs is also differentially refined during critical or sensitive developmental periods in response to learning or environmental enrichment (59–61), suggesting that experience-dependent synaptic plasticity affects variability in excitatory synaptic strength across these neurons. Thus, developmental alterations in the intrinsic and/or experience-dependent mechanisms that regulate excitatory input strength to PVIs could result in an abnormal distribution of synaptic strengths across these neurons in schizophrenia.

Increasing Variability in Excitatory Synaptic Strength Across PVIs Reduces Gamma Power: Computational Evidence

Based on our findings showing greater variability in excitatory synaptic strength across PVIs in schizophrenia, we used a PING model network to explore whether synaptic variability regulates gamma power. Increasing variability (CV_g) progressively lowered gamma power, simulating lower prefrontal gamma power observed during cognitive tasks in persons with schizophrenia (5–7). In addition, greater CV_g increased the CVISI of network neurons without affecting their firing rates, similar to previous findings that demonstrated a desynchronizing effect of variability in model networks (20, 25–27). These simulations suggest that greater synaptic variability across PVIs disrupts synchronous neuronal firing in the PFC and could contribute to the lower prefrontal gamma power reported in schizophrenia.

Lower mean density of excitatory inputs to PVIs and lower mean levels of inhibitory strength from PVIs have also been proposed to reduce prefrontal gamma power in schizophrenia (10, 28). Simulating these synaptic alterations (lower $Conn_{ei}$ and lower $\bar{g}_{ie}$, respectively) resulted in lower gamma power in our model network, similar to previous findings that showed a desynchronizing effect of these alterations (26, 48, 62). Finally, shifts in CV_g, $Conn_{ei}$, and $\bar{g}_{ie}$ comparable to those reported in empirical studies of schizophrenia each resulted in a small reduction in gamma power, but in combination these shifts markedly reduced gamma power. Thus, these simulations provide proof-of-concept evidence that modest alterations in individual synaptic parameters of PVIs reported in postmortem studies could synergistically interact to produce a substantial reduction in prefrontal gamma power in schizophrenia.

Several limitations are important to consider in interpreting the findings of this study. First, previous studies have shown that the effect of variability on network synchrony can be regulated by the strength of gap junctions and shunting inhibition among FSIs (12, 63). Our current model network does not permit the inclusion of parameters for gap junction or shunting inhibition, and thus the effect of synaptic variability reported in our findings might differ in models that include these parameters. Second, our model does not simulate the effect of lower PV levels in the axon terminals of PVIs, which have been reported in the PFC of subjects with schizophrenia (50, 64). PV is a calcium-binding protein that is thought to buffer calcium ions, which regulate the synaptic release of GABA (48). However, because previous studies provided mixed evidence for the effect of lower PV levels on the strength of inhibition from PVIs (65, 66), it is not possible to simulate the effect of lower PV levels at this time. Finally, our model does not simulate the sparsity of excitatory inputs onto pyramidal neurons found in the neocortex (67), but uses all-to-all connectivity with a reduced number of total neurons in the network to decrease the substantial computational demands associated with exploring multiple parameter combinations. However, our previous study showed a comparable effect of network inhibition in the generation of gamma power in networks with sparse or all-to-all connectivity (35).

Prefrontal gamma oscillations are thought to be generated, at least in part, by a local circuit that consists of excitatory pyramidal neurons and inhibitory PVIs in layer 3 (10). In addition to alterations in the PVI component of this circuit, alterations in synaptic inputs to PFC layer 3 pyramidal neurons have also been reported in schizophrenia, which could contribute to lower prefrontal gamma power (68). Given that interactions among synaptic parameters in excitatory and inhibitory neurons can shape the dynamics of neural networks in computational models (69, 70), future studies investigating the interplay of synaptic alterations in pyramidal neurons and PVIs may further inform the nature of

the disease process that contributes to altered network properties of PFC circuitry and impaired working memory in schizophrenia.

CONCLUSIONS

The present findings suggest several important perspectives on the disease process underlying PFC dysfunction in schizophrenia. First, our empirical findings suggest that schizophrenia is associated with alterations in the variability, even in the absence of differences in the central tendency, of synaptic measures in the PFC. Second, our computational findings suggest that such variability can regulate the physiological properties of cortical circuits. Finally, our computational findings suggest that even modest alterations in different synaptic parameters can, in combination, have a profound effect on gamma power. Thus, our study reveals synaptic variability as an important element of the disease process of schizophrenia and suggests that PFC dysfunction in the illness may emerge from the dynamic interaction of relatively modest alterations in multiple elements of PFC neural circuitry.

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Examination Questions for Synaptic Variability and Cortical Gamma Oscillation Power in Schizophrenia

1. **Cognitive dysfunction, such as impaired working memory, is one of the core features of schizophrenia. Which of the following is considered as the neural substate of impaired working memory in the illness?**
   A. Lower power of alpha-frequency oscillations in the sensory motor cortex.
   B. Lower power of gamma-frequency oscillations in the prefrontal cortex.
   C. Greater power of beta-frequency oscillations in the visual cortex.
   D. Greater power of gamma-frequency oscillations in the prefrontal cortex.
2. **The generation of cortical gamma oscillations is thought to depend on excitatory synaptic inputs to parvalbumin interneurons and this study showed greater variability in excitatory synaptic strength across these neurons in the prefrontal cortex of schizophrenia. Which of the following correctly describes the predicted effect of this synaptic alteration on prefrontal gamma power in schizophrenia based on the model network simulation?**
   A. Decreases prefrontal gamma power by disrupting neural synchrony.
   B. Decreases prefrontal gamma power by reducing neural activity.
   C. Increases prefrontal gamma power by strengthening neural synchrony.
   D. Increases prefrontal gamma power by increasing neural activity.
3. **This study showed that, in isolation, each of the three synaptic alterations reported in parvalbumin interneurons in the prefrontal cortex of schizophrenia (i.e., greater synaptic variability, lower mean density of excitatory inputs, lower mean strength of inhibitory outputs) modestly decreases gamma power in the model network. Which of the following correctly describes the predicted effect of an interaction among these synaptic alterations on prefrontal gamma power in schizophrenia based on the model network simulation?**
   A. Produces an expected additive reduction in prefrontal gamma power.
   B. Produces a milder reduction in prefrontal gamma power than expected due to antagonistic interaction.
   C. Produces a more substantial reduction in prefrontal gamma power than expected due to synergistic interaction.
   D. Completely abolishes the generation of gamma oscillations in the prefrontal cortex.