Multifactoriality in Psychiatric Disorders: A Computational Study of Schizophrenia

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The search for biological causes of mental disorders has up to now met with limited success, leading to growing dissatisfaction with diagnostic classifications. However, it is questionable whether most clinical syndromes should be expected to correspond to specific microscale brain alterations, as multiple low-level causes could lead to similar symptoms in different individuals. In order to evaluate the potential multifactoriality of alterations related to psychiatric illness, we performed a parametric exploration of published computational models of schizophrenia. By varying multiple parameters simultaneously, such as receptor conductances, connectivity patterns, and background excitation, we generated 5625 different versions of an attractor-based network model of schizophrenia symptoms. Among networks presenting activity within valid ranges, 154 parameter combinations out of 3002 (5.1%) presented a phenotype reminiscent of schizophrenia symptoms as defined in the original publication. We repeated this analysis in a model of schizophrenia-related deficits in spatial working memory, building 3125 different networks, and found that 41 (4.9%) out of 834 networks with valid activity presented schizophrenia-like alterations. In isolation, none of the parameters in either model showed adequate sensitivity or specificity to identify schizophrenia-like networks. Thus, in computational models of schizophrenia, even simple network phenotypes related to the disorder can be produced by a myriad of causes at the molecular and circuit levels. This suggests that unified explanations for either the full syndrome or its behavioral and network endophenotypes are unlikely to be expected at the genetic and molecular levels.

Key words: schizophrenia/computational model/parametric exploration/attractor network/multifactoriality/complexity

Introduction

Diagnostic classifications as described in the Diagnostic and Statistical Manual of Mental Disorders and International Classification of Diseases have become a dominant concept in psychiatry over the last decades, and much effort has been spent to understand their underlying neurobiology.[1,2] However, the search for biological causes of mental illness has up to now met with limited success: susceptibility genes described for most disorders have little individual impact on phenotypic variation within populations,[3–6] and proposed biomarkers are still far from attaining diagnostic accuracy.[7–9] This has led some to believe that such categorical systems might not be ideal for studying the pathophysiology of mental illness, as symptom-based classifications might not necessarily map to clear-cut neurobiological alterations.[10,11]

Many have argued that research in psychiatry should move away from these categories and that disorders should be broken down into endophenotypes,[12,13] cognitive domains,[14] or, in the more recent National Institute of Mental Health proposal, Research Domain Criteria.[15] The expectation is that simpler phenotypes (eg, fear, reward learning, or laboratory measures such as prepulse inhibition) might correlate more clearly with genetic variants or biomarkers, allowing nature to be "carved at its joints" and leading the way to effective diagnosis based on genetic, molecular, or imaging studies.[7,10]

There is no guarantee, however, that simpler behavioral phenotypes will consistently map to unique molecular alterations in the general population. For instance, the few genome-wide association studies (GWAS) involving specific cognitive tests or phenotypes have fared no better than those trying to detect genetic associations for psychiatric disorders.[16–18] Thus, an alternate view is that most disturbances in behavior have a large number of possible causes at the molecular level and that any complex behavior or clinical syndrome is likely to be multifactorial by default. In this case, the hope for specific genetic or molecular biomarkers for psychiatric disorders[7,19] might be somewhat of an oxymoron, irrespectively of the classification adopted at the psychological level.

Such a view is supported by in silico models of simple neural systems, such as the lobster pyloric circuit, which have shown that very similar network phenotypes can be derived from disparate synaptic and molecular parameters.[20] Moreover, evidence suggests that similar patterns of network behavior can be produced through different combinations of molecules and synapses in different neurons and circuits.[21] Thus, one would expect that a complex behavioral alteration such as a psychiatric syndrome might similarly be caused by distinct molecular and cellular alterations in different individuals.

The use of computational models of psychiatric disorders is an alternative to integrate basic neurobiological data with brain functions and symptoms. These models typically aim to reproduce dysfunctions associated with brain disorders in simplified in silico neurons or networks.[22–24] Most of them, however, have ultimately relied on the assumption that psychiatric disorders can be linked to specific microscale causes. Thus, the usual process involves (a) generating a computational model of a network phenotype related to a disorder and (b) studying whether one or a few specific alterations (eg, in neurotransmitter receptors, channel conductances, or brain connectivity) can account for this phenotype.[25–29] However, the possibility that other combinations of molecular and network features might produce the same effect is rarely investigated (but see Siekmeier and vanMaanen[30] for a significant exception).

To evaluate the hypothesis that similar network alterations can be produced by a myriad of low-level causes, we performed a large-scale parametric exploration of 2 published network models of schizophrenia.[25,31] We found that numerous combinations of molecular and microcircuit alterations could give rise to similar schizophrenialike network dysfunctions in both models. These results highlight the complexity of mapping between the molecular and network levels and put into question whether unified reductionist explanations for mental disorders should be expected in the general population.

Methods

Network Model

For most of our simulations, we used a previously published computational model of schizophrenia-related network alterations.[22,25] It is based on a widely used cortical network model, consisting of biophysically realistic integrate-and-fire spiking neurons that receive excitatory and inhibitory inputs through α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), N-methyl-D-aspartate (NMDA), and type-A γ-aminobutyric acid (GABA-A) receptors.[32] Background excitation to the network is delivered as a 2400-Hz Poisson process that excites AMPA receptors, representing the input of 800 excitatory neurons at a 3-Hz firing rate (FR), compatible with experimental observations.[33,34]

The network possesses pools of strongly connected excitatory neurons, which represent established memories or activity patterns (figure 1a). These pools, through their recurrent connections, function as attractors that lead network activity toward specific patterns of activation, thought to underlie specific mental representations in the brain.[35,36] Thus, when the network enters an attractor state, FR in the corresponding neuronal pool increases sharply, as shown by electrophysiology data during working memory tasks in animals.[37] Slow NMDA-mediated currents are particularly important for this kind of dynamics, in agreement with the effects of NMDA antagonists on working memory.[38,39]

In the original model, simultaneous reductions in GABA-A and NMDA conductances were shown to cause 2 network phenotypes reminiscent of schizophrenia. The first is the frequent emergence of spontaneous patterns of activity (figure 1b), related by the authors to positive symptoms such as delusions and/or hallucinations caused by unwarranted cortical network activity.[40] The second is a difficulty in maintaining induced patterns of network activity as attractors (figure 1c), which was related to negative and cognitive symptoms such as working memory deficits, as electrophysiology studies strongly suggest that attractor dynamics in the prefrontal cortex mediates this function.[41] Details of the model are similar to those in the original publication and are described in supplementary methods.

Simulations

For replication purposes (figures 1e and 1f), we ran 1000 simulations in the 4 conditions used in the original report[25]: normal conductances, reduced GABA conductance (9% decrease), reduced NMDA conductance (4.5% decrease), and reduced GABA and NMDA conductances (combining both alterations). Networks in each condition were tested in 3 simulation protocols: (a) spontaneous activity, in which the network received only background stimulus; (b) persistent activity, in which an additional 120-Hz stimulus (representing input from neurons carrying sensory information) was applied selectively to a pool of strongly connected neurons (S1) for 500 ms, leading to a persistently high FR in these neurons after this period due to attractor dynamics; and (c) distraction simulations, in which persistent activity was induced as in (b), followed by a distractor input of variable frequency applied to a separate pool of strongly connected neurons (S2) between 1000 and 1500 ms. To evaluate network performance, we used the same measure used by the original article: the percentage of simulations in which FR in S1 neurons was higher than 10 Hz during the last second of simulation, reflecting maintenance of the S1 attractor. As baseline activity was around 3 Hz, while attractor states led to frequencies above 20 Hz, this cutoff point was optimal in discriminating between them (figure 1d).

For evaluation of changes in network activity caused by individual parameter variations (figure 2), we ran 100
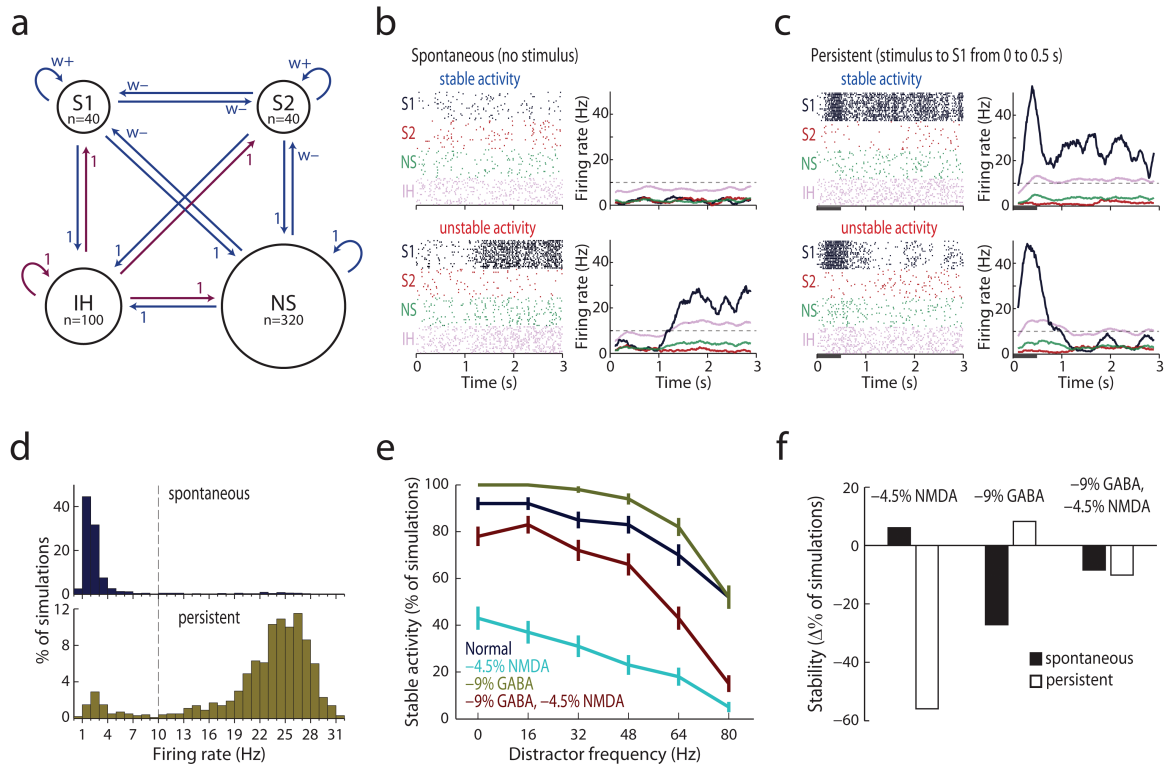
Fig. 1. Model description and validation. (a) Schematic depiction of the model. Excitatory neurons are divided into 3 groups: 2 selective pools (S1 and S2), with strong recurrent connections within pools (w+) and weak interpool connections (w−), and a nonselective pool (NS), with standard connections to other pools. Inhibitory neurons (IH) connect equally to all excitatory neurons and among themselves. There are also connections from 800 external neurons firing at 3 Hz, simulated as a 2400-Hz background excitatory input to each neuron. (b) Examples of simulations with stable (top) and unstable (bottom) spontaneous activity in the S1 pool, observed in the normal and schizophrenia-like (−9% GABA, −4.5% NMDA) networks, respectively. Left panels show spike times of 20 neurons in each pool, while right panels show the mean firing rate of the pool (200-ms sliding window). Notice spontaneous emergence of the S1 attractor in the schizophrenia-like network, characterized by increased firing rate in this pool after ~1 s. (c) Examples of simulations with stable (top) and unstable (bottom) persistent activity, observed in the normal and schizophrenia-like networks, respectively. A 120-Hz stimulus is applied to S1 neurons from 0 to 0.5 s, leading to a persistent increase in their firing in the normal network. In the schizophrenia-like network, they return to baseline activity shortly after the stimulation, indicating impaired attractor maintenance. (d) Histogram depicting S1 firing rates in the normal network during the last second of simulation in the spontaneous (top) and persistent (bottom) protocols. Notice peaks at 2–4 Hz during baseline and 20–30 Hz in the attractor state, with an optimal cutoff at 10 Hz (dashed line). (e) Effect of conductance variations on the stability of persistent activity after a distractor. A 120-Hz stimulus is applied to S1 neurons from 0 to 0.5 s, followed by stimulation of S2 neurons from 1 to 1.5 s (distractor stimulus). The percentage (±SEM) of 100 simulations with stable S1 firing rate (defined as >10 Hz) during the last second is shown for various distractor frequencies in the different conductance regimes. (f) Effect of conductance variations on network stability. Bars show changes from baseline in the percentage of simulations with stable activity in the spontaneous and persistent protocols for each conductance regime (1000 simulations each). NMDA reduction leads to decreased stability of persistent activity, while GABA reduction leads to decreased stability of spontaneous activity; reduction in both (the schizophrenia-like phenotype) causes instability in both protocols.

simulations for each parameter value in both the spontaneous and persistent activity protocols (see above). Standard parameters were used, except for the individual variation of AMPA, GABA, and NMDA conductances, inhibitory and excitatory connectivity, and background excitation. As the magnitude of reported molecular changes in schizophrenia patients can vary widely in the literature (ranging from 80% decreases[42] to 2-fold increases[43] in the case of NMDA GluN1 subunit mRNA levels, for example), we initially explored a wide range of variations from −80% to +80% (with 5% steps). Variations of other parameters were also explored and are shown in supplementary figures S1–S3.

To evaluate the effect of combined variations of multiple parameters[20,30] (figure 3), we ran 100 simulations for each of 5625 parameter combinations in the spontaneous and persistent activity protocols, setting background excitation and conductances for AMPA, GABA, and NMDA at 1 of 5 different levels (90%–110% of normal, with 5% steps) and excitatory and inhibitory connectivity at 1 of 3 different levels (90%, 95%, or 100%). We selected as "valid networks" those in which the median FR during the last second in nonselective excitatory (ie, not pertaining to the S1 or S2 pools) and inhibitory neurons was within the observed range of 2000 simulations of spontaneous activity using the original model parameters for
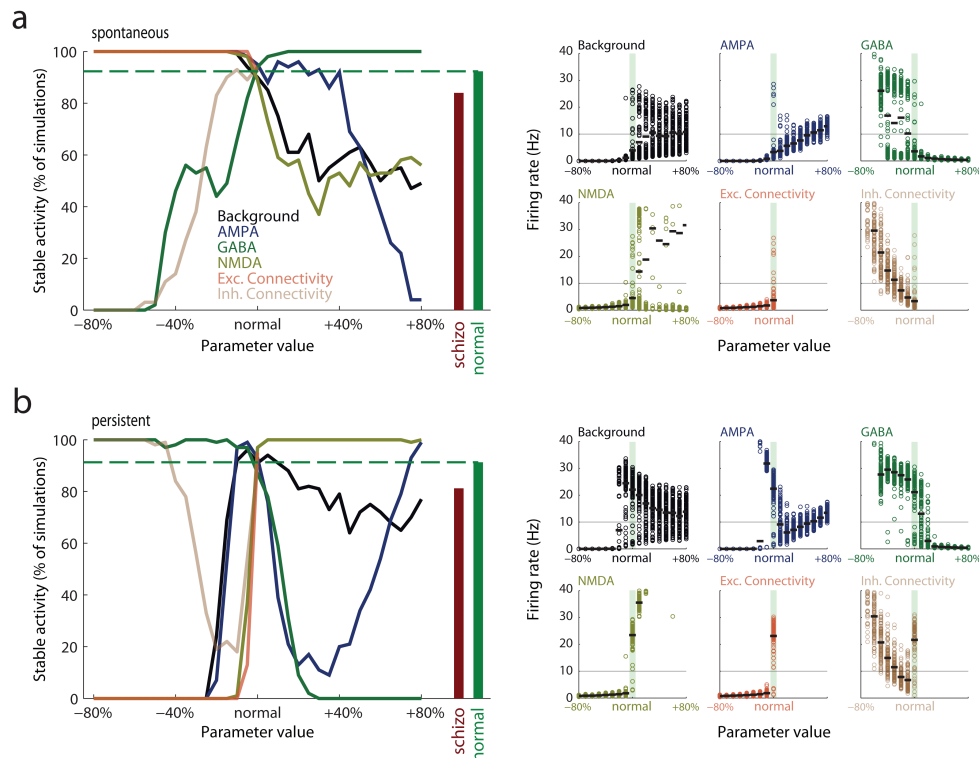
Fig. 2. Effects of isolated parameter variations on network activity. Effect of variations in individual parameters on the stability of spontaneous (a) and persistent (b) network activity. Lines on the left panels represent the percentage of 100 simulations exhibiting stable activity (S1 firing rate <10 Hz in [a] or >10 Hz in [b]) for different values of the 6 parameters explored (−80% to +80%, 5% steps). Percentages obtained for 1000 simulations with the normal (green bars and dashed lines) and original schizophrenia-like (−9% GABA, −4.5% NMDA, red bars) networks are shown for reference. Right panels show firing rate of S1 neurons during the last second of simulation for 100 simulations (dots) with each parameter value. Black traces indicate the mean, and green shaded area indicates the normal value for each parameter.

normal and schizophrenia-like phenotypes (1.2–5.88 Hz for excitatory neurons and 5.74–15.24 Hz for inhibitory neurons). This was a way to select simulations in which network activity was within plausible ranges and did not present major abnormalities that might be incompatible with a functioning cortical circuit. However, we also present an analysis of all simulated networks in supplementary figure S4 and analyses using other definitions of valid activity in supplementary table S1.

A network was defined as schizophrenia-like whenever it presented alterations in the stability of spontaneous and persistent network activity that were equal to or greater than those observed in the 1000 simulations with the original schizophrenia-like phenotype.[25] More specifically, this meant (a) >16% of simulations with S1 FR > 10 Hz during the last second in spontaneous activity simulations—corresponding to a high frequency of spontaneously emerging attractors and correlating with positive symptoms—and (b) <81.2% of simulations with S1 FR>10 Hz during the last second in persistent activity simulations, corresponding to difficulty in maintaining an established attractor and corresponding to negative symptoms.

Receiver operating characteristic (ROC) curves were constructed to analyze the sensitivity and specificity of each parameter in identifying schizophrenia-like

networks (figure 4b). We also performed an information theory–based analysis to discriminate parameters (or combinations) with the most information about network phenotype (figure 4c; see supplementary methods). Finally, we constructed ROC curves for excitatory/inhibitory FR, obtained by dividing the mean FR in excitatory neurons by that of inhibitory neurons during the last second of spontaneous activity simulations (figure 4d).

Additionally, we also performed simulations using a second published cortical network model[31] in which schizophrenia-like cognitive deficits were modeled as a reduction in precision when encoding a spatial stimulus (supplementary figure S5), as shown to occur in patients.[44] Simulations performed with this model followed the same approach of those with the first one and are described in supplementary results.

Results

Figure 1 shows that our simulations could successfully reproduce the results of the original model.[25] Figure 1e presents the percentage of simulations with stable persistent activity of S1 neurons after stimulation with various distractor frequencies. Both isolated reductions in NMDA conductance
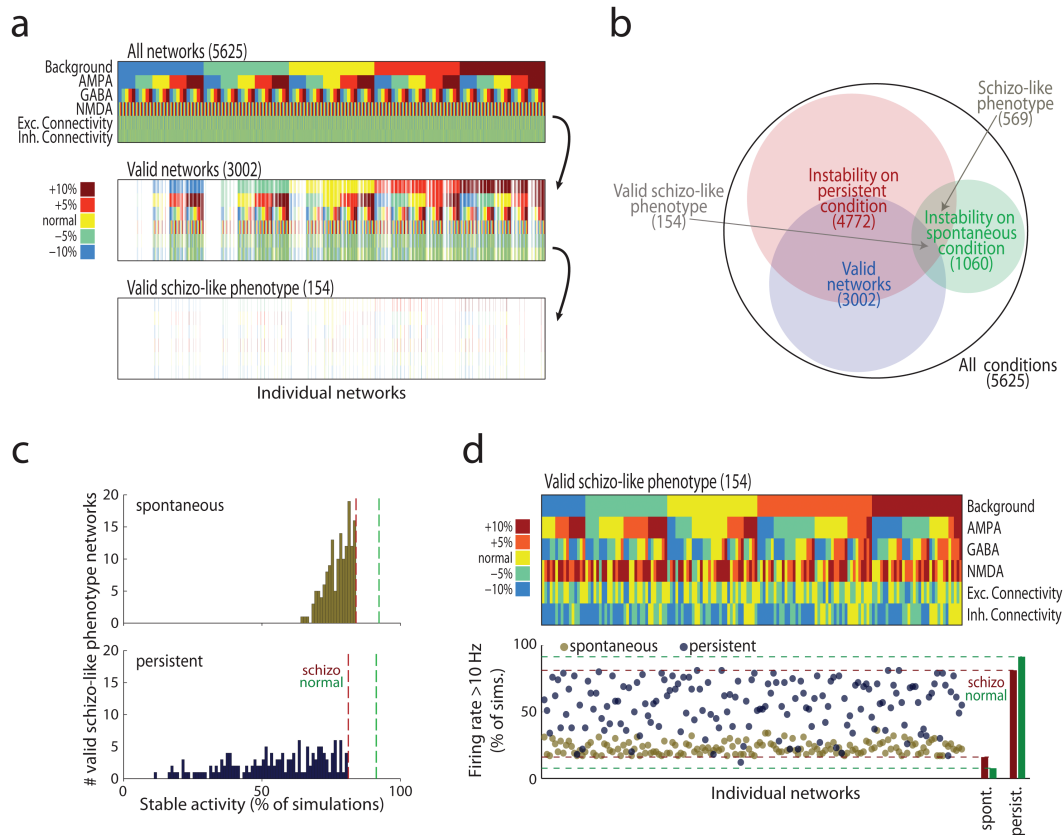
Fig. 3. Multiple schizophrenia-like phenotypes revealed by parametric exploration of the model. (a) Color maps representing all 5625 parameter combinations (top), the 3002 presenting firing rates within the valid range (middle) and the 154 presenting schizophrenia-like phenotypes (bottom). Each column corresponds to a particular combination of parameters, as indicated by the color scale. (b) Venn diagram representing all 5625 networks, the 4772 with unstable persistent activity, the 1060 with unstable spontaneous activity, and the 3002 with firing rates within valid ranges. Valid networks with schizophrenia-like phenotypes lie at the intersection of the 3 circles. (c) Histogram showing the stability of the 154 valid schizophrenia-like networks in the spontaneous and persistent activity protocols, measured as the percentage of simulations with stable activity in the S1 pool (FR <10 Hz for spontaneous simulations, >10 Hz for persistent ones). Green and red dashed lines indicate results for the normal and original schizophrenia-like (−9% GABA, −4.5% NMDA) conditions, respectively; schizophrenia-like networks are left of the red line. (d) Color map representing the distribution of parameter values among valid schizophrenia-like networks (top). The percentage of simulations with stable activity in the spontaneous (light brown) and persistent (blue) protocols for each individual combination is shown in the scatter plot (bottom). Green and red bars show results for the normal and original schizophrenia-like networks, respectively.

and concomitant reductions in NMDA and GABA conductances decreased the stability of persistent activity in the network, but only combined reductions decreased stability in spontaneous activity as well (figure 1f).

We then investigated the effect of varying individual parameters in the model to evaluate whether a similar network phenotype could be observed with other alterations. Figure 2 shows the effect of varying conductances, background excitation, and network connectivity on the percentage of simulations exhibiting stable activity in the spontaneous (figure 2a) and persistent (figure 2b) activity protocols. The results show that the schizophrenia-like phenotype (ie, a reduction in the stability of both types of activity) can be obtained in other ways besides those originally explored, such as by decreasing inhibitory network connectivity or increasing AMPA conductances (see supplementary figures S1–S3 for variation of additional parameters).

For our large-scale parametric exploration of the model, we used the 6 parameters shown in figure 2, setting conductances and background excitation at 5 different levels and connectivities at 3 different levels, thus generating 5625 ($5^4 \times 3^2$) combinations. Among these, 3002 (53.3%) had FRs within valid ranges, of which 154 (5.1%) presented schizophrenia-like phenotypes (figures 3a and 3b). Thus, the same network alterations resembling schizophrenia described in the original model could be obtained by a large number of alternative parameter combinations. Without filtering valid networks by FR, the number of schizophrenia-like combinations criteria rises to 569 (10.1% of simulations) (supplementary figure S7 and table S1). Data on the stability of schizophrenia-like networks in the spontaneous and persistent activity protocols are presented in figures 3c and 3d.
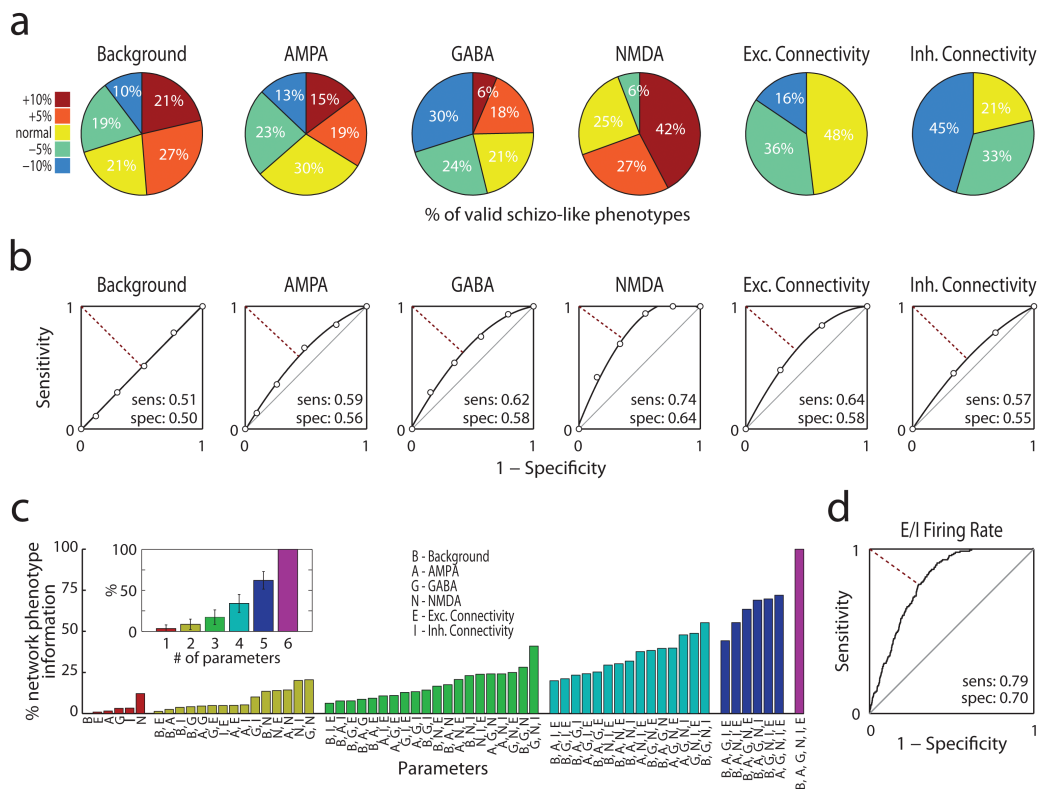
Fig. 4. Isolated network parameters do not predict the occurrence of schizophrenia-like phenotypes. (a) Pie graphs showing the percentage of valid schizophrenia-like combinations presenting each individual parameter value (eg, 21% of schizophrenia-like networks have background excitation at maximum values). (b) Receiver operating characteristic (ROC) curves showing the sensitivity and specificity of each individual parameter in identifying schizophrenia-like networks. (c) Percentage of the information on network phenotype contained in isolated or combined model parameters. Inset shows mean phenotype information (±SD) for different numbers of combined parameters. (d) ROC curve as in (b), but for the ratio between excitatory and inhibitory firing rates. Note that sensitivity and specificity values are higher than any of those obtained for individual parameters.

To explore which parameters were more important in determining network activity, we investigated their distribution among networks presenting schizophrenia-like behavior. Strikingly, we found that there was little correlation between individual parameters and network phenotype: with a single exception, schizophrenia-like network behavior could be generated with any of the individual parameters set at any of the values, at least for some combinations of the remaining parameters (figure 4a). And although schizophrenia-like behavior was rarer for some values, no parameter could reliably predict whether a network would be labeled as schizophrenia-like: the best diagnostic performance for an individual parameter was a sensitivity of 74% and a specificity of 64% for NMDA conductance (figure 4b).

We explored how combining parameters could improve this classification and found that including more known parameters consistently increased the amount of information about network phenotype (figure 4c). Among these, combinations of GABA conductances, NMDA conductances, and inhibitory connectivity were the most informative. Based on this, we decided to explore higher order parameters derived from network activity and found that the ratio between excitatory and inhibitory

FRs was a better predictor of schizophrenia-like alterations than any of the individual parameters (figure 4d), although it was still far from diagnostic accuracy. This suggests that intermediate-level markers of network activity might be more closely correlated to network behavior (and presumably to psychiatric symptoms) than microscale alterations such as receptor conductances or synaptic architecture.

Exploration of the second network model[31] yielded a similar picture. Of 3125 networks generated by combinations of 5 different parameters, 834 (26.7%) had activity within valid ranges and 41 (4.9%) of these exhibited schizophrenia-like alterations in encoding precision (supplementary figure S6). Schizophrenia-like alterations were observed for all values of every parameter, and the highest sensitivity and specificity values observed were 78% and 67%, respectively (for NMDA conductance in inhibitory neurons) (supplementary figure S7). Once again, the ratio between excitatory and inhibitory had better accuracy than any parameter in isolation. As in the first model, qualitatively similar results were observed with different filters for valid ranges of activity (supplementary figure S8 and table S1).

Discussion

By varying multiple parameters in 2 computational models of schizophrenia representing different aspects of the disorder, we found that many distinct parametric combinations could lead to similarly altered network phenotypes. Our results are akin to what has been shown in a simple model of the lobster enteric nervous system[20] and in a smaller scale study of gamma frequency alterations related to schizophrenia in a detailed hippocampal model, which varied 3 parameters in combination.[30] In this latter study, most schizophrenia-like phenotypes were found to cluster around reductions in both NMDA receptor function and pyramidal cell connectivity. However, by using more simplified networks that allowed us to vary a larger number of parameters, we found that schizophrenia-like alterations could occur in a much broader range of parametric combinations.

Whether this holds for complex biological systems such as the human brain is a wider question, but experimental evidence suggests that it might be the case. A screening of 206 gene knockouts in mice, for instance, showed that 39 (19%) of them presented fear-related alterations in an open field task.[45] More significant still is the evidence arising from GWAS, which have failed to find genes consistently leading to odds ratios greater than ~1.3 for developing schizophrenia.[4,6,46] Thus, recent views of schizophrenia genetics have drifted toward either widely polygenic inheritance[3,47] or rare high-risk mutations,[48] with little evidence that a common unified genetic explanation can be found for the disorder.[49] Our study shows that independent alterations at the molecular (eg, receptor conductances) and microcircuit (eg, network connectivity, background excitation) levels can interact in determining schizophrenia-like phenotypes, providing a plausible explanation for this genetic complexity.

Many authors have argued that diagnostic criteria for schizophrenia are too wide and that simpler endophenotypes might correlate better with molecular alterations.[13] In this sense, the network models we studied constitute vastly simplified versions of a cortical circuit, and the alterations described in them are far from the full complexity of schizophrenia. Nevertheless, even these simple network phenotypes correlate poorly with specific microscale alterations. These results challenge the view that endophenotypes should correlate better with molecular features than complex psychiatric disorders—in fact, our model suggests that the opposite could be true, as a simpler trait could actually be easier to produce through multiple genetic influences than a complex syndrome.[18]

Our results are also a computational demonstration of a general epistemological lesson that has been voiced by many authors[11,50–52]: namely, that different levels of analysis are needed to describe complex phenomena and that lower level (eg, molecular) descriptions are not necessarily more accurate than higher level (eg, behavioral) ones. On the contrary, the difficult mapping between levels of complexity suggests that mental illness will not be understood by reductionist approaches alone and that the best descriptions for complex entities such as psychiatric disorders will often lie at higher levels.[11] Thus, the frequent assumption that psychiatry should aim to replace symptoms by molecules and biomarkers as diagnostic tools[53] might be overly optimistic, as low-level markers might not be sufficiently informative in terms of their correlation with behavior.

Naturally, this does not mean that one should consider the brain only in psychological or network terms due to the understanding that its microscale interactions are too complex. In fact, our results show that network alterations can result from changes in specific microscale parameters, as is known to be the case for disorders such as Huntington's chorea, or for rare mutations that strongly cosegregate with psychiatric disorders.[54] But they do suggest that intermediate levels of complexity are needed to provide neurobiological theories with explanatory power in psychiatry, as exemplified by the fact that a simple measure of excitation/inhibition had better predictive power than any low-level parameter in our study. This view is also supported by other areas of medicine: although genetic studies of type 2 diabetes have yielded a picture as complex as that of schizophrenia,[55] its multiple genetic influences converge upon common pathways such as insulin secretion, peripheral insulin resistance, and glucose levels. Thus, the genetic complexity of a disorder does not preclude biological descriptions, but it requires diagnostic markers to be sought at a higher level than that of isolated molecules.

In summary, our study shows that a large number of low-level alterations such as receptor conductances and network architecture can account for schizophrenia-like network dysfunctions in 2 computational models of this disorder. Our results call attention to the complex nature of even simple behavioral phenotypes and suggest that the frustration in finding consistent genetic associations and molecular biomarkers for psychiatric disorders is to be expected, not only because current diagnostic classifications are fallible but also because the gap between molecules and behavior is very wide. In this sense, it is possible that reductionist paradigms have underestimated the complexity of describing the working brain at the molecular level and that a vast middle ground has to be breached to generate biological theories for psychiatric disorders.

Supplementary Material

Supplementary material is available at http://schizophreniabulletin.oxfordjournals.org.

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