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Letter to the Editor

Impaired network stability in schizophrenia revealed by TMS perturbations

Dear Editors,

A growing body of work based on graph theory and statistical physics tools is revealing abnormalities in the schizophrenia connectome. These include anomalies in network metrics such as connectivity, clustering, modularity, global efficiency, hierarchy and robustness, which impact network architecture and dynamics (e.g., Alexander-Bloch et al., 2010). Such abnormalities, when framed within a dynamical systems theoretical framework, suggest that the schizophrenic state can be described as a network configuration of altered energetic landscapes with reduced stability relative to healthy brain networks (Loh et al., 2007; Levit-Binnun et al., 2010).

Transcranial Magnetic Stimulation (TMS) has recently emerged as a means of probing the susceptibility of schizophrenia brains to perturbations (Levit-Binnun et al., 2007). When TMS was applied over primary motor area during a finger tapping task, it affected higher brain processing in schizophrenia patients, causing lapses in attention that did not occur in healthy subjects. This perturbational approach was enhanced by Electroencephalography (EEG) measurements (TMS-EEG) to test for the effects of TMS on the entire thalamocortical system (Levit-Binnun et al., 2010). Here we go on to apply graph theory tools to study network stability and dynamics under the influence of TMS perturbations in schizophrenia.

The data used in this study was taken from the study reported in Levit-Binnun et al. (2010). $N = 6$ healthy participants and $N = 7$ participants with schizophrenia took part in this work. In brief, EEG was monitored while a single-pulse TMS perturbation was applied at Cz ('TMS' condition) while sham TMS ('Sham' condition) served as control condition (see Levit-Binnun et al., 2010 for details). Network analysis was done using the Complex Networks Analysis Package (Muchnik et al., 2007) and an in-house code.

The processed and artifact-free EEG signals described in Levit-Binnun et al. (2010) resulted in four sets of 64 EEG signals covering an epoch time of 300 ms. Each signal is the measurement from one EEG electrode for each group of participants (schizophrenia patients and controls) averaged over the group. This was done for two conditions (Sham and TMS) for a total of four measurement sets. From each of these sets of data, a directed, weighted network connecting 64 nodes (electrodes) was constructed and the cutoff threshold determined (see Fig. 1A for details).

We tested the dynamic properties of the networks by applying robustness analysis — a mathematical method which probes the connectivity and resilience of the network (Gallos et al., 2006). Nodes are mathematically removed and the integrity of the system (i.e., how many clusters in the network are connected to all other clusters) is tested after each step (see Fig. 1B for details). This mathematical attack should be distinguished from the TMS perturbation — a real world perturbation that serves to define the network. Two modes of node removal were applied. In "sequential removal" nodes were removed in decreasing order of their degree (number of out-going connections). In "random removal" a randomly selected node was removed in each step. Such analysis reveals the underlying connectivity pattern because hub-dominated networks are typically more vulnerable to sequential attack while relatively resilient to random attack.

Fig. 1B shows that in the healthy brain both the TMS-perturbed network and the non-perturbed (Sham) network behave similarly and in a manner expected from hub-dominated networks — i.e., exhibiting vulnerability to the sequential attack and resilience to the random attack. In contrast, in schizophrenia the non-perturbed (Sham) and TMS-perturbed networks showed different responses to the attacks. The Sham schizophrenia network exhibited decomposition before the healthy one.

Most significantly, the TMS-perturbed network in schizophrenia was resilient to both modes of attack. Network disintegration occurred only after almost all the nodes were removed and network fragmentation occurred much later than in all other networks. This response of the schizophrenia network to node attack resembles the behavior of a network with homogeneously distributed links and very few hubs.

In summary, the unperturbed schizophrenia network is more sensitive, and loses connectivity earlier than the healthy network, while the TMS perturbation pushes it into a state that responds like a random network. These findings suggest that schizophrenic functional networks are more vulnerable than healthy networks, and that relatively small perturbations can perturb their network architecture.

We propose that the observed effects of TMS perturbations provide an indication of the effects that real world perturbations from a variety of external and internal sources may have on the schizophrenia state. A healthy network is expected to exhibit relatively high resilience to these perturbations, and an ability to cope with disturbances. On the other hand, the schizophrenia network is in a state with altered dynamical properties due to an abnormal connectivity, and may thus be more affected by such perturbations. We propose that the relative ease by which schizophrenia networks can be perturbed by external and/or internal processes can underlie some of the cognitive and behavioral dysfunction of schizophrenia.

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Authors 2 and 4 designed the study and wrote the protocol and wrote the first draft of the manuscript. Author 3 recruited and handled the schizophrenia patients. Author 1 undertook the statistical analysis. All authors contributed to and have approved the final manuscript.

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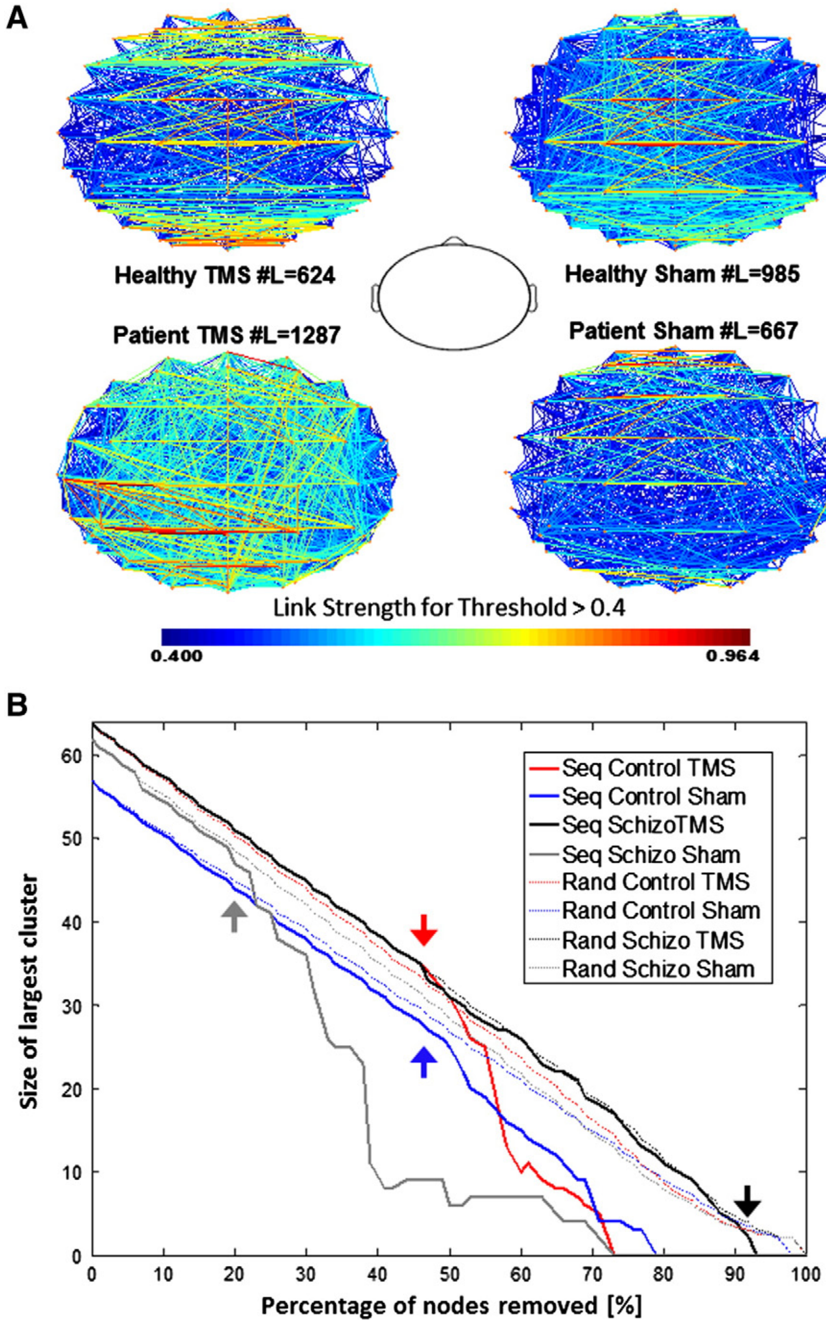

Fig. 1. Network construction and attack analysis. A. Weighted networks as constructed for each condition and group. For each pair of electrodes E_i and E_j we calculated max $[C_{ij}(\Delta t) = \int E_i(t) * E_j(t + \Delta t)dt]$, for varying time shifts $+300$ ms $> \Delta t > -300$ ms. This maximum correlation was taken as the weighted graph link W_{ij}. The direction of the link (if electrode E_i influences electrode E_j or vice versa) was determined based on the sign of Δt at the maximum correlation. A minimal strength of the links in the network was set by a threshold for all W_{ij}. At $W_{ij} > 0.4$ the difference between schizophrenia and control groups in both conditions was greatest. At this threshold, the difference between conditions (TMS versus Sham) is significant for both schizophrenia and control groups, as is the difference between groups for the TMS and Sham conditions (t-test, $p > 0.000001$ in all cases). A Kolomogorov–Smirnov test yielded that the difference between groups in change between Sham to TMS was significant ($p < 0.001$). The number of links with $W_{ij} > 0.4$ is designated in A as #L. All subsequent analyses were done using this threshold. B. Robustness analysis of the four networks. The y-axis displays the size of the largest cluster that survives after each step of node removal. The x-axis displays the percentage of nodes removed in each step. The solid line represents the "sequential removal" mode — a harmful attack in which highly connected hubs are removed at earlier stages. Dashed line presents the random removal attack, in which central hubs may remain even after many nodes are removed, averaged over $N = 1000$ random choices. All four networks behaved similarly in the random removal mode. More than 90% of the nodes had to be removed before the networks lost all their clusters (a "percolation" transition). In the sequential attack, both healthy networks exhibited a percolation transition (deviation from linear slope) after about 50% nodes were removed (red and blue arrows). For the Sham schizophrenia network the percolation transition occurred much earlier (after a removal of approximately 20% of the nodes — see gray arrow). In stark contrast, the TMS-perturbed schizophrenia network responded similarly to both modes of attack mode, i.e. a constant linear decrease with no percolation transition. Logrank statistical analysis showed that the curve describing sequential removal attack for the schizophrenia TMS network was statistically similar to the random attack and significantly different from sequential attack on both healthy networks as well as the Sham schizophrenia network.

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