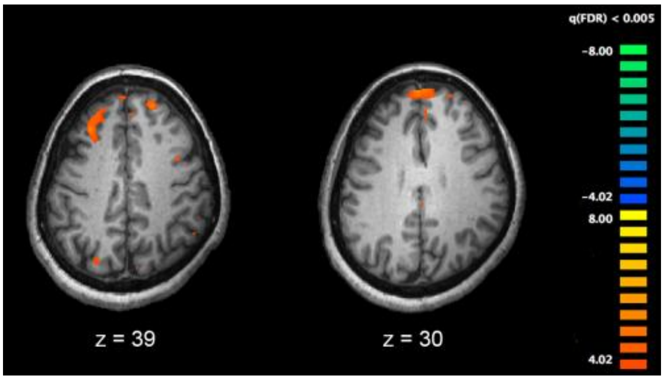
Schizophrenia and the resilience of brain functional networks

10 July 2015, by Christopher Packham



Functional magnetic resonance imaging (fMRI) and other brain imaging technologies allow for the study of differences in brain activity in people diagnosed with schizophrenia. The image shows two levels of the brain, with areas that were more active in healthy controls than in schizophrenia patients shown in orange, during an fMRI study of working memory. Credit: Kim J, Matthews NL, Park S./PLoS One.

(Medical Xpress)—Neuroscience has come to view schizophrenia as a disorder of brain network organization in which the topology of nodal connections is abnormally random. The origin of such network dysconnectivity, whether genetic or environmental, has not been clearly established. To bring clarity to the discussion, an international group of researchers recently conducted a study that used fMRI to compare the functional brain networks of schizophrenic subjects with those of their first-degree relatives. The researchers have published their results in the *Proceedings of the National Academy of Sciences*. Surprisingly, their findings bear similarities to known properties of communications networks such as the Internet.

The researchers recruited 35 patients with schizophrenia, 39 first-degree relatives of those patients, and 36 healthy volunteers. All of the schizophrenia patients were receiving their normal antipsychotic medication at the time of the experiment. The researchers acquired resting-state fMRI data from all of the subjects and used patterns of brain activity to map putative networks of activity between brain structures.

Healthy human brain networks are characterized by topologies intermediate on a so-called "small-world" spectrum between high-order lattice clusters and the clustering of a random graph. The brain networks of schizophrenic people are shifted toward the random end of this small-world spectrum.

The researchers identified specific topological abnormalities of brain functional networks in the non-psychotic, first-degree relatives of the schizophrenia patients. The relatives also demonstrated an abnormal shift to greater randomization of brain network topology. The authors consider this to be possible evidence of a hereditary risk for schizophrenia.

Once they had obtained imaging data of functioning brain networks for all subjects, the researchers built computer models of the networks and tested, in silico, the resilience of the networks in conditions of random failure. Under random node failure, the global networks of schizophrenics typically remained very high—at about 90 percent efficiency, even after more than half of the nodes had been deleted.

However, under targeted attacks in which the highest-degree nodes were knocked out, the networks of all volunteers fell below 90 percent efficiency, with schizophrenic subjects and their close relatives all demonstrating the highest degrees of resiliency. The authors write, "Complex networks like the brain, the Internet, and many other nonrandom systems, are more vulnerable to targeted attack because they have more heterogenous degree distributions than a random graph, and the deletion of high degree hubs consequently has a more serious effect on the global integrity of the network."

Thus, they assert, it is predictable that the more random brain network distributions of schizophrenia would be more resilient to targeted attack. They hypothesize that topological resilience is an advantageous adaptation because it protects global network integrity, citing evidence from previous studies that gray matter lesions tend to be concentrated in high-degree hub regions of the brain. Random network structure as an adaptive trait would also be supported by the finding of a hereditary component to schizophrenia.

However, the researchers note that it would require a twin study in the future to rule out alternative possible interpretations, for instance, the possibility of environmental causes.

More information: "Randomization and resilience of brain functional networks as systems-level endophenotypes of schizophrenia." *PNAS* 2015 ; published ahead of print July 6, 2015, DOI: 10.1073/pnas.1502052112

Abstract
Schizophrenia is increasingly conceived as a disorder of brain network organization or dysconnectivity syndrome. Functional MRI (fMRI) networks in schizophrenia have been characterized by abnormally random topology. We tested the hypothesis that network randomization is an endophenotype of schizophrenia and therefore evident also in nonpsychotic relatives of patients. Head movement-corrected, resting-state fMRI data were acquired from 25 patients with schizophrenia, 25 first-degree relatives of patients, and 29 healthy volunteers. Graphs were used to model functional connectivity as a set of edges between regional nodes. We estimated the topological efficiency, clustering, degree distribution, resilience, and connection distance (in millimeters) of each functional network. The schizophrenic group demonstrated significant randomization of global network metrics (reduced clustering, greater efficiency), a shift in the degree distribution to a more homogeneous form (fewer hubs), a shift in the distance distribution (proportionally more long-distance edges), and greater resilience to targeted attack on network hubs. The networks of the relatives also demonstrated abnormal randomization and resilience compared with healthy volunteers, but they were typically less topologically abnormal than the patients' networks and did not have abnormal connection distances. We conclude that schizophrenia is associated with replicable and convergent evidence for functional network randomization, and a similar topological profile was evident also in nonpsychotic relatives, suggesting that this is a systems-level endophenotype or marker of familial risk. We speculate that the greater resilience of brain networks may confer some fitness advantages on nonpsychotic relatives that could explain persistence of this endophenotype in the population.