COMMENTARY

Schizophrenia report: making sense of the latest news in schizophrenia and neurodegenerative disorders

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Abstract

Psychiatry continues its slow transition from the neurochemical to the molecular paradigm; there was an increased search for biological markers. Connectomics aims to physically map the complete set of neural circuits that collect, process and archive information in the brain. De novo mutations could account for replenishing the genetic variants removed by natural selection. Epigenetics continue to be focused on micro ribonucleic acids (miRNAs) and their role in schizophrenia. "Jumping genes" are known to be active in various parts of our brain. Some psychotropic medications (such as valproate) are able to activate human endogenous retroviruses (HERVs). It is currently believed that minocycline has neuroprotective effects in schizophrenia and neurodegenerative diseases.

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Schizophrenia is one of the most disabling forms of mental illness. One of the most important challenges is to establish biological markers which can accurately identify individuals with the disorder as well as at-risk individuals in preclinical stages.

Psychiatry continues its slow transition from the neurochemical to the molecular paradigm that started in 2002 with the completion of the Human Genome Project. In 2012, there was an increased search for biological markers in neurodegenerative disorders, schizophrenia and autism spectrum disorders (ASD).

Possible biological markers of schizophrenia

Connectomics (white matter tractography) is the number one topic at most neuroscience meetings in 2012. It was the most discussed theme at the third Biennial Schizophrenia International Research Society Conference held in Florence, Italy on April 5-9, 2012. Similar to the Human Genome Project, which charted every one of the three billion chemical base pairs that comprise in human DNA, connectomics aims to physically map the complete set of neural circuits that collect, process and archive information in the brain. This growing field has the potential for testing a long-standing hypothesis on the pathophysiology of schizophrenia—the "disconnection" hypothesis. Treatments of the future will be dependent on the circuits affected by the pathologic process. An important study on schizophrenia connectomics this year was: Schizophrenia, neuroimaging and connectomics completed at the University of Melbourne, Australia by Fornito *et al*.[1]

Genomics continues to take a high interest in Copy Number Variation (CNV) in 2012. CNV is caused by microdeletions or microduplications of genomic DNA with a size larger than 1 Kb. This type of structural variation is emerging as an important genomic cause of psychiatric disease. A large five years study published March 26 in Schizophrenia Bulletin is entitled De Novo Mutations in Schizophrenia.[2] It shows that de novo CNV provides the strongest evidence to date for the association with schizophrenia. De novo mutations could account for replenishing the genetic variants removed by natural selection and could, in part, explain why schizophrenia prevalence has remained stable in the general population despite low birth rate among patients.

Epigenetics continue to be focused on micro ribonucleic acids (miRNAs) and their role in schizophrenia. MiRNAs represent about 50% of small non-coding ribonucleic acids (snRNAs) that control gene expression. A snRNA that we heard of in the past is interference RNA or iRNA (Nobel Prize was given for its discovery in 2006). iRNA moderates the activity of genes by post transcriptionally binding to specific messenger RNA (mRNA) molecules and either increase or decrease their activity (for example by preventing a mRNA from producing a protein). A study from February 2012 identified miRNA 132 as being incriminated in the aetiology of schizophrenia: MiRNA-132 dysregulation in

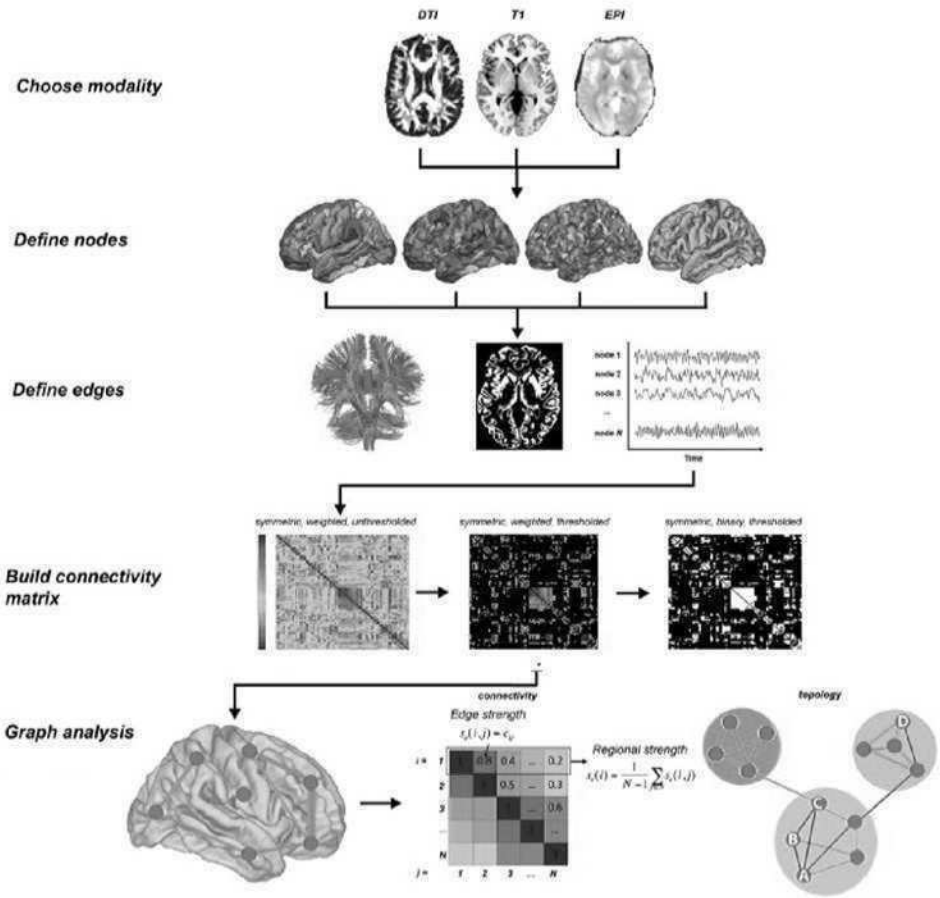

Figure 1 Illustration of the main steps involved in graph analysis of human neuroimaging data. Top row: the most commonly used imaging modalities are diffusion-tensor imaging (DTI). Second row: the raw data are parcellated into distinct network nodes. Third row: once the network nodes have been delineated, the interconnecting edges must be defined. Fourth row: once the edges have been defined, inter-regional connectivity is represented as a continuously weighted matrix. Bottom row: the matrix is used to construct a graph-based representation of brain network connectivity, termed a brain graph. (Reprinted with permission from NeuroImage).

schizophrenia has implications for neurodevelopment and adult brain function.[3] This study showed that administration of N-methyl-D-aspartate (NMDA) antagonists, such as memantine, leads to downregulation of miRNA 132 in the prefrontal cortex. Prior studies demonstrated that miRNA 132 had a role in dendritic arborisation and dendritic spine density.

Another researched area of epigenetics in 2012 is that of the "jumping genes" or retrotransposones. They are mobile genetic elements that can copy and insert themselves anywhere within a genome causing mutations in dividing cells. "Jumping genes" are known to be active in various parts of our brain, but their involvement in schizophrenia and autism is novel. This new discovery suggests that deoxyribonucleic acid (DNA) variations occurring in the developing brain could contribute to mental illness, just as mutations in mature cells in tissues may contribute to cancer. These surprising findings open a whole new vista in the biology of schizophrenia.

Along these lines a study from Germany by Olivia Diem published in January 2012 is very interesting because it raises the possibility that some psychotropic medications (such as valproate) are able to activate human endogenous retroviruses (HERVs).[4] Elevated expression levels of various HERV groups have been repeatedly described in patients with schizophrenia and were thought to be associated with the disease. Now for the first time, the research team at Helmholtz Zentrum München has shown that this stimulation may be caused at least in part by the patients' medication.

Early detection of schizophrenia (during the prodromal phase) is still in its infancy in 2012, but there are some encouraging signs that the risk of developing the disease can be lowered. A study done at Stavanger University Hospital, in Norway by Wenche ten Velden Hegelstad and her team showed a double remission rate in the early detection group without using pharmacologic treatment.[5] Anyone who thought that they may be experiencing psychosis could call the team and speak with a psychiatric nurse. If psychosis was detected, the individual would be given a

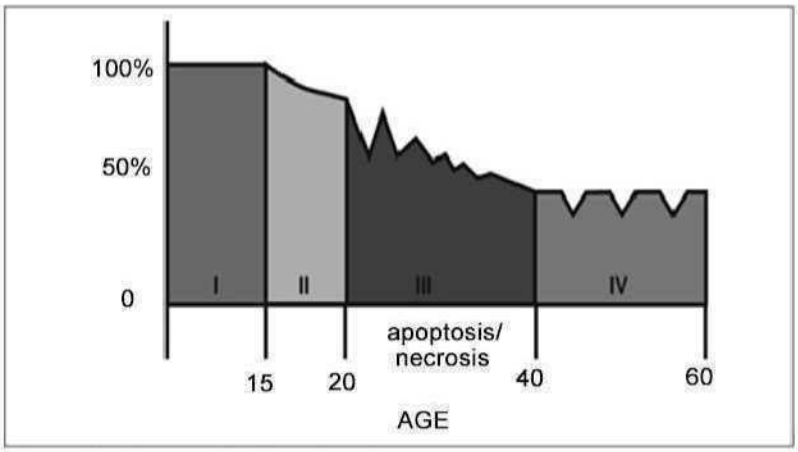

Figure 2. Stages of Schizophrenia
Stage 1. The patient is fully functioning early in life, and is virtually asymptomatic
Stage 2. Prodromal phase starts in the teens, there may be odd behaviours and subtle negative symptoms
Stage 3. The acute phase of the illness in the twenties with positive and negative symptoms
Stage 4. "Burn out" in the forties or fifties with prominent negative and cognitive symptoms

preliminary examination within 24 hours and treatment started only if psychosis was detected. Ten years after detection of initial symptoms twice as many patients from the early-detection group met criteria for recovery compared to those from the usual-detection group. These findings are in line with the National Institute of Mental Health (NIMH) project Recovery After an Initial Schizophrenia Episode (RAISE) that seeks to fundamentally change the trajectory and prognosis of the disease by diagnosing and aggressively treating in the earliest stages of illness. Early treatment consists of supportive psychotherapy, while antipsychotics are reserved for cases in which psychosis was detected.

Neuroprotection

Neuroprotection refers to treatments that aim to prevent or slow disease progression and secondary injuries by halting or slowing the loss of neurons. Common mechanisms of neurodegeneration include increased levels in oxidative stress, mitochondrial dysfunction, excitotoxicity, inflammatory changes, iron accumulation and protein aggregation.

It is currently believed that minocycline has neuroprotective effects in schizophrenia and neurodegenerative diseases.

Minocycline is a tetracycline antibiotic that is normally prescribed for pneumonia and acne. Clinical trials in Israel, Pakistan and Brazil have shown significant improvement of the symptoms of schizophrenia in patients treated with the drug. Starting in April, 2012, the National Institute for Health Research in the UK started funding a large clinical trial on the use of minocycline in psychosis.[6]

Further reading

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