The Schizophrenia Research Forum

ESSAY CONTEST

for the
2nd Schizophrenia International Research Society Conference

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The Schizophrenia Research Forum Essay Contest for the 2nd Schizophrenia International Research Society Conference
April 10-14, Florence, Italy

Applicants were asked to choose five compelling facts from various fields and describe a unifying hypothesis for schizophrenia based upon these (to include predictions, i.e., testing hypotheses). Essays were scored independently for originality, argument and implementation.

Winner
Rajiv Radhakrishnan, Yale University School of Medicine

Honorable Mention
Anna Docherty, University of Missouri-Columbia
Thomas Whitford, University of Melbourne/Harvard Medical School

Rest of the Top 12
Pauline Belujon, University of Pittsburgh
Kathryn Gill, University of Pittsburgh
Richard Keefe, Duke University Medical Center
Matcheri Keshavan, Harvard University
El-Wui Loh, National Health Research Institutes, Taiwan
Neely Myers, University of Virginia
Nathalie Picard, Abbott
Naren Rao, National Institute of Mental Health and Neuroscience Bangalore
James Walters, Cardiff University
WINNER

Rajiv Radhakrishnan
Yale University School of Medicine
New Haven, Connecticut

Fact 1: Exposure to amphetamine can result in schizophrenia-like symptoms in some individuals. This effect is observed in chronic, but not acute, amphetamine use (Segal et al., 1997).

Fact 2: The electrophysiological characteristics of prefrontal cortex neurons begin to change after just a few doses of the drug, and amphetamine exposure has opposite effects in two subregions of prefrontal cortex—a progressive hyperactivation of orbitofrontal cortex and hypoactivation of medial prefrontal cortex (mPFC) (Homayoun et al., 2006).

Fact 3: mPFC abnormalities are present in schizophrenia on multimodal imaging (Pomarol-Clotet et al., 2010). In first-episode antipsychotic-naïve patients with schizophrenia, the mPFC is smaller compared to controls (Venkatasubramanian et al., 2008).

Fact 4: The mPFC is an important hub of the default mode network (DMN). An aberrant functional connectivity of the DMN is seen in schizophrenia (Garrity et al., 2007) involving the mPFC, in particular (Camchong et al., 2009).

Fact 5: The endocannabinoid system is abnormal in schizophrenia (Fernandez-Espejo et al., 2009). Inhibition of interneuron firing extends the spread of endocannabinoid signaling (as has been shown in the cerebellum) (Kreitzer et al., 2002). The rate of firing can determine if the endocannabinoid system causes a net inhibitory long-term depression (LTD) or disinhibitory LTD (Adermark et al., 2009).

Hypothesis
Conversion from ultra high risk to schizophrenia is characterized by spread of activation of the mPFC to the dorsolateral prefrontal cortex (DLPFC), resulting in a disruption of the normal feedback regulation of the mPFC. This leads to progressive denervation of the mPFC. This process is mediated by the endocannabinoid system. It is predicted that: 1) There would be a decrease in activation of mPFC and increase in activation of DLPFC in both a working memory paradigm and a DMN paradigm as ultra high-risk patients progress to schizophrenia; 2) Cannabinoid receptor number and density will increase in the mPFC during progression from ultra high risk to schizophrenia and subsequently decrease with denervation.

Testing the Hypothesis
1. Characterization of the activity and volume of mPFC and DLPFC in DMN and working memory task paradigms in prodromal, ultra high-risk subjects over time to conversion to schizophrenia. The hypothesis suggests that the current discrepancy with regard to working memory tasks (with some studies showing hyperactivity and others showing hypoactivity in DLPFC) can be explained by the functional integrity of the mPFC; with progressive denervation of mPFC, DLPFC activity will decrease.

2. Characterization of temporal pattern of cannabinoid receptor (CB1, CB2) number and density in prodromal, ultra high-risk subjects until conversion to schizophrenia.
3. Demonstration of inhibitory LTD and disinhibitory LTD in the medial PFC in an animal model mediated by endocannabinoid signaling.

4. Demonstration of spread of activation from mPFC to DLPFC in an animal model by modulating endocannabinoid signaling.

References:


Honorable Mention

Anna Docherty
University of Missouri-Columbia

There is growing evidence that anhedonia, or the extent to which an individual reports pleasure in social and physical stimuli, is associated with genetic liability in schizophrenia (Clementz, 1991; Kendler, 1996; Docherty and Sponheim, 2008) and predicts future development of schizophrenia-spectrum disorders (Kwapil, 1998; Gooding, 2005). At the same time, in patients with schizophrenia, anhedonia is associated with poor long-term outcome (Fenton and McGlashan, 1991) and anhedonia, as well as other negative symptoms, are found to be treatment-refractory to dopamine-inhibiting medication. Despite the apparent importance of anhedonia to schizophrenia, there are unanswered questions about what anhedonia is and how it fits into schizophrenia pathogenesis.

One hypothesis might be that anhedonia results in part from a decrease in dopamine, such that sporadic spikes in dopamine associated with positive symptoms may be superimposed on underlying, low levels of tonic dopamine. In characterizing anhedonia, it has long been thought that anhedonia might reflect emotion deficits (i.e., Burbridge and Barch, 2007), and previous research has consistently found evidence of that for an involvement of dopamine in the experience of positive affect (PA; DePue, 1999). In multiple studies using emotion stimuli, we have found that anhedonia in non-clinical individuals is associated with decreased self-reported PA intensity (Kerns et al., 2008). In addition, in one prior study we found that first-degree relatives with a high-activity polymorphism of the Val158Met COMT gene (rs4680; responsible for a significant decrease in dopamine to prefrontal cortex) have higher levels of anhedonia (Docherty and Sponheim, 2008). This also suggests that anhedonia is related to dopamine regulation.

While important for prefrontal function, dopamine also plays an important role in white matter development (i.e., Wahlstrom, 2009). Myelination projections, influenced by dopamine, result in a variation in right hemisphere (RH) white matter integrity, and some evidence of this association can be found in at least one study showing an association between COMT and RH white matter integrity (Thomason, 2010). In patients, deficit symptoms have been associated with white matter integrity between prefrontal and parietal areas in RH (Rowland, 2009). Moreover, in studies of patients, Berenbaum and colleagues have found anhedonia to be related to lateralized function (Berenbaum et al., 2009), and our studies of schizotypal anhedonia show a similar relationship (Docherty and Kerns, in preparation). Altogether, there is converging emotion, genetic, and cognitive evidence that dopamine may play a key role in the presence of anhedonia. The NIMH is currently seeking enhancements in studies of genetic etiology, and one promising avenue may be endophenotype research. Future research into anhedonia and dopamine could include a study of diffusion tensor imaging to examine an association of COMT, PA intensity, and white matter integrity in the context of schizotypal anhedonia in patients and relatives.

References:


Honorable Mention

Thomas Whitford
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Five compelling facts about schizophrenia:

Fact 1. The symptoms of schizophrenia typically first present in adolescence/early adulthood (1).

Fact 2. Structural abnormalities in the white matter have consistently been observed in schizophrenia patients (both in vitro [2] and in vivo [3-5]), particularly in fasciculi connecting the frontal lobe with the rest of the brain (e.g., uncinate, arcuate, cingulum). These fasciculi are among the last to mature, with myelination typically continuing through adolescence and early adulthood (6).

Fact 3. The passivity experiences (including delusions of control and delusions of thought insertion) are among the most pathognomonic symptoms of schizophrenia (7). At a basic level, these symptoms seem to reflect a difficulty in distinguishing between internally generated and externally generated actions (8).

Fact 4. Schizophrenia patients typically exhibit subnormal levels of cortical suppression to self-generated sensations (9,10), ostensibly because of an abnormality in the “corollary discharge” mechanisms normatively involved in suppressing the sensory consequences of self-generated actions (11,12).

Fact 5. Schizophrenia patients typically show elevated levels of the neurotransmitter dopamine—a primary role of which is to modulate the salience of otherwise neutral environmental stimuli (13).

A unifying hypothesis (14): Schizophrenia is ultimately caused by abnormalities in the genetically triggered, neurodevelopmental processes of myelination that normatively occur in frontal fasciculi at peri-adolescence (Facts 1 and 2). Just as myelin damage to the optic nerve causes conduction delays in visually evoked potentials in patients with multiple sclerosis (15), myelin damage to the frontal fasciculi causes conduction delays in the corollary discharges that are normally initiated in the frontal lobe in response to willed actions, and arguably willed cognitions more generally (11). This causes the corollary discharges to arrive at their cortical destinations too late to suppress the sensory consequences of self-generated actions (Fact 4), which leads to these actions being perceived as externally generated (Fact 3) (16). This confusion of agency represents a neurologically salient event which causes a release of dopamine from brainstem nuclei. The resulting hyperdopaminergia (Fact 5) causes innocuous events to be perceived as salient, which worsens the passivity experiences and leads to other pathognomonic symptoms such as delusions of reference 17.

Predictions of the theory:
1. Delaying sensory feedback of self-generated actions by the length of the inferred conduction delay (i.e., in the order of milliseconds) will lead to the simultaneous arrival of the corollary discharge and the sensory-evoked activity in the sensory cortex, and hence a normalization of the supranormal cortical response typically exhibited by schizophrenia patients to self-generated sensations (for preliminary evidence, see reference 18).
2. Structural damage to the white-matter fasciculi connecting the frontal lobes with the rest of the brain will result in a) conduction delays and b) hyperdopaminergia (for preliminary evidence, see reference 19).

3. Remyelinating medications may be effective in preventing the onset of psychosis in people at high risk of developing schizophrenia.

References:


14. Whitford, T.J., Kubicki, M. and Shenton, M.E. The neuroanatomical underpinnings of schizophrenia and their implications as to the cause of the disorder: a review of the structural MR and


Premorbid cortical dysfunction signals vulnerability to stress and subsequent psychosis. Schizophrenia is a complex brain disorder which consists of a variable range of disturbances of perception, thought, emotion, motivation, and motor activity. Several studies have reported on abnormalities in the nervous system of individuals with schizophrenia, but information is limited on patients destined to develop schizophrenia but who are not psychotic yet. Some studies of high-risk individuals have focused on evaluating the changes that take place during this premorbid phase. Evidence suggests that individuals at risk for schizophrenia often show executive functioning deficits (Morey et al., 2005; Chung et al., 2008), suggesting that these cognitive changes may serve as a behavioral marker of genetic liability for schizophrenia (Park et al., 1995). Dysfunction of the medial prefrontal cortex (mPFC) has been shown to induce deficits comparable to those observed in schizophrenia (working memory deficits), suggesting that disruption of the mPFC might be involved in the early phase of the disease, and imaging studies showed hyperactivity within the hippocampus that correlates with psychosis in schizophrenia patients (Silbersweig et al., 1995).

Evidence suggests that stress is a risk factor for schizophrenia and may trigger episodes of psychosis. Indeed, the Edinburgh study has shown that in high-risk individuals, people who develop psychosis are hyper-responsive to stressors (Miller et al., 2001; Johnstone et al., 2002). Moreover, prior to the onset of psychosis, there is an increase in pituitary volume, suggesting activation of the hypothalamic-pituitary-adrenal (HPA) axis that controls physiological reactions to stress (Garner et al., 2005) and, in addition, to hippocampal modifications that can lead to the onset of psychosis. The amygdala is known to be activated during stress responses (LeDoux, 2000), and the mPFC can modulate this response by inhibiting the amygdala (Rosenkranz et al., 2003). Thus, dysfunction of the mPFC can lead to hypersensitivity to stress as observed in high-risk individuals who develop psychosis. Prolonged exposure or hypersensitivity to stress will induce increased release of glucocorticoids that can lead to structural brain damage, especially in the hippocampus (Thompson et al., 2004). Damage to the hippocampus from stress has ramifications on HPA axis activity such that the stress response is constitutively active, leading to cognitive impairment (Hoschl and Hajek, 2001).

Therefore, premorbid dysfunction of the mPFC might lead to unregulated stress inducing hippocampal damage that further exacerbates hyper-responsivity to stress, hippocampal damage-induced hyperactivity leading to dysregulation of the dopamine system, thereby leading to psychosis. Thus, treating hypersensitivity to stress by enhancing extinction of fear using catecholamine pharmacotherapeutics may prevent the onset of psychosis and symptom severity.

References:


The preponderance of research on the neural underpinnings of schizophrenia has focused on cortical dysfunction and the association with dopaminergic and glutamatergic mechanisms. Like most psychiatric conditions, there is disruption across a broad network encompassing several brain regions, accounting for the complicated array of symptoms attributed to schizophrenia. Indeed, there are multiple sources of evidence that support a role of hippocampal dysfunction, in addition to cortical alterations, in the development of schizophrenia. Like volume changes observed in the prefrontal cortex, there is also a widespread atrophy of the hippocampus in patients diagnosed with schizophrenia measured postmortem (Brans et al., 2008). While it has not been ascertained whether hippocampal alterations precede those observed in the prefrontal cortex, it is possible that symptom severity increases as the disease progresses from an initial disturbance in the hippocampus.

It has been shown that there are simultaneous, and opposing, changes in the activation of the prefrontal cortex and temporal lobe, encompassing the parahippocampal regions, in patients with schizophrenia during a word encoding and recognition task (Ragland et al., 2004). Patients demonstrated an underactivation of the prefrontal cortex along with a hyperactivation of parahippocampal regions. These data are consistent with evidence from the rodent MAM neurodevelopmental model of schizophrenia in which hyperactivation of the dopamine system is caused by an overactivation of the ventral hippocampus (Lodge and Grace, 2007). Ultimately, altered output from the ventral hippocampus can cause widespread changes in a broad neural network, encompassing the prefrontal cortex as well as subcortical dopamine systems. Intra-hippocampal oscillatory activity is disrupted in the MAM model of schizophrenia, and there are corresponding reductions in the number of parvalbumin-expressing (PV+) neurons (Lodge et al., 2009).

Based on the evidence summarized above, we hypothesize that abnormal activation of the hippocampus in patients with schizophrenia is a result of aberrant interneuron activity, specifically PV+ interneurons. It has been shown elsewhere that PV+ interneurons are important for the synchronization of hippocampal networks during the processing, transfer, and storage of information during oscillatory activity (Buzsaki and Draguhn, 2004; Mann and Paulsen, 2007). This implicates a GABAergic mechanism in the hippocampus for the coordination of phasic activation of pyramidal neurons. Consequently, by stabilizing the activity of pyramidal neurons via selective manipulations of GABAergic interneurons, the hyperactivation of the hippocampus will be ameliorated and have downstream consequences on the dopamine system as well as cortical targets.

References:


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Schizophrenia Is a Disorder of Learning-Dependent Predictive Perception

Facts:
Fact 1. People with schizophrenia exhibit hallucinations and delusions.

Fact 2. People with schizophrenia demonstrate a variety of cognitive and perceptual deficits.

Fact 3. There is loss of both GABAergic and pyramidal neurons in multiple areas of the cerebral cortex.

Fact 4. Many of the genes linked to schizophrenia such as DISC1 and neuregulin affect synaptic regulation in the cerebral neocortex.

Fact 5. Famine during fetal development increases risk of schizophrenia.

Model: The neocortex is arranged into repeating units of vertical columns of cell bodies. These cortical columns are highly interconnected and form strong connections with the thalamus and hippocampus. The circuitry’s basic function is learning-dependent predictive perception, in which bottom-up inputs are matched in a hierarchy of recognition. Each hierarchical level stores previously observed temporal sequences of input. Higher levels predict future input by projecting expectations to lower levels. When an input sequence matches a top-down prediction at a given layer of the hierarchy, a defined output is propagated up the hierarchy eliminating details. This process produces a more compact, efficient signal and increased invariance at higher levels. When a mismatch occurs, a more complete representation propagates upwards. This causes alternative “interpretations” to be activated at higher levels, in turn generating other predictions at lower levels. This process is fundamental to the perception of reality. The associative areas of the cortex, thalamus, and hippocampus are key regions in this process. We propose that in schizophrenia there is impairment in learning-dependent predictive perception due to neuronal loss or synaptic deregulation in higher-order association areas. Difficulty with formation and storage of invariant representations disrupts the capacity of higher levels to provide sufficient input to lower levels for solving the nature of stimuli. This impaired predictive process causes increases in inaccurate perceptions throughout development. It leads to incorrect beliefs about the nature of reality and a tendency to favor idiosyncratic interpretations of stimuli and their interactions. This, we hypothesize, is the mechanism behind hallucinations, delusions, and perceptual and cognitive impairment. This hypothesis can be tested, and we expect the following:

1. In high-risk individuals, impairment on tests of learning-dependent predictive perception, such as binocular depth inversion and closure paradigms, will predict later schizophrenia.

2. Changes in cortical development will occur in the higher-order hierarchical levels prior to illness onset.

3. Structure and function in the neocortex and hippocampus will be impaired.
4. Genetic risk factors will be those that affect development of structures involved in higher-order hierarchical recognition and those that affect synapse structure and regulation.

5. Early damage during neonatal development from injury or infection will contribute to the abnormal genesis of this crucial circuitry and function.

**References:**


Matcheri Keshavan  
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Pathophysiology of Schizophrenia: A Neurochemical Cascade Model  

Any theory that seeks to provide an integrative understanding of schizophrenia needs to explain known “facts” of this illness (1,2). Distilled into five key facts, these are: a) schizophrenia is heritable, with many glutamate-associated genes implicated; b) dopamine mesolimbic overactivation mediates pathogenesis of psychosis but glutamatergic alterations may be operant as well; c) psychosis begins during adolescence, while d) premorbid cognitive alterations date back to early childhood; and e) social, vocational, cognitive, and neurobiologic deterioration occur early during schizophrenia. Connecting these dots is critical to an integrative formulation of schizophrenia.

The first two facts point to the role of glutamate and dopamine, and the last three facts strongly point to role of early (intra- or perinatal) or late (peri-adolescent) neurodevelopmental as well as post-illness onset neuroprogressive impairment in schizophrenia pathogenesis. We propose that a genetically mediated hypofunction of the excitatory glutamatergic system (via N-methyl D-aspartate, or NMDA receptors) leads to a downstream compensatory dopaminergic imbalance, parsimoniously connecting these “dots.” Hypofunctioning NMDA receptors could account for the premorbid cognitive and psychosocial dysfunction. Onset of psychosis in adolescence may be related to an excessive elimination of excitatory glutamatergic synapses and secondarily, phasic glutamatergic and limbic dopaminergic overactivity.

Following illness onset, these neurochemical alterations in relation to continuing untreated psychosis may lead to further excitotoxic glutamatergic neuronal loss (3), perhaps explaining progressive gray and white matter alterations seen in some schizophrenia patients over time. Activity of the excitatory glutamatergic pyramidal neurons is under inhibitory regulation by cortical gamma amino butyric acid (GABA) interneurons; failure of such inhibition might cause unregulated glutamatergic function, disrupt neuronal synchronization at gamma frequencies, and thereby cause the characteristic cognitive deficits in schizophrenia (4). Thus, a genetically mediated alteration in the excitatory (glutamate)-inhibitory (GABA) balance in the corticolimbic networks might predispose to schizophrenia and the persistent cognitive impairments, while a phasic-dopaminergic and glutamatergic overactivity could be the proximal cause of psychosis beginning in adolescence and subsequent illness progression.

This neurochemical “cascade” model of schizophrenia pathogenesis generates several key predictions: a) glutamatergic and GABA deficits in adolescents at high risk for schizophrenia using magnetic resonance spectroscopy (MRS) will predict conversion to psychosis; b) MRS and positron emission tomography (PET) studies will show increases in glutamatergic and dopaminergic activity during conversion to psychosis; and c) reversing the excitatory/inhibitory imbalance in the premorbid phase pharmacologically (e.g., with glycine, d-cycloserine, GABA-enhancing agents will reduce likelihood of conversion to full-fledged clinical psychosis.

References:


Metabolic Abnormality as a Differentiable Phenotype and in Schizophrenia

The health issues associated with schizophrenia are not merely mental. The most frequent physical problems associated with schizophrenia are various types of metabolic abnormality, such as diabetes and metabolic syndrome, which are associated with the complex but commonly seen phenotype—obesity. A few studies have pointed to an increased risk of impaired fasting glucose or diabetes in younger schizophrenia patients, especially in female patients (Chien et al., 2009; Chiu et al., 2009; Hung et al., 2005; Huang et al., 2009). Compelling facts support that metabolic abnormality may play a role in the pathogenesis and pathology of a type of schizophrenia.

First, antipsychotics, especially atypical antipsychotics, may induce metabolic abnormality in some schizophrenia patients but not other schizophrenia patients. Interestingly, the more potent the antipsychotics, the more likely they may induce metabolic abnormality (Girgis et al., 2008).

Second, studies predating the invention of antipsychotics reported an increased prevalence of impaired glucose tolerance within schizophrenia (Kohen, 2004), and this supports that glucose metabolic abnormality can be a pre-schizophrenia sign, which is not necessary induced by the therapeutics.

Third, family studies indicate a higher risk of diabetes in the relative of schizophrenia patients (Wright et al., 1996). The notion of prior glucose metabolic abnormality before onset of schizophrenia is strengthened by a study that observed an increased risk of diabetes among the parents of non-affective psychosis subjects (Fernandez-Egea et al., 2008a); a significant increase of the mean glucose level in the siblings of schizophrenic subjects compared to controls was also observed (Fernandez-Egea et al., 2008b). Such aggregation suggests a possibility of shared biological pathways between schizophrenia and diabetes and related phenotypes (e.g., obesity related phenotypes), which are possibly genetic in nature.

Fourth, Kirkpatrick et al. found that non-deficit schizophrenia patients showed a higher glucose level in glucose tolerance tests than deficit schizophrenia patients, and normal controls (Kirkpatrick et al., 2009), suggesting that the degree of deficiency in glucose metabolism is not unique in some schizophrenia, but may be related to the cognitive deficits.

Fifth, susceptibility genes that contribute to both diabetes and schizophrenia have been identified by unrelated genetic studies which investigated diabetes or schizophrenia, suggesting that schizophrenia with pre-metabolic abnormality may be caused by a set of shared bio-susceptibility genes (Bellivier, 2005; Chagnon et al., 2004). We hypothesized that metabolic functions of some schizophrenia patients may be dysregulated. Testing of the following hypotheses may help to resolve our unifying hypothesis:

1. Psychotic syndromes are associated with specific metabolic indexes.
2. Patterns of cognitive deficits in schizophrenia are associated with specific metabolic index.
3. Some diabetes-related genes may contribute to the development of schizophrenia.
References:


Neely Myers
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Three subsequent generations of World Health Organization studies (1-6), including follow-up studies of two to five years at 30 research sites in 19 countries “robustly” confirmed that the short- and long-term outcomes of people diagnosed with schizophrenia in “developing” countries are better than the short- and long-term outcomes of people with schizophrenia who live in “developed” countries (7-13). As Hopper (12) explained, there are “relatively constant . . . odds of recovery ratio of roughly 1:5 favoring the non-industrial group.” “Sociocultural factors” like increased family involvement, reduced expectations of economic independence, easier employment in an agrarian economy, community cohesion, and less stigmatization of the mentally ill in “developing” nations may explain some differences (14-18). People with schizophrenia in “developed” nations often live marginalized lives (19-23) cut off from their families and social worlds by stigma (24-27), unemployment (28,29), poverty, and homelessness (18,30,31). The differences in outcomes between the “developing” group and the “developed” group, I propose, may be summarized as resilience to stress.

The “diathesis-stress model” of schizophrenia (32-34) maintains that people with schizophrenia have an increased vulnerability to everyday stress (35-41). Activation of the HPA axis, which governs the individual’s “stress response,” precipitates and exacerbates psychosis via a “stress cascade” of neural events (35,41-43). People diagnosed with schizophrenia may be intolerant of even normal amounts of everyday stress (36). Childhood trauma arrests vulnerable people’s ability to cope with stress (44). Experiences of political and economic disenfranchisement may also be experienced as chronic stress and increase the incidence of schizophrenia in those populations (45-51). Stressful sociocultural conditions exacerbate clinical symptoms. The difference between the people with schizophrenia in the “developed” and “developing” world may also depend on culturally available therapies for stress relief, such as built-in non-pharmacological stress reduction techniques that prevent symptom exacerbation and psychosis. Non-pharmacological mind-body therapies like meditation, yoga, participation in peer groups, and deep breathing techniques have been promoted for their symptom-stabilizing effects by people who are in recovery from schizophrenia in the U.S. (52-54). Practicing mind-body therapies may strengthen psychophysiological pathways that reduce the impact of stress (e.g., the HPA axis) and thereby modify clinical symptoms (55).

I hypothesize that mind-body therapies that reduce the impact of stress may be able to prevent or modify clinical symptoms leading to psychosis.

To test this, my colleagues must identify interventions used by people who experience “recovery” that may increase resilience to stress. What are the impacts of these therapies on, for example, the HPA axis? If they reduce overactivity of the HPA axis, can they prevent or reduce psychosis conversion? If so, we may be able to design early interventions that increase the resilience of people with schizophrenia and reduce their development of psychotic symptoms.

References:


18. Luhrmann, T., Social defeat and the culture of chronicity: or, why schizophrenia does so well over there and so badly here. Culture, Medicine, and Psychiatry, 2007. 31(2): p. 135-172.


Schizophrenia is often described in terms of positive, negative and cognitive symptoms, which are considered orthogonal since current antipsychotics cannot address all. Various theories have been formulated to model the etiology of schizophrenia including biochemical (dopamine, glutamate, serotonin, GABA), neurodevelopmental, gene-X-environment, and neurogenesis/synaptic plasticity hypotheses. However, none of these models accounts for all of the data available, and a unifying hypothesis for schizophrenia is still missing.

Five major lines of evidence coming from independent fields suggest that this unifying hypothesis could stem from the DISC1/NDEL1 pathway. Genetic studies have linked DISC1 with schizophrenia (3-5,7,10,20,24,28) and shown epistasis interaction with NDEL1 (2,14,22). Animal models disrupting NDEL1/DISC1 interaction (11,16-18,25) display in adolescence, subtle behavioral and histological features reminiscent of positive, negative, cognitive, and anatomical symptoms of schizophrenia. Furthermore, the mild schizophrenia-like endophenotypes of Dn- DISC1 transgenic mice are boosted when combined with the induction of a strong neonatal innate immune, as expected by the GeneXEnvironment hypothesis (12). Consistent with the neurodevelopmental hypothesis, DISC1 and NDEL1 are neurodevelopmentally regulated (1), and their decrease impairs neurite outgrowth, dendrite orientation, and leads to retarded neuronal migration and abnormal corticogenesis (13,23). These processes depend on DISC1/NDEL1 interaction (14), DISC1-dependent stabilization of catenin (19) and on cycles of NDEL1 palmitoylation (26).

In adults, DISC1 controls hippocampal neurogenesis by regulating the integration of new neurons in active neuronal networks (8). Loss of function of DISC1 leads to premature cell cycle exit and accelerated integration of glutamatergic and GABAergic newly generated neurons. Knockdown of NDEL1 leads to a milder phenotype with an additive effect observed when both genes are decreased (6). DISC1 and NDEL1 are acting as integrators of the cytoskeletal function. They both interact with the dynein molecular motor (13,15), regulate microtubule dynamics, intracellular trafficking (1,20), as well as the necessary cytoskeleton reorganization necessary to ensure cell proliferation, cell motility (27), and dendritic spine plasticity (9). DISC1 and NDEL1 affect neurosignaling: The cellular desensitization system for cAMP depends on both DISC1 and NDEL1 (1,21). DISC1 controls the multi-firing capability of GABAergic and glutamatergic synapses of adult-born neurons (6). Short-term loss of DISC1 potentiates NMDAR signaling, but continuous loss of DISC1 induces structural shrinkage of spines and functional alteration of NMDAR signaling (9). NDEL1’s role in spine function is yet to be published. The DISC1/NDEL1 pathway emerges as a promising unifying hypothesis for schizophrenia.

To strengthen this hypothesis, additional studies are needed to elucidate the implication of DISC1 and NDEL1 in the mesocortical dopamine system. A better understanding of the NDEL1-dependent subcellular targeting of the scaffold protein DISC1 is also missing. Validation of this model in schizophrenic patients by the use of appropriate biomarkers is critical to guide the search for innovative therapeutic treatments for schizophrenia.

**References:**


5. Devon RS et al. (2001) Identification of polymorphisms within Disrupted In Schizophrenia 1 and Disrupted In Schizophrenia 2 and an investigation of their association with schizophrenia and bipolar affective disorder. Psychiatr Genet 11:1611-1617.


18. Li et al. (2007) Specific developmental disruption of disrupted in schizophrenia 1 function results in schizophrenia related phenotypes in mice. PNAS 104 (46):18280-18285.


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**Neuroimmune-endocrine Model for Schizophrenia: Gene-Environment Crosstalk?**  
Compelling evidence from different research studies over the past few decades has supported the notion of schizophrenia as a multi-systemic disorder. Data from different sources, namely epidemiological, neurobiological, and pharmacological studies, have documented aberrations in nervous, immune, and endocrine systems:

1. Prenatal maternal infections are associated with increased risk of development of schizophrenia (Brown and Derkits, 2010; Limosin et al., 2003). Stressful life events are known to precipitate psychotic episodes in patients with schizophrenia (Shevlin et al., 2008) possibly through neuro-immuno-endocrine interactions through cortisol (Docherty et al., 2009).

2. Various cytokine abnormalities are noted in patients with schizophrenia with increased activity of Th2 system and decreased activity of TH1 system, suggesting a hyperactive pro-inflammatory response (Meyer et al., 2009; Patterson, 2007).

3. Hyperactive pro-inflammatory response can induce a change in tryptophan metabolism through the kynurenic pathway and cause glutamatergic-NMDA dysfunction, which in turn leads to development of schizophrenia symptoms (Kim et al., 2009). Different candidate genes implicated in schizophrenia like neuregulin, DAAO, G72, and RSG4 are linked to glutamatergic transmission through NMDA receptors (Harrison and Owen, 2003).

4. Antipsychotics have been shown to reverse these abnormalities in the immune system, decreasing TH2 activity (Pae et al., 2006).

5. There are elevated levels of left-handedness and impaired cerebral lateralization in schizophrenia with reversal of normal cerebral asymmetries (DeLisi et al., 1997). Recent studies also suggest left-handed individuals have increased risk for immune abnormalities (Lengen et al., 2009), supporting Geschwind’s hypothesis of prenatal sex hormone influence in cerebral lateralization and immune development (Geschwind and Behan, 1982; Geschwind and Galaburda,1985). Thus, with the available evidence, I propose a “neuro-immune-endocrine model” for schizophrenia: a developmental anomaly due to maternal infection and aberrant sex hormone levels could result in impaired lateralization and a dysfunctional immune-endocrine system. When vulnerable individuals are exposed to stressful situations later in life, it could initiate a cascade of immune-endocrine reaction with hyperactive pro-inflammatory response. This in turn could result in neurochemical aberrations through the kynurenic pathway and subsequently the symptoms of schizophrenia. Antipsychotics reverse the imbalance in immune-endocrine pathways and result in symptom remission. A concurrent multilevel investigation involving neuroimaging (examining cerebral laterality using structural and functional imaging, neurochemical abnormality using magnetic resonance spectroscopy and ligand-based imaging) and immune-endocrine (cytokine-cortisol-related endocrine changes) assessments can yield insights into pathogenic mechanisms. Examining patients before and after treatment will help assess the mechanism of action of antipsychotics in immune modulation. This could have potential clinical implications in the development of newer molecules targeting immune pathways. Another important clinical utility will be identification of immune biomarkers for diagnosis and prediction of treatment response. In addition,
longitudinal studies in at-risk individuals can also yield significant information regarding gene environment interaction. In summary, this model has potential to unravel the pathogenesis of schizophrenia and could have preventive and therapeutic clinical utility.

References:


The last three years will be considered a tipping point for the molecular genetics of schizophrenia. During this time international collaboration has enabled research which, as well as identifying novel neurobiological pathways (1-4), has corroborated clinical experience (3-7) in questioning the demarcation between schizophrenia and related disorders (1-7). The genetic overlap between schizophrenia and bipolar disorder has been demonstrated on an epidemiological scale (8), and genetic studies suggest that the two disorders have in common polygenic variation (5). The shared risk between schizophrenia and autism seems to be conferred by structural genetic variation (1,2,5-7). One of the most interesting copy number variant (CNV) locations, 16p11.2, has also been shown to be associated with obesity (9,10). Whilst the underlying genetics of these findings requires further elucidation, now is an opportune time to consider the value of phenotype in this context.

The theory promoted in this essay rests on the belief that the genetic dissection of schizophrenia, and hence its neurobiological underpinnings, will emerge by comparison of gene/phenotype association in schizophrenia and populations with phenotypic overlap. Comparisons thus far have been with healthy controls, and whilst such designs have provided crucial insights, they fail to differentiate between symptom domains or disorders. Comparative phenotype research across related disorders has the potential to address this shortcoming; it is this approach that this theory promotes. Testing this theory, researchers would investigate risk variants for schizophrenia and autism for association with candidate phenotypes that the conditions have in common (neurocognitive deficits or social cognitive impairment), comparing those with and without these deficits. This challenging but achievable approach relies upon reliable, comparable phenotype and endophenotype data being available across research centers and disorders (11).

The theory could be criticized as naïve in assuming simple gene/phenotype relationships and ignoring issues of pleiotropy. There will undoubtedly be variants that have pleiotropic effects: risk variants for schizophrenia, autism, and learning disability that are “generalist” genes involved in processes central to neurodevelopment. However, it seems likely that in this scenario, additional factors will also be in operation, be they genetic (“second hits” [12]) or environmental, which are associated with endophenotypes or clinical features, and set an individual on a trajectory to a particular phenotype. Whilst pleiotropy may operate at the clinical phenotype level, it also seems reasonable to expect convergence of the action of risk variants at some endophenotypic level, be that gene expression or imaging/neurocognitive measures. Crucial to combing such levels of data and advancing this approach will be the increasing sophistication of systems biology, gene pathway, and network analysis. Not only will such a strategy inform better diagnosis, it will elucidate the neurobiology of dimensions of illness and ultimately could lead to the treatment of disorders in a domain-specific way.

References:


