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# New Perspectives On Gene-Environment Interactions In Schizophrenia

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## Abstract

We review the salient recent findings on gene-environment interaction in schizophrenia. The issue of cognitive impairment and metabolic risks in modulating pharmacological treatment responses remain a challenge. The intriguing nature-nurture diathesis is discussed in light of recent breakthroughs in genetic studies from genome association scan methodology and epigenomics. Stem-cell driven neurogenesis offers fresh paradigm to unravel nature-nurture interaction. We highlight the relevance of genetics towards resolving Krapaelian dichotomy of classification in schizoaffective disorder at the cross-roads of psychosis and affective disorders. We envisage that future advances in Pharmaco-genomics, Bioinformatics will catalyse the application of personalized medicine in practice of clinical psychiatry.

## INTRODUCTION

Schizophrenia is the commonest psychotic disorder affecting 1 % of the population around the world, carried substantial burden of functional impairment on the affected individual. Impaired reality testing with perceptual and bizarre behavioural disturbances captures the psychiatric syndrome of schizophrenia. (1, 2). Some advances have been made in alleviating the positive symptoms (hallucinations and delusions bizarre behavioural disturbances) with the advent of the second-generation of atypical antipsychotics (clozapine, olanzapine, risperidol, quetiapine, and ziprazodone). The vocational status of schizophrenia remains marginal and poor vocational and is thought to be related to the negative symptom domain of schizophrenia. Deficit syndrome, defined as a disease entity characterized by the presence of primary enduring negative symptoms: blunted affect, anaerobia, apathy, and reduced in speech content (alogia), appears to be relatively refractory to towards most pharmacological and psychosocial interventions (3).

There has been considerable interest to incorporate impaired neurocognition to the core symptom cluster of schizophrenia. Expert consensus (4) concludes that the negative outcomes are strongly related to the severity of neurocognition deficits. The recent NIMH initiative, MATRICS (Measurement and Treatment Research to

Improve Cognition in Schizophrenia) identifies relevant domains of neurocognition in providing comprehensive assessment of schizophrenia: speed of processing, attention/vigilance, working memory, verbal learning, visual learning, reasoning and problem solving and social cognition (5). Decline in psycho-social functioning and community living skills reflects the cognitive impairment and determines the course of schizophrenia. These criteria are fully endorsed by Diagnostic Statistical Manual (DSM IV-R) endorses these criteria for the diagnosis of schizophrenia. Preliminary positive results have been reported with novel drugs targeting unexplored neuro-receptors or neurotransmitter systems to improve cognitive impairment in schizophrenia (6). Neuronal nicotinic receptor agonist interacting specifically alpha-7 subunit is a promising candidate (7).

Outcome meta-analysis of Second Generation of antipsychotics (SGA) for treatment of schizophrenia has yielded mixed discrepant findings (1). In general, SGA as compared with First generation of antipsychotics, are less likely to produce frequent and serious adverse events in extra pyramidal motor symptoms including Parkinsonism and tardive dyskinesia. Weight gain and metabolic effects appear to account for differences in discontinuation rates in atypical antipsychotic therapy. Global health outcomes draw equal attention from health policy makers and advocacy

groups for patients diagnosed with schizophrenia.

Systematic literature review of cross sectional and longitudinal studies concludes that vascular and metabolic risk factors: hypertension, dyslipidemia, diabetes mellitus Type 2 diabetes mellitus, and obesity, are associated with cognitive decrements. (8). Decline was found in all cognitive domains, although the effects on cognitive speed, mental flexibility and memory were the most consistent. Interventions focusing on life style and risk factors modifications hold great promise for ameliorating the negative symptoms and cognitive impairments.

Taken together, the issue of SGA-related cardio-metabolic risks in schizophrenia highlights heated debate on the nature-nurture dichotomy as etiological mechanisms in schizophrenia. In the following sections, we will review selected developments in epigenetics

Neural stem cell dynamics may offer unique opportunities to unlock the complexities of gene-environmental interaction and to identify novel drug targets for schizophrenia. We endeavour to interpret certain key findings in

### **NATURE VS NURTURE IN SCHIZOPHRENIA**

For the last decade, the classical Nature versus Nurture debate in our understanding of etiology of schizophrenia has experienced fresh waves of advances in genetics, neurobiology and pharmacology.

Accumulating evidence from family, twin and adoption studies strongly suggest that genetic susceptibility plays a pivotal role in schizophrenia. The heritability for the liability of schizophrenia is estimated to be around 80 %. (8, 9, 10, 11). Findings from genetic studies fail to support the classical Mendelian or monogenetic inheritance pattern of disease. Individual affected gene within the human genome has small effect; however, multiple genes within the same human genome interact synergistically with environmental determinants to produce the gene-product, the polygenic disease of schizophrenia. It is estimated to involve no more than 10 genes as schizophrenia susceptibility genes. Replication of studies of gene linkages and genetic variants associated with schizophrenia provides further confirmed evidence for the contribution of predisposing schizophrenia genes towards the onset and course of schizophrenia.

Meta-analysis of linkage studies has found the following genetic loci relevant to schizophrenia: 8p, 22q, 2q, 3p, 6p, 1q, 5q, 11q, 13q, and 20 p (9). Genetic breakthroughs consist

of successful application of molecular genetic techniques to identify single nucleotide polymorphisms (SNP) or genetic variants within the linked loci (1). More than half a dozen candidate genes have been identified. The genes are implicated in signal transduction, cellular differentiation, and communication networks, pathways for neurotransmitter and neuro-modulator synthesis and degradation. The most significant candidate genes (10, 11) include:

1. Neuregulin 1;
2. Disc I (Disrupted in Schizophrenia I);
3. Dysbindin;
4. G72;
5. Deaminoacid oxidase;
6. Regulator of G-protein signaling;
7. Catechol-o-methyl-transferase;
8. Proline dehydrogenase

A new genetic frontier recently explored has been highly productive in explaining the heterogeneity of schizophrenia and related neuropsychiatric disorders and open new therapeutic targets for drug discovery. The phenomenon of Copy Number Variations (CNV) refers to the type of genetic variation in which stretches of DNA strands are duplicated, deleted and sometime rearranged (12). This CNV variant appears to be increased in frequency and occurs at strategic points within the genome. Functional consequences affecting neural networks and behavioural regulation occur downstream. The growing body of evidence is gathered primarily from DNA micro-array studies reinforced by application of bioinformatics of database mining. Genes affected by CNV are good candidates for research into identifying susceptibility candidate genes for schizophrenia.

A Danish group of investigators (13) found in a cohort of schizophrenia patients with prominent deficit syndrome the following genes interrupted by rare CSV's: MYT1L, CTNND2, NRXN1, ASTN2. Except for the elusive function of the gene NRXN1, these genes play vital roles in neuronal differentiation. Emerging evidence that schizophrenia and bipolar disorder have a few susceptibility genes disrupted by polymorphic CNV. A recent study reported that a CNV in the glycogen synthetase kinase3beta (GSK3beta) locus at chromosome 3q13.3 appears to disrupt the gene's 3' coding

elements in bipolar disorder, but not in schizophrenia (14). The specificity of CNV's in GSK3beta gene adds credence to the heuristic values of CNV as genetic tools for solving the nature vs. nurture puzzles in schizophrenia and bipolar disorder.

Consistent findings find evidence for epigenetic abnormalities in SCZ. A recent report shows that down-regulation of reelin and glutamic acid decarboxylase (GAD9670) mRNA consistent with aberrant methylation during the transcription cascade (15, 16). It is not known whether SAD similar epigenetic changes occur as SCZ. These considerations highlight another exciting level of genomics regulation at the loci of chromatin remodeling: the field of epigenomics. Evidence is accumulating the epigenetic mechanisms play significant in modulating the severity of a variety of neuro-psychiatric disorders. Histone interaction with the DNA strand through Histone deacetylase (HDAC) and the conformational changes mediate the epigenetic effects.

### **SCHIZOAFFECTIVE DISORDER AT NOSOLOGY CROSS-ROADS**

Recent advances in genetic studies in schizophrenia and bipolar disorder has paradoxically rekindled serious interest in examining the nosology issue of classifying schizoaffective as a distinct clinical entity. For a few decades, psychiatric diagnostic scheme has followed closely the Kraepelinian dichotomy in proposing diagnostic criteria for schizophrenia and bipolar disorder as two separate and distinct psychiatric disorders (17, 18). Schizophrenia, termed "dementia praecox" has an unremitting and progressive course. In contrast, bipolar disorder runs an episodic remitting and relapsing course. However, the consistent clinical findings of hybrid affective and psychotic symptoms can occur concurrently within the same individual has given rise to the diagnosis of schizoaffective disorder. DSM IV-R (19) has taken a peculiar position in acknowledging schizoaffective disorder as distinct from schizophrenia and bipolar disorders, but exhibits overlapping boundaries with both schizophrenia and bipolar disorder. These considerations question the validity of schizoaffective disorder as a separate psychiatric disorder.

Systematic reviews of data conclude that schizoaffective disorder, schizophrenia and bipolar disorder are not as sharply demarcated on the basis of findings from studies of brain imaging, molecular neurobiology and genetics (20, 21). Schizoaffective disorder (SAD) stands at the nosology

cross-roads of schizophrenia (SCZ) and bipolar disorders (BPD). Genetic evidence suggests that schizoaffective disorder has shared genetic liability and heritability cutting across psychotic and affective disorders as well as disease-specific factors. DISC-1 gene is implicated from analyzing the results of extended pedigree studies in which balanced chromosomal translocation at loci (1:11) (q41; q14.3) provided strong evidence for linkage to the spectrum of phenotype encompassing schizophrenia, bipolar disorder and recurrent unipolar depression. The translocation disrupts two genes on chromosome 1: DISC1 and DISC2. The results are confirmed in another genome wide linkage study of schizoaffective disorder, bipolar disorder subtype (22).

Meta-analysis of brain imaging in SCZ and BPD (21, 20) finds structural brain abnormalities common to both SCZ and BPD: enlarged ventricles, while matter volume reduction and asymmetry of posterior amygdala-hippocampal complex. Functional imaging studies under cognitive activation found differential activation of brain regions. For schizophrenia, dorsolateral prefrontal cortex (DLPFC) activation is noted. In contrast, in BPD during working memory tasks hyperactivity of striatal-thalamo-frontal networks and hypoactivity of anterior cingulate cortex was observed. Findings from comparative SAD studies are lacking. Postmortem brain studies (23) report in both SCZ and BPD decreased neuronal size in DLPFC, along with reduced hippocampal synaptic and dendritic markers and glial cell size.

Genetic variation in DISC-1 and NRG1 genes confer susceptibility to the hybrid disorder encompassing clinical features of mania and schizophrenia termed schizoaffective disorder, calling into question validity of categorical classification of schizophrenia and bipolar disorder. Systematic evidence-based reappraisal of psychiatric nosology to delineate the genotype-phenotype relationships has become a priority issue. In this respect the construct of endophenotypes as intermediate phenotypes that segregate with the demonstrated genetic risk of schizophrenia proves to be the most promising approach. Carpenter et al (24) has critically reviewed the list of endophenotypes in schizophrenia with their biological correlates and heritability factors. For example, objective neurophysiological measures are used to measure the deficits in smooth eye pursuit tracking. The abnormal P50 wave of the evoked potential as measure of attentional deficits has been localized to the locus on the long arm of chromosome 15 containing the alpha-7 subunit of the neuronal nicotinic receptor (25). End

phenotypes lead to novel drug discovery nicotinic receptor agonist has shown positive results in clinical studies in schizophrenia.

### **NEUROGENESIS MODEL IN SCHIZOPHRENIA**

Research in schizophrenia has moved beyond descriptive nosology to etiological approaches to delineate perturbations of brain-behaviour inter-relationships underlying core symptoms of schizophrenia. Converging evidence suggests that schizophrenia is best construed as a complex multifactorial disorder arising from dysregulation of multiple neural networks in the brain: the heuristic neurodevelopmental model (26, 27). Misreading genetic programs and altered reactivity towards burden of environmental determinants interacts in intricate ways and pathways in schizophrenia. The developmental model of schizophrenia has gained substantial validation from concerted studies of molecular and cellular genetics, pharmacology, developmental biology and epidemiology. Risk factors such as migration can be subsumed under the classical dopamine hypothesis of schizophrenia in that multiple environmental risk factors sensitize the mesolimbic dopamine pathway, hence triggering psychosis (28). On the other hand, the developmental highlights the pivotal importance of neurogenesis throughout the entire life span. The model takes into account various prenatal and peri- and postnatal factors: exposure to toxins and substances of abuse, transmission of infectious agents, nutritional status and early childhood trauma.

The discovery and identification of STEM CELL biology has stimulated worldwide interest to explore the therapeutic potentials of stem cell-based modalities in the treatment of diverse serious medical disorders ranging from cardiomyopathy, multiple sclerosis and spinal cord injury (30, 31, 32, 33, 34). The dogma of neurogenesis occurring only during the embryonic and early post-natal crucial periods in mammals has been challenged with the breakthrough discovery of neurogenesis persisting in adult nervous system. In the two brain regions implicated in learning and cognition: the hippocampus and olfactory bulb behavioural integration and affective regulation, *de novo* functional neurons arise regularly from progenitor cells, coupled with differentiation of oligodendrocytes and astrocytes. We summarize the following features of NST role in brain-environment-behaviour interrelationship in the Figure I. We emphasize the process of NST differentiation and proliferation in early prenatal and post-natal periods and how the various factors play positive or negative modulation

on the cell dynamics.

Modulation of NST-mediated neurogenesis is the primary mechanism through the hierarchy of neural network: from neurons, glia to neuronal pathways adapts to changes in the micro- and macro-environment while maintaining the homeostasis of the organism. Re-alignment of cell-to-cell and neuron-to-glia communications in response to environmental demands speaks for the plasticity of the NST dynamics. The NST can decide to “turn on” or “turn off” certain genes. Hence the responses of the downstream cascade of signaling form the basis for plasticity of central nervous system. For the past decade, significant advances have been made in identifying the determinants for enriching neurogenesis *in vitro* and *in vivo*: hormones, neurotrophic factors and growth factors including Insulin growth factor, neurotransmitters and neuromodulators, psychotropic drugs, physical activities and acquisition of hippocampus-dependent learning tasks. (34) On the other hand, factors attenuating and suppressing neurogenesis have also been found: environmental cues over-loading the corticotrophin releasing factor (CRF)-hypothalamic-pituitary-adrenal axis, aging, supra-threshold stressful stimuli and non-therapeutic dosages of gluco-corticoids.

The novel findings on NST have been translated successfully to our understanding of neurological and neuropsychiatric disorders. In schizophrenia, Alzheimer Dementia, major depression and preliminary evidence is emerging that imbalance occurs between promoting and suppressing NST-mediated neurogenesis. (33, 34). Signal pathways have been shifted away from neural repair and recovery towards accelerated neuronal loss and programmed cellular death (apoptosis). Interestingly enough, studies show that exposure to the protozoa, *Toxoplasma gondii* through contact with the household feline fecal materials during pregnancy, may increase the risk of schizophrenia through interacting with predisposing gene (35, 36). Similar findings have been reported with cytomegalovirus exposure during pregnancy.

In adult and adolescence years or their equivalent in animal models, the NST remodeling is not static. Stressors are defined in both quantitative and qualitative frameworks as likely triggers for the onset of psychosis. Exposure to drugs of abuse and metabolic risks reflected in insulin resistance and signaling pathway derangements can influence the NST functioning, whereas atypical antipsychotics and mood stabilizing drugs exert neuroprotective and neurorescue effects and can be interpreted in the light of enhancing NST milieu. More significantly, the paradigms of enriched social

learning experiences and physical exercises have recently been shown to stimulate NST repair. These novel findings indirectly validate the synergistic benefits of integrated approach towards clinical care by combining the threshold “dosages” of psychosocial rehabilitation with pharmacotherapy.

From the neurobiological perspective, olfactory epithelium (OE) possesses unique biological properties reminiscent of neural stem cells (37). While neuron birth and differentiation is largely completed by the end of gestation, OE becomes an integral component of the central nervous system. OE undergoes constant regeneration and repairs throughout the life cycle. In view of the recent growing evidence implicating neurodevelopment abnormalities in schizophrenia, OE will be valuable paradigm to validate the neural development model of schizophrenia. A recent autopsied study from elderly schizophrenic subjects matched with age-controls found evidence for abnormal densities and ratios of OE neurons at different stages of

Development: basal cells neurons, postmitotic immature neurons and mature olfactory receptor neurons (38, 39).

Review of the studies has identified changes in activity of the signal cascades involved in embryonic and adult neurogenesis and neuronal maturation: Neuroregulin-1, Wnt (Wingless/Int oncogene), TGFBR (Transforming Growth Factor beta receptor), BDNF-p75 (Brain Derived Neurotrophic Factor), and DISC-I (Disrupted in Schizophrenia I) (40). Imbalance between the hypoactive Wnt and the hyperactive TGFBR, BDNF-p75 and DISC-I is consistent with preclinical data. The disequilibrium in signal transfer most likely catalyses abnormal dendrite development in NST. The dyschronized sequence of events as outlined in the Figure 1 results in accelerated and misguided migration and aberrant integration into the neural network in the developing and to some extent, the mature brain. The findings are consistent with the relatively robust discovery on the risk factor of haplo-insufficiency of the DISC-I gene in schizophrenia.

Taken together, the results studies corroborate evidence for disturbances in signal pathways underlie aberrant stem cell maturation in schizophrenia. The finding provides the rationale for applying agents displaying neurotropic properties to facilitate the repair and regenerative capacity of OE and by extrapolation, olfactory-limbic neurons.

Research in NST has been hampered inadvertently by the

myth that embryonic stem cells are the only viable sources of stem cells for medical research purposes. Stem cells offer promising therapeutic advances for a plethora of serious medical disorders ranging from cancer, cardiomyopathy, and spinal cord injury to multiple sclerosis. The vistas for neuro-psychiatric disorders is still in the infancy. However, for the past decade, heated worldwide debates on the ethical constraints of using embryonic stem cells appear regularly in the media. Marginal attention has been drawn to germline Stem cells utilization bypassing the Embryonic stem cell controversies can be harvested from umbilical cord blood to mimic the embryonic stem cell development dynamics and hence can be explored with equal efficacy and safety for therapeutic clinical trials in humans (41).

### **PHARMACOGENOMICS AND PERSONALIZED MEDICINE**

Pharmacogenomics considered as the hallmark achievement in the post-genomic era, has unraveled some of the intriguing puzzles of differences in therapeutic responses in psychiatry. Evidence suggests that genetic variants in the drug metabolizing enzyme: CYP contribute towards the variations in the responses towards antipsychotics (42). It is now feasible to predict the extent of inter-individual variations of plasma levels of antipsychotics and antidepressants by analyzing the CYP P-450 enzymes such as CYP2D6. However, routine clinical practice with “gene chips” has not yet adopted the pharmaco-genomics approach towards individualized pharmacotherapy. Co-variables can affect the phenotypes of slow- and fast-metabolizers. In this respect, integrating genetic, functional genomic, and bioinformatics data in a systems biology approach may prove to be the most innovative and productive in schizophrenia. Antipsychotics differ in their capacity to produce extrapyramidal side effects (EPS) and metabolic risks of obesity and diabetes mellitus. Studies to explore relevant gene to predict the metabolic risks have shown that the 5-HT-2C receptor gene located on the x-chromosome, confer risks of atypical antipsychotic-induced weight gain. The odds ratio appears to be influenced by ethnicity: greater effects were observed with the Chinese population as compared with the Caucasian population.

Taken together, pharmacogenomics has stimulated pharmaceutical development towards a rational drug design through analysing the molecular template and scaffolding for the drugs to interact with the sites of action. The construct has been expanded to the ideal “personalized medicine” whereby it may be feasible to individualize and optimize

treatment responses based upon the individual's gene printout. The environment determinants will also take into consideration by analysing another branch of genetics: epigenomics. Epigenomics is another exciting field of discovery in schizophrenia. Chromatin remodeling leads to differential gene expression profiles and can be modulated by diverse environmental factors: nutrition and drugs. Epigenetics therapeutics coupled with pharmacogenomics and bioinformatics, will gather momentum in the next wave of breakthroughs in prevention and treatment of schizophrenia (43, 44).

## CONCLUDING REMARKS

In summary, the DSM V initiative of "Deconstructing psychosis" most likely will modify and transform the traditional Kraepelin's dichotomy classification a new construct of SCZ, SAD and BPD (32). New versions of International Classification of Disorders (ICD-11 and Diagnostic and Statistical Manual (DSM-V) on diagnostic schema will be available in 2014 and 2012. Translational challenges consist of bridging research advances with nosology in refining the diagnosis and treatment of schizophrenia. . In this respect, integrating genetic, functional genomic, and bioinformatics data in a systems biology approach may prove to be the most innovative and productive in schizophrenia.

In addition, the next wave of Reconstructing Psychosis initiative will come in schizophrenia from collaborative clinical-research networks comprising panels of experts from social sciences (psychology, sociology, anthropology) and computational sciences, bioinformatics and biomedical sciences (genetics, molecular and development biology, pharmacology, pathology, and neurobiology) The ultimate goal is to consolidate the various facets of breakthroughs and to facilitate the timely application of research findings to the clinical area through validating the relevant therapeutic targets. In the near future, Behaviour informatics and Genomics emerging from proposed studies of allelic variations in behavioural responses will complement the rapidly growing fields of Pharmaco-genomics and Epigenomics. New perspectives in diagnosis, treatment and prevention of Schizophrenia psychosis will enhance and optimize clinical care in schizophrenia.

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