To what extent is schizophrenia a case of nature rather than nurture?

Maryam Mammadova
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By: Maryam Mammadova

To take a side on the infinite debates of nature v. nurture first raised by Mendel’s pea plants, one needs to know the basics of schizophrenia. Schizophrenia is the seventh most costly illness that is known to our society.¹

What is schizophrenia?

Schizophrenia is a psychotic disorder characterized by loss of contact with the environment, by noticeable deterioration in the level of functioning in everyday life, and by disintegration of personality expressed as disorder of feeling, thought (as delusions), perception (as hallucinations), and behavior.²

There are many symptoms of schizophrenia but the main ones are:

<table>
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<tr>
<th>Hallucinations</th>
<th>can occur in any of the five senses: vision, hearing, smell, taste or touch. Auditory hallucinations are most common in people who suffer from schizophrenia. Research suggests that auditory hallucinations occur when people misinterpret their own inner self-talk as coming from an outside source.</th>
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<td>Delusions</td>
<td>are one of the most common symptoms of schizophrenia occurring in more than 90% of the patients. The most frequent is the delusion of prosecution when one believes that others, often a vague “they”, are out to get him.</td>
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² http://www.merriam-webster.com/dictionary/schizophrenia
The onset of schizophrenia most commonly occurs in the second or third decade of life, though onset age may vary from childhood to old age. Subtle abnormalities of cognition, social interaction, motor function, and physical morphology are frequently observed in individuals who later develop schizophrenia. This is a symptom of a developmental vulnerability.

**Neurobiology of schizophrenia**

While the psychotic phenomena of schizophrenia are quite striking, more indirect cognitive problems are starting to be recognised as central to the disease. People suffering from the disease may be affected by damaged attention, working memory, learning, verbal fluency, motor speed etc. On contrary to positive and negative symptoms that fluctuate in their appearance in patients, the cognitive impairments are quite stable and appear in patients even before they receive any antipsychotic medicines.

As a result of recent advances in imaging technology (fMRI and diffusion tensor imaging (DTI)) it has become known that abnormal brain structure is a significant cause of schizophrenia. For example working memory dysfunction has been linked to dysfunction of the dorsolateral prefrontal cortex (DLPFC). However, the most consistent structural abnormalities that occur in almost all schizophrenic patients are alterations in ventricular size and cortical grey

<table>
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<tr>
<th>Disorganised speech</th>
<th>may manifest itself in loose associations, neologisms, preservation and clang. Schizophrenia disrupts goal-directed activity, causing impairments in a person’s ability to take care of him or herself, work, and interact with others, thus the disorganised behaviour appears.</th>
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<tr>
<td>The “negative” symptoms</td>
<td>refer to the lack of normal behaviours found in a healthy individual, such as lack of enthusiasm, emotional expression and interest in the world. Speech difficulties and abnormalities are also a sign of “negative” symptoms.</td>
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![Figure 1. Shows the difference in ventricular sizes in normal vs. schizophrenic brain.](image)

Source in the bibliography
matter as shown in Figure 1. Compared to an average of 5% overall grey matter changes in other mental disorders or as a result of aging, schizophrenic people show more disproportionate local changes generally in the range of 15% in the mesial temporal, temporal neocortical, prefrontal, and parietal regions, with possible alterations in thalamus, basal ganglia, and cerebellum.\(^3\)

### Chemical abnormalities of schizophrenia

As opposed to structural abnormalities however, neurochemical abnormalities are thought to be a more prominent cause of schizophrenia. Neurochemical studies in schizophrenia have focused on several major neurotransmitter systems — dopamine, serotonin, GABA, and glutamate.

**Dopamine hypothesis**

The dopamine hypothesis of schizophrenia is based mainly on the pharmacological evidence from trials conducted. Dopamine agonists (a compound that activates dopamine receptors in the absence of dopamine) are known to provoke positive symptoms in schizophrenic people. Moreover all known drugs used for treatment of schizophrenia are dopamine antagonist. Several post-mortem chemical data documented an increased number of ganglia dopamine receptors in schizophrenia, but these results may have been a result of an unrelated illness, or an artefact caused by treatment-related homeostatic changes caused by dopamine receptor blockade. In vivo, however, this issue was addressed by Laurelle, who reviewed 15 brain imaging studies comparing indices of dopaminergic function in drug-naive or drug-free patients with schizophrenia compared with healthy controls and concluded that schizophrenic patients possess a significant but mild and variable elevation of D2 receptor density parameters.\(^4\) SPECT studies of presynaptic activity reveal an increase in dopaminergic transmission in response to amphetamine challenge, which is why it has been suggested that neurocognitive complications in the patients may be related to reduced dopaminergic activity in prefrontal cortex. There are at least five known types of dopamine receptors, with varied cortical and subcortical distributions. The genes coding for these receptors are candidate genes both for schizophrenia and for drug treatment response variability.\(^5\)

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\(^3\) Pearlson GD, Marsh L. Structural brain imaging in schizophrenia: a selective review. Biol Psych 1999;46:627


\(^5\) https://www.researchgate.net/publication/12298802_Neurobiology_of_schizophrenia
Serotonin

The first testable theory of modern biological psychiatry that stated that schizophrenic psychosis is related to dysfunctions in central serotonergic systems, was formulated by Woolley and Shaw in the early 1950s. However the theory did not get the attention it deserved because antipsychotics were just discovered and it was evident that they block dopaminergic transmission, so most of the biological psychiatry for the next few years was focused on dopaminergic system. Serotonin inhibits dopamine function at both midbrain nuclei and terminal dopaminergic fields that’s why it is not yet known whether serotonergic lesions contribute directly to the occurrence of schizophrenic psychopathology or via alterations in the dopaminergic system.

NMDA

Another neurochemical abnormality has been linked with alterations of N-methyl-D-aspartate (NMDA)/glutamate function in patients. The driving force in linking NMDAs to schizophrenia was the long recognized psychogenic effect of dissociative anaesthetics such as ketamine and phencyclidine (PCP). The two chemicals can reproduce some symptoms of schizophrenia in normal not affected by the disease individuals.

GABA

The last significant chemical abnormality that might cause schizophrenia may occur in GABAergic system. The system is principally involved in the balance of excitation and inhibition in the brain. Some studies have found abnormal GABAergic activity in the anterior cingulate and hippocampus in schizophrenia, while post-mortem studies have shown an increased number of GABA receptors in the brains of schizophrenic patients.

Neurodevelopmental vs. Neurodegenerative

It is important to know whether schizophrenia is neurodevelopmental or neurodegenerative because it is useful to identifying various treatment approaches. For instance if it’s neurodevelopmental it is enough to focus on the etiology of the disease and refine the preventative strategies. However, if it’s neurodegenerate, then it is more useful to focus on prevention, early intervention and treatment strategies.

On the one hand, some scientists classify schizophrenia as a developmental disease (a group of psychiatric conditions originating in childhood that involve serious impairment in different areas). Despite the fact that schizophrenia has a clinical onset, the neural

abnormalities are hypothesized to occur early in brain developmental for several following reasons: epidemiological evidence of an association with pregnancy, obstetrical, and prenatal abnormalities; evidence of childhood behavioural and neurological abnormalities prior to adult onset of the disorder; pathological and neuroimaging evidence consistent with early developmental brain defects (disturbed brain asymmetries and abnormalities of sulcogyral patterns); and developmental defects in associated structures (eg, craniofacial) of ectodermal origin. According to Weinbergs conceptualisation, schizophrenia is a fixed brain lesion acquired early in life that later on interacts with maturation of an individual “The lesion itself is static but its effects on neurologic function change. . . . If a lesion affects the brain structure or region that has yet to mature functionally, the effect of the lesion may remain silent until that structure or system matures.”

On the other hand, it is possible to classify schizophrenia as a neurodegenerative disease (a disease that occurs as a result of loss of structure or function of neurons), however, it is considered to be more complicated than all of the other neurodegenerative disorders. DeLisi and many others claim that a clinical onset is followed by a continuing active neurodegenerative process either in all patients or a very large subgroup. Now it may be possible that some deterioration occurs in a subgroup, however, the studies based on neuroimaging do not provide unambiguous results due to the fact that most of the images obtained are cross-sectional and not all of the studies employ suitable controls. A progressive developmental mechanism active into adult life can reconcile the neuropathological and imaging data while being compatible with both early onset and late deterioration in schizophrenia. Thus schizophrenia may both be developmental and have some signs of degeneration without necessarily being “neurodegenerative”.

**Genetics of schizophrenia**

Nobody ever doubts the fact that schizophrenia is partially a genetic disorder, because numerous family twin and adoption studies show that relatives of schizophrenic patients have a higher risk of being ill compared with a 1% general population rate, correlating with their degree of genetic relationship. There is also a higher chance for both

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8 Weinberger DR. Implications of normal brain development for the pathogenesis of schizophrenia. Arch Gen Psychiatry 1987; 44:660–669

monozygotic (MZ) twins to be schizophrenic rather than for both dizygotic (DZ) twins to be schizophrenic, with respective rates being approximately 50% to 15%.

**Phenotype of schizophrenia**

Due to the fact that there is no objective marker for the disorder, we lack obvious neural clues as to its mechanism and a confirmation of the fact that we are studying a correct mechanism or even an individual case.

**Does schizophrenia have subtypes?**

Vast amounts of studies indicate that there has been intensive research in order to determine the subtypes of schizophrenia to be able to define the phenotype of the disease more easily. Crow (1980) suggested that there may two types of syndromes: type I disorder, that is characterised by the presence of positives syndromes and responsiveness to neuroleptics and type II disorder, which is associated with negative symptoms, lack of response to the treatments and impairments in the brain reflected in the CT scan. However due to the small sample size one is unable to form a definite conclusion, in additions Crow’s own views on clinical basis for a type I and type II split are changing and evolving.

The problem is that when viewing the results there are often good agreements with the hypothesis that the writers set about the subtypes, however, almost always there is never convincing evidence for split extending back to a genotypic level in schizophrenia. Therefore it feels like we are always a step away from a revelation that may lead to a common agreement on the issue.

A more interesting way of classifying schizophrenia, in my opinion, is best described in the earlier work of Gottesman and Shields (1986, 1972), who took a straightforward approach to the question of severity of the illness. The article is a review of adoption and twin studies conducted from 1967-1976. There were 711 participants in total in the adoption studies in the twin studies a total of 210 monozygotic (identical) twin pairs and 319 dizygotic (non-identical) twin pairs were studied. The probands from identical twin pairs were divided according to the time spent in a hospital. The rate of concordance was only 27% where the proband has spent less than 2 years in a hospital, as opposed to the rate of concordance of 77% where the probands have spent more than 2 years in a hospital since the onset of the illness. The rate of schizophrenia in the co-twins that couldn’t stay out of the hospital for more than 6 months was 75%. Due to a large sample size this research is thought to be reliable, however the use of secondary research may leave space for bias and many other issues. Moreover, the quantitative reasoning of the study makes the
findings easy to compare and analyse, and makes it easier to extrapolate the causality of the disorder; this adds to the validity of the study.

This data and the absence of objective evidence for subtypes of schizophrenia serve as the bedrock to the idea of classifying schizophrenia due to severity, rather than subtypes.

**Traditional approach**

However, one of the biggest issues is that the disorder does not follow the classic mendelian genetic inheritance models. For instance, the concordance for MZ twins is not 100% nor it is 50% for DZ twins. Additionally, the offspring of unaffected discordant MZ twins have the same (15%) risk of transmitting the disorder to their children as affected MZ twins, and the risk for a child with two schizophrenic parents approximates 45% rather than 100%\(^\text{10}\). A single locus model for the inheritance of schizophrenia was not found, and despite several promising leads, there has not yet been a definitive association of a gene variant with the illness.

**Other approaches**

Lack of success of traditional genetic models has encouraged many new approaches towards what might constitute schizophrenia risk genes. For example some started looking not for one major gene that may cause the disorder, but several genes that may each have a subtle effect on the patient. While single gene disorders such as Huntington’s disease or cystic fibrosis increase the susceptibility to an illness by 500 to 5000 times, schizophrenia increases the susceptibility by as little as 2 or 3 times, thus the unusual inheritance patterns.

Other theory suggests that a patient may have a genetic predisposition to the disease that is further affected by one or more environmental factors during brain development that trigger the disease. As in Alzheimer’s disease, many genetic pathways in a large population sample may lead to a common phenotype. Although these seem to be very complicated theories, they are also used to explain diseases such as type 2 diabetes, hypertension and obesity.

There are also numerous other details that make the genetics of schizophrenia so intricate such as incomplete penetrance, etiological heterogeneity or pleiotropism.

Candidate genes identified by genetic approach have an advantage over genes identified by pharmacotherapies or other pathological studies in that they are a necessity for the phenotype to show, at least in populations tested. The genes identified in linkage or

\(^{10}\) Kringlen E, Cramer G. Offspring of monozygotic twins discordant for schizophrenia. Arch Gen Psych 1989;46:873–877
association studies indicate that it’s most likely that there are several genes of modest effect interacting to produce the phenotype. The relative risk at the loci identified so far is quite low ranging from 1.5-2.0. Despite the fact that linkage and association studies haven’t been of much use when implicated in the traditional approach (Mendelian genetics) chromosomal translocation studies have been a useful alternative and were used to identify several candidate genes. Furthermore, positional genetic approaches were more useful than many others because it doesn’t depend on the knowledge of the disease or pathophysiology.

**Neuregulin 1**

*Neuregulin 1* has been identified as a candidate gene via fine mapping of a locus of chromosome 8p linked to schizophrenia. (Harrison and Law 2006; Stefansson et al. 2002)\(^{11}\). The gene is very complex with over 25 exons\(^{12}\) spread over a megabase\(^{13}\) with extensive alternative promoter usage and splicing that may result in multiple proteins being produced. The region in the 5’ end of the gene seems to associate with the disease the most. Most neuregulin 1 isoforms are transmembrane proteins that perform proteolytic cleavage to release intracellular fragments, extracellular fragments, membrane bound signalling fragments or transmembrane receptors. The problem of schizophrenia is the fact that the function of neurolgin1 in schizophrenia is still uncertain, especially since many different alleles and haplotypes\(^ {14}\) have been discovered. However, the studies conducted in post-mortem tissue suggests that in schizophrenia the neurolgin 1 signalling may be enhanced leading to the suppression of NMDA receptor function (Hahn et al., 2006). One possible explanation is that there are polymorphisms that lead to alternative splice variants that encode proteins with enhanced function. Unfortunately, no functional polymorphisms\(^ {15}\) have been identified.\(^ {16}\)

**Dysbindin**

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\(^{11}\) Christopher A. Ross et al. Neurobiology of Schizophrenia; Neuron 52, 139-153, October 5, 2006

\(^{16}\) Christopher A. Ross et al. Neurobiology of Schizophrenia; Neuron 52, 139-153, October 5, 2006
Dysbindin is short for dystrobrevin binding protein I. It was identified through linkage to chromosome 6p22.3 as a gene associated with schizophrenia. It was first reported by Straub and colleagues. Dysbindin localizes broadly in the brain and the muscles. The function of dysbindin in the brain is not yet well understood, but it’s known that it’s widely distributed over the brain in pre and post synaptic areas, including synaptic terminals in the hippocampus. It also has been known to affect glutamate neurotransmission (Numakawa et al., 2004).

While association of dysbindin with schizophrenia has been fairly well replicated, no protein mutations have been discovered that may cause schizophrenia. Moreover, there are inconsistencies in the specific risk alleles and haplotypes that suggest that if the gene is indeed the susceptibility gene, there is either a single susceptibility allele carried on a wide range of haplotypes or there are multiple susceptibility and protective alleles. No causative variant has been identified so far, however, the absence of associated non-synonymous coding alleles suggests that the disease depends heavily on the variation that affects the mRNA expression. This is supported by the recent studies conducted on post-mortem brain tissue from probands with schizophrenia that shows reduced levels of mRNA.

It is associated with glutamatergic systems because a recent study conducted by Tablot et al. shows that the presynaptic dystrobrevin-independent fraction of dysbindin is reduced in schizophrenic brain within certain intrinsic glutamatergic neurones of the hippocampus, and this is associated with increased expression of vesicular glutamate transporter type 1. Furthermore, there has been a reduction in glutamate release in cultured neurons with reduced DTNBP1 expression. These data suggest that DTNBP1 may affect the glutamate trafficking or release.

D amino Acid Oxidase Activator

The chromosome 13 locus is linked strongly to schizophrenia because along with other genes this locus contains G 72 now called D amino acid oxidase activator (DAOA). Several individual replication studies and a meta-analysis have supported the association of DAOA with schizophrenia, although as with DTNBP1 the associated alleles and haplotypes are not identical throughout the studies. The function of DAOA is to activate


the D amino acid oxidase (DAO) which then oxidizes D-serine. D-serine is the coagonist\textsuperscript{20} at NMDA glutamate receptors; therefore there is some plausibility for the DAOA as a candidate gene based on the glutamate hypothesis.

**COMT and Chromosome 22 Region**

Another linkage region is on chromosome 22 (Harrison and Weinberger, 2005; Owen at al., 2005)\textsuperscript{21, 21} although this theory has been supported by many though not all, linkage and association studies, the strong genetic concordance between schizophrenia and the chromosomal microdeletion syndrome VCFS, provides evidence for genetic contribution to schizophrenia from this region. VCFS is caused by deletion of 1.5 to 3 Mb in chromosome 22q11, and approximately 20-30% of patients with VCFS have schizophrenia or other major mental illness that includes psychosis. (Murphy et al., 1999)\textsuperscript{22} Patients with schizophrenia also have increased frequency of the microdeletion syndrome compared to general population. (Karayiorgou et al., 1995)\textsuperscript{23}

The gene on chromosome 22q11 called *catechol-O-methyltransferase (COMT)* has however received the most attention. COMT produces an enzyme that participates in the clearance of dopamine from the synapses, and therefore could be involved in regulation of schizophrenia related neurotransmission. A functional polymorphism at codon 108 that involves the presence of either methione or valine is known to be affecting the enzyme activity. Methione allele has less activity because it is thought to be less stable, suggesting the hypothesis that individuals with a deletion of one copy of COMT or ot two copies of methione, would be expected to have higher dopamine levels in critical central synapses, especially in the prefrontal cortex.

**Epigenetics of schizophrenia**

The complications of schizophrenia have led the researchers to propose the employment of endophenotypes because they have the utility of simplicity, higher penetrance,

\textsuperscript{21} Harrison PJ, Weinberger DR. 2005 Schizophrenia genes, gene expression, and neuropathology: on the matter of their convergence.

\textsuperscript{22} Murphy FV 4th, et al. (1999) The structure of a chromosomal high mobility group protein-DNA complex reveals sequence-neutral mechanisms important for non-sequence-specific DNA recognition. EMBO J 18(23):6610-8

improved operational definition and more objective diagnosis. They are also believed to exhibit greater reliability and validity and represent features closer to the genes that are relevant.

It is likely that a proportion of relatives classified as unaffected by the syndrome carry several pathogenic genes themselves, if all of the biological abnormalities in the family are taken into account. Multiple studies show a higher prevalence of nonschizophrenic first-degree relatives of schizophrenia patients towards biological and psychological abnormalities. For example Holtzman, Levy and many other researchers have investigated the proportion of eye tracking dysfunction, which is identified as “cofamilial” by them. The dysfunction is found in approximately 50% of schizophrenics, a large proportion of unaffected first degree relatives and discordant identical twins. Therefore researchers believe that biological markers are more related to the genotype rather than the clinical features.

An emerging agreement between researchers is that the biological markers that are the most useful are those that are more frequent in patients than control populations; more frequent in families of schizophrenic patients than control populations; are stable over time and intensive to gender, age and medication status; and that have a tendency to segregate with schizophrenia and spectrum diseases in multiply affected families. Other possible endophenotypes are sensory motor gating deficits, various event related potentials measured by electroencephalography, eye tracking dysfunction and impairments in working memory.

References:


In seminal studies, where the genetics of COMT valine/methione polymorphism were combined with imaging studies, the valine allele was said to have a lower synaptic dopamine confer risk for schizophrenia via variation in cognitive function as opposed to the dopamine hypothesis, which proposes increased synaptic dopamine as the mechanism responsible for the disease. (Egan et al., 2001)\(^\text{32}\)

Other genes in the deletion syndrome region may also contribute to the risk for schizophrenia. For example, the genetic variation of the \emph{proline dehydrogenase (PRODH)} affects the availability of glutamate, and mutant mice with the loss of PRODH function show some behavioural abnormalities.

Other candidate genes

Other candidate genes are shown in Table 1 that was adapted from the Straub and Weinberger 2006.

\textbf{Environmental factors that may lead to schizophrenia}

\textbf{Neural Diathesis stress model}

Because, there is no definite answer as to what causes schizophrenia, scientists propose a diathesis stress model that suggests that schizophrenia is a result for combination of biological, environmental and genetic factors. Although some researchers have argued the importance of environmental factors in causing the schizophrenia phenotype, the (McGuffin, Asherson, Owen, & Farmer, 1994)\(^\text{33}\), stating that “it is also possible that 'non-genetic' factors consist entirely of stochastic events affecting gene expression or structure”, the model still stays as the basis for contemporary theorising about the origins of schizophrenia.

\textbf{Effects of Stressors on schizophrenia}

On the basis of the review of Norman and Malla (1993a, 1993b) of the literature on stressful life and schizophrenia, two general conclusions can be drawn:

First, there is very little evidence on the idea that schizophrenic patients are exposed to higher levels of post-natal stress compared to general population. The main goal of this

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research was to find out whether the stressors play a causal role in either triggering or exacerbating the illness. Therefore, the researchers have been concerned with differentiating the stressful events that may have been a consequence of the illness from the events that are independent. Thus the conclusion that they derived that exposure to psychosocial stressors is not elevated in schizophrenia refers to events that are unlikely to have been induced by the individuals behaviour.\(^{34}\) It is important to note that psychiatric symptoms interfere with functioning in such a way that they induce stressful interpersonal, occupational and financial experiences, as well as causing general subjective stress.

Second, is that there is a causal relationship between stressful life events and severity of the symptoms of the illness. Both prospective (Birley & Brown, 1970)\(^ {35}\) and retrospective (Ventura, Ventura, Nuechterlein, Hardesty, & Gitlin, 1992; Ventura, Nuechterlein, Lukoff, & Hardesty, 1989)\(^ {36}\) have revealed that the occurrence of stressful events that is not common to the patient’s behaviour predicts substantial worsening of symptoms.

There is also evidence for a causal relation between psychosocial stressors and symptom exacerbation shown by studies conducted to analyse the relationship of patients and their relatives. The probability of relapse increases significantly when patients are exposed to family members that are emotionally intense, express harsh and critical comments. And on contrary when the actions of the family are aimed at reducing critical reactions, the likelihood of the relapse seemed to reduce. Barrelet, Ferrero, Szigethy, Giddey, & Pellizzer, 1990; Nuechterlein, Snyder, & Mintz, 1992; Vaughn, Snyder, Jones, Freeman, & Falloon, 1984).\(^ {37\text{a}38\text{b}}\)

However, the psychosocial factors have not yet been proven to trigger the illness, only exacerbate it. Moreover it may speed up the onset of the first clinical episode. This


\(^{35}\) BIRLEY J. L. T., BROWN G. W.; Crises and Life Changes preceding the Onset or Relapse of Acute Schizophrenia: Clinical Aspects; The British Journal of Psychiatry Mar 1970, 116 (532) 327-333;

\(^{36}\) Denise Gretchen-Doorly, Nicole R Detore, Joseph Ventura, Gerhard Hellemann, Kenneth L. Subotnik, and Keith H. Nuechterlein; Relationships between perceptions of the family environment and of negative life events in recent-onset schizophrenia patients; Schizophr Res. 2011 Apr; 127(1-3): 266–267.


\(^{38}\) Nuechterlein, Snyder, & Mintz, 1992; The role of family systems in severe and recurrent psychiatric disorders: A developmental psychopathology view

\(^{39}\) Vaughn CE, Snyder KS, Jones S, Freeman WB, Falloon IR.; Family factors in schizophrenic relapse. Replication in California of British research on expressed emotion.; Arch Gen Psychiatry. 1984 Dec;41(12):1169-77
suggestion is backed up by the fact that children that are at high risk of schizophrenia (e.g. offspring of a schizophrenic parent), show higher behavioural dysfunction if they are exposed to parental maltreatment (Walker, Downey, & Bergman, 1989). High risk children grow up in institutional settings are more likely to develop the onset of the disease than those that remain in nuclear or extended family (Walker, Cudeck, Mednick & Schulsinger, 1981). Tienari (1991) stated that the risk for psychiatric maladjustment is much higher in the biological offspring of schizophrenia patients that have been taken care for in dysfunctional adoptive families. Furthermore, there is evidence that high level of critical and intense attitudes can be a sign of the onset of schizophrenia-spectrum disorders in adolescents.

The real answer to the question of whether the likelihood of schizophrenia onset throughout the lifetime is increased by the psychosocial stressors will only be clear after follow-up assessment of the high risk probants mentioned above. Assessments should be conducted after the major risk period for schizophrenia in all of the participants has passed.

**Biological responses to physiological stress**

The human response is extremely complex and it involves multiple systems. This involves adrenomedullary hormonal systems, the sympathetic and parasympathetic systems and the hypothalamic–pituitary–adrenal axis (HPA) system. The HPA system is the set of direct influence and feedback interaction among three endocrine glands: the hypothalamus, the adrenal gland and the pituitary gland. These interactions constitute the HPA axis that controls stress response, and numerous body processes such as digestion, the immune system, mood and emotions, energy storage and sexuality. The HPA system is important for the following reasons:

1) there is evidence that the activation of the HPA axis is a representative of one of the primary manifestations if the stress response.
2) there is also evidence that the HPA axis is dysfunctional in some schizophrenic patients
3) some features of the axis make it an appropriate system for bringing about the effects stress on the symptoms.

Corticotropin releasing hormone, adrenocorticotropic hormone and glucocorticoids are

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40 Elaine Walker, Geraldine Downey and Andrea Bergman; The Effects of Parental Psychopathology and Maltreatment on Child Behavior: A Test of the Diathesis-Stress Model


the three chemical messengers involved in the HPA axis. Cells in periventricular nucleus (PVN) of the hypothalamus releases corticotropin releasing hormone (CRH). The receptors for CRH that are located in the pituitary release adrenocorticotrophic hormone (ACTH). Then ACTH stimulates the adrenal cortex to release glucocorticoids (cortisol in primates).

Glucocorticoids are located throughout the body and are very important when it comes to the physiological changes that are used for the adaptations to stress. Glucocorticoid receptors serve to regulate the activity of the HPA axis. Because the hippocampus is believed to have a high density of GRs, it is thought to be playing a heavy role in modulating the activation of the HPA system.

**Chronic and acute stress exposure**

Numerous studies are collecting evidence on the effects of stress exposure by measuring the glucocorticoids in plasma urine and saliva. Cortisol release is known to be linked with stress exposure. For example, brief maternal separation is known to cause cortisol release in infants (Larson, Gunnar, & Hertsgaard 1991) and those who are not securely attached show a more conspicuous cortisol response (Spangler & Grossman 1993). In adults cortisol release may be linked to the anticipation of unpleasant experiences such as public speaking and examinations (Kirschbaum, Wust, & Hellhammer, 1992).

Several factors determine whether the glucocorticoid response shows habituation or sensitization in mammals. In human infants, stressor intensity and differences in neonatal health status influences the likelihood of sensitization. Moreover, studies conducted by Kirchbaum and colleagues (Lirshbaum et al. 1995) that measured the cortisol responses in healthy human subjects that were exposed to 5 days public speaking showed that there was a substantial group of adults who did not habituate to repeated stressors.

It has also been established that when the exposure to stress is continuous, and heightened glucocorticoid release is chronic, there can be permanent alterations in the HPA axis. Most importantly, the impairment of the negative feedback system that serves to dampen the HPA axis. The impairment of the negative feedback system may enhance stress responses. Although all of the experimental research on biological stress responses was conducted on animals, there is a reason to believe that the mechanism is similar in human subjects, because there is an inverse correlation between the hippocampal volume and cortisol levels in humans.

**HPA axis and activation of a dopaminergic neurotransmission**

The evidence for a causal effect of the HPA activation on dopamine (DA) release is provided by numerous experiments in which corticosteroids are administered closely. In animals, this administration often results in augmented DA metabolism in the nucleus accumbens (Mittleman, Blaha, & Philipps 1992). Recent findings also indicate that the increased DA synthesis is in part due to the effect corticosteroids have on tyrosine hydroxylase (TH). Tyrosine hydroxylase is the main rate-limiting enzyme of

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catecholamine biosynthesis. Glucocorticoids augment the TH levels along with the transcription rate of the TH gene, levels of TH messenger RNA, which causes an increase in the levels of TH enzyme protein.

Other researchers suggest that the activation of the HPA axis can bring about a change to the DA receptors. For example Henry et al. (1995) suggest that prenatal stress exposure results in elevated D2 receptors and decreased D3 receptors, and no change in the DA-D1 receptors in the nucleus accumbens of rats. This change however, can’t be observed until the animals reach adulthood. In rat striatum, the adrenalectomy reduces the concentration of both D1 and D2 receptors, while glucocorticoid release augments the binding of DA to both of these receptors.

Overall it is possible to assume that the changes in the DA receptors are due to prolonged stress exposure. More specifically that the modulation of the HPA axis can be changed if a subject was under long lasting stress of sufficient magnitude. The modulation of the HPA axis may bring about heightened corticosterone release and change the hippocampal receptors. This is most likely to enhance the DA receptor densities and consequently DA release. This process is somewhat cyclical because DA in its own turn can cause HPA activation.

Analysis of the Neural Diathesis-Stress Model

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Figure 2. Neural mechanisms of individuals who are vulnerable to schizophrenia.

This model may be considered viable for the following reasons. First, as explained before, the activation of the HPA axis increases DA neurotransmission. Therefore we assume that DA activation represents either the primary abnormality of schizophrenia or a consequence that appears later on of some other primary factor. HPA axis on the other hand is the representative of the mediator of the relationship between the stressor and the symptom. Moreover, because the HPA axis has the potential of changing DA neurotransmission even after the stressor has been removed (for example by increasing DA synthesis or receptor density) it can be considered as the moderator of the expression of the diathesis as well. So the link between biological vulnerability and psychiatric outcome varies along with the level or persistence of HPA activation.

The findings in the article point to abnormalities in the striatal DA receptors that lead to a heightened sensitivity to DA. The expression of the biological diathesis is decreased by the HPA axis because of the heightened effect of cortisol on DA activity. But at the same time, the diathesis influences HPA activation making the patient hyperresponsive to the stress.

Figure 2 summarizes what has been said above, however, it is important to keep in mind that it is not meant to be exhaustive. The DA activity is influenced by other factors apart from the HPA system. Furthermore, psychiatric symptoms can also have evocative effects and increase vulnerability to stressors and increase poor coping mechanisms are expected to magnify the effects of daily stress on schizophrenia patients.

Second, the neural diathesis-stress model offers a credible explanation for the gradually escalating behavioral problems observed in preschizophrenic patients at a modal age of onset. Human cortisol release gradually increases throughout as a person ages throughout the childhood, and then shows a very rapid rise in adolescence. This changes that occur as the person matures, could be one of the factors that moderate premorbid behavioral changes during the childhood and make the age of adolescence and early adulthood the peak period for the disease onset.

The fact that the HPA activation enhances the DA activity explains why schizophrenia only gets worse when it’s not treated with neuroleptics. The longer the wait between the onset of the illness and the start of the treatment, the worse the long-term effect is going to be. Reduction in the cortisol elevations associated with psychosis decreases the chances of the hippocampal or other systemic changes from occurring. Therefore, the shorter the period between the start of the cortisol release and the initiation of the treatment, the less chances that the patient is going to suffer from permanent impairments of the HPA axis.

Third, although research finding are vague and not systematic, there is evidence that male patients have a higher level of cortisol release when compared to female participants. If

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the HPA axis is really triggering or exacerbating the behavioral alterations, this might cause a more defined premorbid behavioral dysfunction and an earlier onset of symptoms found in male patients.

Other environmental Factors

Some recent immunologic, epidemiologic and neuropsychiatric studies have shown that infections such as rubella, influenza, Herpes Simplex Virus-1 and -2, cytomegalovirus, poliovirus, and *Toxoplasma gondii*. It’s not the virus itself that directly causes schizophrenia, but rather the cytokine response developed by the infected mother.

Infections during pregnancy can affect the fetus as a result of the release of stress hormones, hypoxia production, malnutrition, or by setting off the proinflammatory cytokine responses of the mother, the placenta, or the fetus.

Some other environmental insults are thought to be obstetric complications, such as premature birth, low birth weight, rhesus incompatibility, preeclampsia, resuscitation at birth, emergency Cesarean delivery, and prenatal nutritional deficiency.

Glossary:

Adrenal medullary hormones- substances secreted by the adrenal medulla, including epinephrine and norepinephrine.

Clang- Clanging involves choosing words based on their sound rather than their meaning. This involves rhyming or alliteration. An example of a clanging sentence is "He walked the dog eggnog, frog, clog, soggy, simple sentence."

Co-agonist- A substance that can combine with a receptor on a cell to initiate signal transduction

Diffusion Tensor Imaging- an MRI based imaging that is used to visualise the location and direction of the brain’s white matter tracts.

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Electroencephalography- neurological test electrical activity in the brain is measured and recorded by electric monitoring device.

Exon- any part of the gene that will encode for the final RNA produced after splicing.

Haplotypes-a set of alleles of a group of closely linked genes, such as the HLA complex, which are usually inherited as a unit, an individual inheriting a complete haplotype from each parent.

Megabase- unit of length for DNA fragment that is equal 1 million nucleotides.

Nucleus accumbens- a nucleus forming the floor of the caudal part of the anterior prolongation of the lateral ventricle of the brain and receiving dopaminergic innervation from the ventral tegmental area as part of the mesolimbic pathway.

Polymorphism- from the Greek meaning “having multiple forms”. the characteristic of being able to assign a different meaning or usage to something in different contexts - specifically, to allow an entity such as a variable, a function, or an object to have more than one form.

Seminal study- A study that involves the presence of semen or seed.

Sensory gating- the process of filtering out all of the unnecessary stimuli in the brain from the environment to prevent information overload in the higher cortical centres of the brain.

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