Is Schizophrenia

Nature or Nurture?

(Trial Version)

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September 26, 2010

Facts about Schizophrenia:

- *Schizophrenia affects an estimated one percent of the world's population.*
- *Symptoms usually appear between the ages of 15 and 35.*
- *Schizophrenia affects males and females equally, although symptoms often appear earlier in males.*
- *In the U.S., about 2.5 million people have this illness.*
- *About 80 percent of people with schizophrenia can live either full, productive lives or relatively independent lives with treatment.*
- *The other 20 percent of sufferers will require long-term, structured care.*
- *People with schizophrenia have a higher rate of suicide than the general population. Approximately 10 percent of people with schizophrenia (especially younger adult males) commit suicide.*
- *Schizophrenia accounts for about 40 percent of all long-term hospitalization.*
- *Schizophrenia can run in families. The risk for inheriting schizophrenia is 10 percent in those who have an immediate family member with the illness, and 40 percent if the illness affects either parents or an identical twin.*
- *Heredity does not explain all cases, however. About 60 percent of people with schizophrenia have no close relatives with the illness.*
- *Early treatment of schizophrenia and newer treatment options may control the illness in up to 85 percent of individuals.*

At the outset, I may mention that this debate nature v/s nurture has gone far too long. I think it should be nature AND nurture as both are important for development and growth of individual and community at large. Nevertheless, as the topic has been given to me, my submission is as follows on Schizophrenia.

Before I discuss Nature v/s nurture debate on Schizophrenia it will be worthwhile to know what is Schizophrenia.

What Is Schizophrenia?

Schizophrenia is a serious mental illness that affects how a person thinks, feels, and behaves. The person finds it difficult to tell the difference between real and imagined experiences, to think logically, to express feelings, or to behave appropriately.

People with schizophrenia may hear internal voices not heard by others or may see things that are not really there. These experiences can seem threatening and can make them fearful and withdrawn. They also may have trouble organizing their thoughts and expressing themselves. Their speech and behavior can be so disorganized that they may seem frightening to others.

Schizophrenia is one of the most misunderstood mental illnesses. Contrary to popular belief, it does not involve a "Jekyll-and-Hyde" type of split personality. Instead, it means that all the attributes that go into the makeup of the human personality - logical thinking, feelings and expression, perception, and relating to others - become separated from one another.

Nice to Know:

Schizophrenia literally means "a split mind," and this may be where the misconception of split personality took root. Eugen Bleuler, a Swiss psychiatrist, first used the term in 1911 to describe patients whose thought processes seemed disconnected.

Schizophrenia affects about one percent of the world's population and is found all over the world, in all ethnic and social groups.

People with schizophrenia often have difficulty functioning in society, at work, and in school. The illness can be taxing on both the individuals who are affected and on their families.

But, the symptoms of schizophrenia vary widely from one person to another. In some people, the dissociated feelings caused by the illness are a constant part of life. In others, the symptoms will come and go.

People with schizophrenia do not always act abnormally. They may appear perfectly responsible and in control, even when experiencing hallucinations or delusions.

Schizophrenia cannot be cured, but the symptoms can be reduced significantly with treatment.

Schizophrenia is a disease that has proven difficult for scientists to crack. It is characterized by alterations in the content of consciousness and in spite of the fact that we know much more about the function of the brain today than we did a few years back, we know precious little about how it works as an organ of consciousness. Schizophrenia is a disease without a clear anatomic lesion or a known causative agent. It has, however, a genetic component; there is an inherited predisposition to the development of schizophrenia. Schizophrenia is a disease that highlights the advantages of the human genetics approach to the study of human disease: we know little about the basic function that is perturbed by the disease and it affects an organ that is difficult to biopsy. Therefore, it has proven difficult to advance our understanding of the disease by putting together hypotheses that are subsequently tested. The genetics approach, however, is model independent and allows for the isolation of a disease gene independent of preconceived notions about its pathogenesis. Once you have the gene in hand you can put the protein it encodes, into the context of biological pathways that are already known or use it as a tag for a new pathway. In either case, this defines a key pathway that leads to an understanding of how the disease happens or provides an excellent position from which to construct a hypothesis on the topic. The human genetics approach to common diseases has been difficult, and until recently, it has proven hard to isolate genes that contribute to the pathogenesis of common diseases; schizophrenia has been no

exception to that. However, recent publications have reported the isolation of three schizophrenia candidate genes: the dysbindin gene, the gene encoding G72, and the Neuregulin 1 (NRG1) gene. It is of interest here that all the three may play a part in the glutamatergic system.

Stefánsson *et al* described the isolation of a candidate for a schizophrenia gene from a locus on chromosome 8p22–p11 that has shown up in several genome wide scans for schizophrenia genes. The gene encodes members of the neuregulin family of proteins, NRG1, that may influence both synaptogenesis and synaptic plasticity and in that invites the possibility that the gene may hold, in part, not only the secret to the genetic predisposition to schizophrenia, but also the mechanism whereby the environment contributes to the pathogenesis of the disease.

The environment influences the brain in many ways, and the one that is most specific to the brain is through the experience of the beholder; one of the ways in which the brain responds to experience is through synaptic remodeling that may be influenced by NRG1. Therefore, the NRG1 gene may shed light on how both nature and nurture contribute to the pathogenesis of schizophrenia.

Neurodevelopment and Schizophrenia

Schizophrenia is increasingly believed to be a disorder of abnormal neurodevelopment, linked to dysregulation of various genes that affect neuronal connectivity, synaptogenesis, and NMDA glutamate receptors. It is now recognized that single genes do not directly cause schizophrenia; rather, more than a dozen "susceptibility" genes code for subtle molecular abnormalities that hypothetically provide a genetic "bias" toward inefficient information processing in brain circuits that mediate the symptoms of schizophrenia (Table). **The coupling of sufficient genetic bias with stressful input from the environment is the modern formulation for how nature and nurture conspire to produce schizophrenia.**

TABLE.
Susceptibility Genes for Schizophrenia

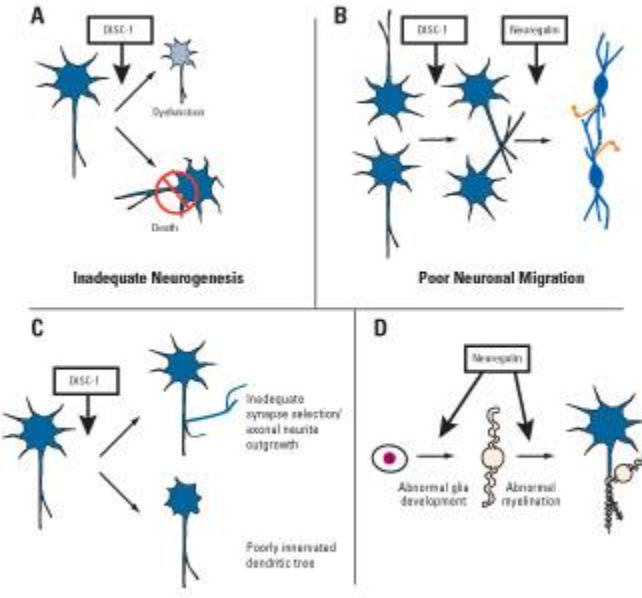
Dysbindin	Erb-B4
Neuregulin	FEZ1
DISC-1	MUTED
DAOA	MRDS1
DAAO	BDNF
RGS4	Nur77
COMT	MAO-A
CHRNA7	Spinophylin
GAD1	Calcyon
GRM3	Tyrosine hydroxylase
PPP3CC	Dopamine$_2$ receptor
PRODH2	Dopamine$_3$ receptor
AKT1	

DISC-1=disrupted in schizophrenia-1; DAOA=D-amino acid oxidase activator (G72/G30); DAAO=D-amino acid oxidase; RGS4=regulator of G-protein signalling 4; COMT=catechol O methyl transferase; CHRNA7=α-7 nicotonic cholinergic receptor; GAD1=glutamic acid decarboxylase 1; GRM3=glutamate receptor, metabotropic 3; BDNF=brain derived neurotrophic factor; MAO-A=monoamine oxidase A.

Stahl SM. *CNS Spectr.* Vol 12, No 8. 2007.

Four key genes that regulate neuronal connectivity and synaptogenesis in schizophrenia are shown in Figures 1–3. The genes for the four key proteins are BDNF, a known trophic factor; dysbindin, also known as dystrobrevin binding protein 1, involved in the formation of synaptic structures; neuregulin involved in neuronal migration and in the genesis of glial cells and subsequent myelination of neurons by these cells; and DISC-1, aptly named for a disrupted gene linked to schizophrenia that makes a protein involved in neurogenesis, neuronal migration, and dendritic organization.

FIGURE 1.
Neurodevelopmental hypothesis of schizophrenia: subtle genetic abnormalities in DISC-1 or neuregulin causing disconnectivity[16]

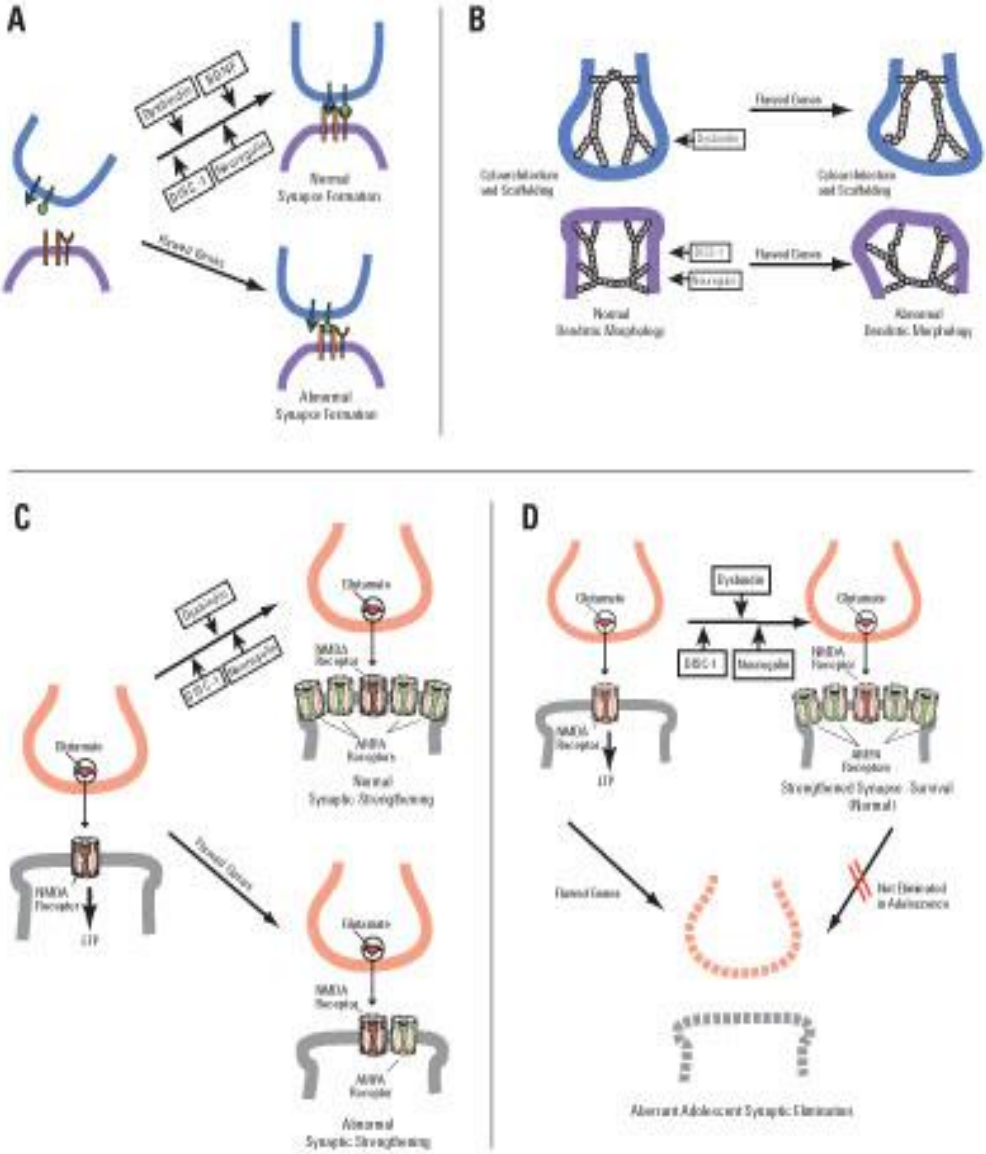


DISC-1=disrupted in schizophrenia.

Stahl SM. *Essential Psychopharmacology.* 3rd ed. New York, NY: Cambridge University Press. In press. Reproduced with permission. Copyright Neuroscience Education Institute.

Stahl SM. *CNS Spectr.* Vol 12, No 8. 2007.

FIGURE 2.
Neurodevelopmental hypothesis of schizophrenia: key susceptibility genes causing abnormal synaptogenesis[16]



BDNF=brain-derived neurotrophic factor; DISC-1=disrupted in schizophrenia-1; NMDA=*N*-methyl-d-aspartate; AMPA=α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic; LTP=long-term potentiation.

Stahl SM. *CNS Spectr*. Vol 12, No 8. 2007.

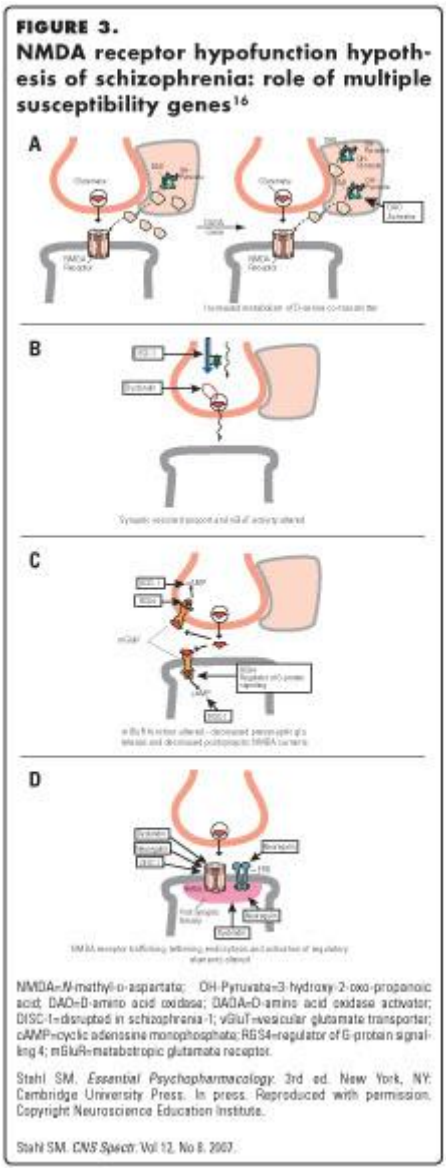


FIGURE 3.
NMDA receptor hypofunction hypothesis of schizophrenia: role of multiple susceptibility genes[16]

A

B

C

D

NMDA=*N*-methyl-D-aspartate; OH-Pyruvate=3-hydroxy-2-oxo-propanoic acid; DAO=D-amino acid oxidase; DAOA=D-amino acid oxidase activator; DISC-1=disrupted in schizophrenia-1; vGluT=vesicular glutamate transporter; cAMP=cyclic adenosine monophosphate; RGS4=regulator of G-protein signalling 4; mGluR=metabotropic glutamate receptor.

Stahl SM. *Essential Psychopharmacology*. 3rd ed. New York, NY: Cambridge University Press. In press. Reproduced with permission. Copyright Neuroscience Education Institute.

Stahl SM. *CNS Spectr*. Vol 12, No 8. 2007.

It is not known exactly how these genes cause the hypothesized subtle molecular abnormalities that are thought to bias neuronal circuits toward schizophrenia, including not knowing whether these genes make abnormal proteins, or just do not turn on and off synthesis of their gene product protein when they should during neurodevelopment. The specific combinations of abnormal genes that are either necessary or sufficient for the development of schizophrenia are also not known. Nevertheless, the fact that several genes linked to schizophrenia are all involved in neurodevelopment strongly implicates that something has gone wrong with the connections between neurons in schizophrenia (Table, Figures 1–3).

Disconnectivity

The results of abnormal genetic programming during critical periods of neurodevelopment could include selecting the wrong neurons to survive in the fetal brain (Figure 1A); having neurons migrate to the wrong places (Figure 1B); having neurons innervate the wrong targets, perhaps from getting the nurturing signals mixed up so that what innervates these neurons is also mixed up (Figure 1C); or having abnormal development of the glial cells so that they are unable to myelinate neurons properly (Figure 1D).

To the extent that something is wrong with major susceptibility genes for schizophrenia during the formation of the brain before birth, DISC-1 could affect early neurogenesis (Figure 1A), neuronal migration (Figure 1B) and dendritic organization (Figure 1C), whereas neuregulin could affect neuronal migration (Figure 1B) as well as myelination of neurons once they have migrated into place in the forming brain (Figure 1D). These neurodevelopmental processes are absolutely critical for normal brain development, occur over large distances, and impact the functioning of the brain for an entire lifetime.

Abnormal Synaptogenesis

Although it is possible that schizophrenia susceptibility genes may impact brain development once and forever in a type of fetal "hit and run" damage that is complete by the time the brain is formed, it is also possible that an abnormal neurodevelopmental process continues in the schizophrenic brain throughout a lifetime. Most neurons are formed, selected, migrate, differentiate, and myelinate before birth, but the process of neurogenesis continues for a lifetime in selected brain areas. Perhaps more importantly, synaptogenesis, synaptic "strengthening," elimination, and reorganization continue over a lifetime. Thus, to the extent that schizophrenia susceptibility genes affect synapse formation, they have the potential to affect ongoing brain function for a lifetime.

Many of the known susceptibility genes for schizophrenia have profound impact upon synaptogenesis (Figure 2A and 2B). Dysbindin, BDNF, DISC-1, and neuregulin all affect normal synapse formation and thus some combination of abnormalities in these molecules could lead to abnormal synapse formation in schizophrenia (Figure 2A). For example, abnormal genetic programming of dysbindin could affect synaptic cytoarchitecture and scaffolding in schizophrenia, whereas abnormal programming of DISC-1 and neuregulin could affect dendritic

morphology, and together lead to structurally abnormal synapses in schizophrenia (Figure 2B).

Back to Nurture:

Most psychiatrists and psychologists will declare that it's not a question of nature versus nurture, inherited versus environmental factors. Both play a part in influencing what we do. But watch carefully: nurture receives lip service these days while nature receives enormous grants (some of them, not surprisingly, from drug companies). Hemlines are on the way up again and biological answers to psychological questions are back in vogue. Researchers -- and, by extension, science reporters and the general public -- take on faith that we are what our genes, hormones, and neurotransmitters have made us.

The press especially loves to cover dramatic "linkage" research, which attempts to find a gene responsible for a given behavior. In 1987 researchers announced that they had found the precise gene that caused bipolar disorder. DEFECTIVE GENE TIED TO FORM OF MANIC-DEPRESSIVE ILLNESS, the New York Times trumpeted. But after expanding the original study and reanalyzing the data two years later, the researchers had to admit they were mistaken.

The same pattern of apparent success followed by retraction has been repeated with linkage research on schizophrenia (in 1988 and 1989) and alcoholism (in 1990). In all three cases, the popular press excitedly announced that the "genetic flaw" responsible for the disorder had at last been found. Later, alert readers noticed follow-up articles, far less prominent than the original reports, acknowledging that the first discovery had been a false alarm.

It seems remarkable that genetic explanations still command a largely uncritical loyalty in the face of such retractions and other data that have raised questions about how much genes really contribute to even the most serious disorders, the ones referred to as mental illnesses. For instance, a recent report in a leading psychiatric journal found little evidence that "hereditary factors are of any importance" in determining who will develop relatively mild depression, the kind that used to be called neurotic. Most of the studies that have claimed some role for the genes are limited to very serious depression or bipolar

disorder (in which depression alternates with periods of frenzied activity).

Even then, several studies have found that nine out of ten individuals with an extreme mood disorder had no close biological relative with the same problem. In looking at people whose parents gave them up for adoption -- which is believed to be the best way of teasing apart nature and nurture -- the strongest predictor of who was going to develop these disorders was the background of their adopted parents or other environmental factors such as how old they were when they were adopted.

As for schizophrenia, the best known psychosis, although almost all specialists now believe that genes play some role*, "the evidence for a genetic contribution,"* Wynne concedes*, "is not overpoweringly strong."*

Wynne has been helping to direct a new Finnish study that is following about 200 children put up for adoption by their schizophrenic mothers. Genetics did play a role in determining who was ultimately diagnosed with the disorder, but only in the context of certain family environments. Of the 49 children who were placed in well-functioning families, not one became schizophrenic.

Meanwhile, a study published in the *New England Journal of Medicine* used MRI (magnetic resonance imaging) to compare the brains of 15 sets of identical twins, one of whom in each pair was schizophrenic. Differences in the brains were noted in almost every pair -- even though identical twins have identical genes. Clearly, something other than genetic factors must have produced those differences.

Does all of this mean that biological factors are unrelated to how we behave? Of course not. Notes Leon Kamin, chair of the psychology department at Northeastern University: "There have to be biological correlates" to behavior. "Every time I emit a word, something has changed in my brain. Everything is a biological condition. So what?"

Just because a behavior or emotion corresponds to a change in a neurotransmitter (the chemical messengers in the brain) doesn't mean the neurotransmitter caused the behavior, says Kamin. That assumption -- which is widely made -- is much like "finding mucus in the nose of someone with a cold and saying, 'Aha! Mucus causes colds.'

"These days people are ready to accept quite uncritically almost any claim that fits in with a framework of biological determinism," Kamin

continues. “As soon as claims are made” about a neurobiological basis of some behavior, “they're on the front page everywhere.”

Why the biological bias? For starters, we might reflect on a comment once made by the psychologist Abraham Maslow: “It is tempting, if the only tool you have is a hammer, to treat everything as if it were a nail.” Translation: Train researchers primarily to do biological research and they'll approach every behavioral problem as if were biological in origin. Eventually these researchers will rise to positions of power and support more research that matches their own orientation.

Under such circumstances, few people are even looking at psychological problems from another point of view, such as a family-environment perspective. Researchers who might do such work “are discouraged about being able to get funding,” says Wynne. “They feel the cards are stacked against them, so they don't apply.”

Biological explanations have caught on for several reasons:

- First, they're easy to understand.
- Second, genetic explanations are reassuring since they allow some people to feel less responsible for how they behave. Organizations composed of people suffering from mental disorders -- or their parents -- are especially fond of the theory that these problems are due to no-fault diseases that simply “happen” to people.
- Finally, genetic theories are widely accepted simply because we've heard so much about them. The popular press seems particularly inclined to publicize research with a biological bent, perhaps because reporters share the general public’s biases or because hard science claims make for sexier stories. Millions of readers open their newspapers and magazines to find articles based on the unproven assumption that our emotions can be explained by our brain chemistry.

Despite much research, environmental influences that can be said to cause a schizophrenic illness remain elusive. When the effects of an (often prolonged) prodromal syndrome are taken into account, the first

episode appears to come from nowhere. However, over the past couple of decades a number of factors have emerged that can be argued to influence, and not merely reflect, the illness onset. The possible effects of season andgeography of birth, urbanisation, immigration, substance misuse, prenatal influenza, famine and other stresses, and obstetric complications are summarised. These varied findings, often of small effect and borderline significance, present a challenge to clinicians attempting to make sense of their patients' life experiences. Any hard conclusions still depend largely on how one formulates the illness.

Although early schizophrenia researchers such as Bleuler and Kraepelin insisted that schizophrenia is, at its core, a disease caused by biological factors, many others believed that schizophrenia was caused by the family. Today, we know that no family can, by itself, "cause" schizophrenia. Research suggests, however, that the family environment does play an important role in a patient's treatment. Some families may have qualities that increase the likelihood that a patient will relapse and experience another schizophrenic episode.

When schizophrenia patients leave the hospital and return to their homes, some fare better than others. Researchers became interested in figuring out why some patients relapse whereas others do not. Clinicians and researchers believed that there might be qualities of the family that protect the patient from relapse and other qualities that increase the likelihood that the patient will experience another episode.

As previously mentioned, a family's communication deviance - vague and confusing speech - is a risk factor in schizophrenia. Another measure of the communication of family members is called expressed emotion. Expressed emotion, or EE, is a measure of the negative communication directed at a patient by family members. EE consists of three parts: criticism, hostility, and emotional over involvement.

"A family member who expresses criticism is expressing disapproval or dislike of the patient. Hostility is a more extreme form of criticism that involves a rejection of the patient. Emotional over involvement involves dramatic, over concerned behaviors directed toward the patient. For example, when questioned about her schizophrenic son,

an emotionally over involved mother might respond, "When he spends all day in bed, I just feel terrible. I wish he knew how hard it was on me. Sometimes I lock him out of his room when he gets up to go to the bathroom. I just have to force him to get out and do something." Not only does this mother emphasize how her son's illness makes her feel, but also she forcibly locks him out of his room. In 1998, Ron Butzlaff and Jill Hooley at Harvard University found that patients living in a high EE home environment were more than twice as likely to relapse in the first year following a hospitalization compared with patients returning to a low EE home. The good news is that EE can be lowered with family therapy. When EE levels are lowered, relapse rates are reduced."

Why might the way a family communicates affect a patient's recovery?

Current understanding suggests that high EE or communication deviance creates a stressful environment for schizophrenic patients. When we are stressed, a substance called cortisol is released in the brain. Cortisol has been found to trigger dopamine activity and to affect glutamate release.

According to this theory, a stressful environment can directly affect the chemicals in the brain that are implicated in schizophrenic symptoms.

To conclude, I would like to end from where I started.

"Schizophrenia is another of those disorders that cannot be classed into either nature or nurture, as both play a significant role in it's development. On one hand, a person with genetics that show a high rate of likelihood of schizophrenia will be likely to contract the disease. However, if there is never a trigger for the disease to develop, those schizophrenic-prone genes may just lie dormant and never develop. It all depends on what type of lifestyle they have. If they're stuck in a high-intensity whirlpool of aggression and noise, and they have schizophrenic prone genes, they may well contract the disease. But if they're in a loving, calm environment, they may never get it.

That Finnish study was extremely conclusive, in terms of studies of schizophrenia, which would probably be my pick, or something replicable to that. Environmental factors on schizophrenia would change from person to person, depending n their phobias, likes, etc.

There wouldn't be a generic 'formula' for schizophrenic-prone people.

As for the debate, it's hard to place schizophrenia in one basket, it's probably result of both.”