Genes, Environment and Behavior (LSCI 2040)

Final Draft of Semester Project - Schizophrenia

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I. Abstract

Despite considerable research, the etiology of schizophrenia is still poorly understood. The challenge lies in the complex pathophysiology of the disease and its interactions with a variety of genomic and epigenomic factors. This paper intends to show that candidate SCHZ susceptibility pathways including NRG1 and NMDAR should be examined both for their neurobiological functions as well as from a pathobiological point of view, particularly their interactions with other pathways.

One of the remarkable discoveries in recent research is a candidate susceptibility gene, NRG1 and role of NMDAR in schizophrenia. Therefore, the first part of the paper will be devoted to illustration of recent discoveries concerning NRG1 and NMDAR, specifically the findings from genome wide scan studies and biochemical tests, involving NMDAR-blocking drug.

In the second part of the paper, I will demonstrate the importance of the pathobiological function of NGR1 and NMDAR in schizophrenic individuals. This will be done by illustrating a study of two scientists, Graham Pitcher and Michael Salter in the article "*Schizophrenia susceptibility pathway neuregulin 1 - ErbB4 suppresses Src upregulation of NMDA receptors*" published in "*Nature Medicine*". Their study of mice models investigates a potential link between glutamatergic dysfunction and the candidate schizophrenia genes NRG1 and ErbB4.

The result of their experiments reveals that schizophrenia might not be NRG1 affecting the function of NMDAR per se but rather a loss of Src- mediated enhancement that results in hypofunction of NMDAR and low synaptic transmission. Further, I will illustrate the importance of both genetic and epigenetic factors in risk of developing the disease by briefly summarizing some important findings from family studies. In the final part of the paper I will provide data on social, political and economic obstacles that schizophrenia and other mental illnesses face today. Most of these challenges are related to social stigmas, poverty and inadequate funding into research on mental illnesses. Here I am not intended to offer solutions but point out specific problems and provide suggestions that might lead to a better future for people with mental illnesses.

II. Introduction

It was in 2009 when my parents first started noticing an aberration in my youngest brother's health condition. He had just turned sixteen and was about to graduate high school. In a family of three children, he was the quietest one, less social and talkative than his older brother and me. Our parents never associated his social withdrawal as a sign of "otherness" or abnormality attributing his behaviour to commendable modesty. Despite difficulties in several school subjects and poor grades, he managed to graduate high school. The graver obstacles began during his freshman year at university when our parents efforts were unable to provide an explanation for the suddenly aggravated symptoms. Due to the severity of his condition including memory loss, inattention, and difficulty performing tasks, he had to withdraw from school. Within the next two years he went through endless medical examinations with a number of professional neurologists, psychiatrists and psychologists but all they were told was that their son was fine with no serious

health threats or brain damage based on their findings and therefore, my parents' concerns were baseless. All of these doctors determined his condition was normal for a boy of his age suggesting his symptoms were caused by stress due to exams and a new university environment resulting in behavioral changes and cognitive function. At the time neither me nor my parents were familiar with schizophrenia since none of our family members had experienced the disease. Four years later, in 2013 (soon after I moved to the United States) it was officially confirmed that my brother had schizophrenia. It was a tragedy for our family and painful for me. My parents and I often blame ourselves that we did not provide my brother with the attention and support he needed to make it through the period when his severe symptoms began. Perhaps, in part it is the fault of the inferior health system in Russia which failed to reveal the disease at its early stage.

This opportunity to take on schizophrenia as the topic of my semester project enabled me with a deeper understanding of the disease and its implications. Learning about it on a molecular and cellular level answered some of the key questions I had which no doctor had been able to provide satisfactory explanations to.

Today nearly 1 percent of the global population is diagnosed with schizophrenia which is quite a lot in comparison to some other mental illnesses. In addition, due to the incurable nature of the disease with life-time symptom persistence, the morbidity and mortality are very high. According, to 2016 data from WebMD, the suicide rate for schizophrenia sufferers is 5%-13% of those diagnosed with schizophrenia.

Schizophrenia(SCHZ) is a complex mental disorder affecting the structure and function of the brain and neurotransmitter pathways of the central nervous system. There are a number of

differentiating qualities making schizophrenia unique. First of all, in contrast to other mental disorders, symptoms of schizophrenia usually appear towards adulthood, between ages 16 and 30. Second, unlike dementia or brain tumors it affects multiple regions of the brain. Third, SCHZ is difficult to identify in its early stages; it often confused with bipolar disorder, clinical depression, or autism. More interestingly, some statistics show that schizophrenia tends to affect males more frequently and more severely than females. (http://www.schizophrenia.com/sznews/archives/002562.html#)

It has been observed that many educated people who have no records of mental illness in their family tend to confuse mental disorders with physical disabilities. They are often surprised when a person who looks absolutely normal suddenly behaves inappropriately as a result of his/her mental illness. One of the major problems with mental illnesses is that they are difficult to distinguish from a state of mind caused by stress and depression which is ordinary for many people. A person with a mental disorder does not show any physical signs of anomaly. Phenotypically they appear to be normal and healthy, but their "otherness" can easily be determined by commonly shared behavioral symptoms and poor physical and intellectual performance. There are three categories of behavioral symptoms: positive, negative, and cognitive. "Positive" symptoms include psychotic behaviors not generally seen in healthy people such as 'losing touch' with certain aspects of reality including hallucinations, delusions, thought disorders (unusual or dysfunctional ways of thinking) and movement disorders. "Negative" symptoms are associated with a disruption of emotions and behaviors that are typical for average people. These symptoms include reduced expression of emotions via facial expression or vocal tone, reduced feelings of pleasure in everyday life, difficulty beginning and sustaining activities,

and reduced speaking. Symptoms of individuals with a cognitive affective disorder are subtle such as changes in memory, an inability to understand information and make decisions, and trouble focusing or paying attention. (https://www.dnalc.org/view/2226-Schizophrenia-.html). More severe symptoms of schizophrenia such as delusions, hallucinations, and other impairments provide a clearly indication for the involvement of multiple regions of the brain, and various connections (pathways) formed by these regions.

As we can see, schizophrenia represents a special category, which I refer to as an "invisible disability". It has symptoms which are not easily determined, yet common, amongst a standard population. Social withdrawal, quietness, reduced expression of emotions and reduced speaking could easily be confused with signs of depression, a specific state of mood or a difficult teenage period. Cognitive symptoms can easily be confused with similar symptoms found in bipolar and autism patients and ADD/ ADHD individuals. This makes schizophrenia difficult to identify in its early stages. Consequently, the current predominant area of study in schizophrenia is deciphering the specific components, molecules, and cell connections between cells called synapses and the larger circuits present in the dorsolateral prefrontal cortex that underlie this disturbance of working memory.

III. Schizophrenia in molecular and cellular levels

The term 'schizophrenia' has led to much confusion about the nature of the illness. The concept of a 'split personality', which is sometimes also referred to as 'multiple personality disorder' still prevails in society. It was first isolated from other forms of psychosis such as depression and bi -polar disorder in 1887 by German psychiatrist Emil Kraepelin. He mistakenly believed that the

illness only occurred in young people and that it inevitably led to mental deterioration. Thus, calling it as "*dementia praecox*" ('dementia of early life'). Later in 1908 the term was recounted into "*schizophrenia"* by a swiss psychiatrist Eugen Bleuler. He disagreed with Kraepelin's concept of mental deterioration and preconsciousness and instead emphasized that splitting of psychic functioning is an essential feature of this disorder. One of the main differences between Kraepelin and Bleuler viewpoints is that the Kraepelin studies of SCHZ were retrospectively, using medical records whereas Bleuler's studies were prospective, involving a careful clinical observations.

It took more than twenty years of studies on schizophrenia to confirm that there is no anomaly in any single area of the brain, rather there are alterations in various aspects of brain development. Now it is known that this neurodevelopmental disorder develops when multiple regions throughout the brain are not connected correctly and therefore lose their coherence and coordination. Deficits in neuronal migration, neurotransmitter receptor expression, and myelination are all potential causes linked to the disease.

A recent breakthrough for the pathology of schizophrenia and its core symptoms of hallucinations and cognitive deficiency found the cause to be a hypofunction of the N-methyl-D-aspartate subtype of the glutamate receptor (NMDAR) signaling. To validate this hypothesis, studies applied NMDA-blocking drugs on people who had no disease diagnosis. The result established the same phenotypical behavior found in patients with schizophrenia. Thereof, NMDAR is a principal source for cognitive dysfunction. Phosphorylation-induced upregulation of NMDARs have shown to play a decisive role for synaptic plasticity. The NMDAR is a multiprotein complex and a constituent of a ligand-gated ion channel in the central nervous

system. Because the NMDAR activity is regulated via the phosphorylation process by NMDAR-associated kinases, these proteins play a crucial role in stability, subunit composition, and function of NMDARs. Multiple studies have suggested that NMDAR tyrosine phosphorylation is reduced in people with schizophrenia.

It has been identified that multiple loci at different chromosomes have a linkage to the disease, giving evidence of the multi-gene's involvement in schizophrenia. Yet the NRG1 locus situated on chromosome 8p is found to be closely linked to schizophrenia (**Figure 1**).

The NRG1 has various non-coding polymorphisms and haplotypes, particularly at the 5' end of its gene. This gene is associated with molecular pathways which are crucial for neurotransmitter signaling, making it a leading susceptibility gene for schizophrenia. (Harrison, 2006; p.132). The encoding of NRG1 belongs to the family of epidermal growth factor genes that are responsible for activating the ErbB receptor tyrosine kinases. Thereof, it acts as a principle mediator of a number of neurodevelopmental and brain functioning processes including plasticity and oncogenesis (Harrison & Law, 2006: p. 132)**.** The prevailing hypotheses suggests that multifarious defects in the expression of ErbB4, one of the NRG1 receptors, occur in the prefrontal cortex of patients with schizophrenia. For a considerable amount of time, an alteration of NRG1 in people with the disease was unclear.

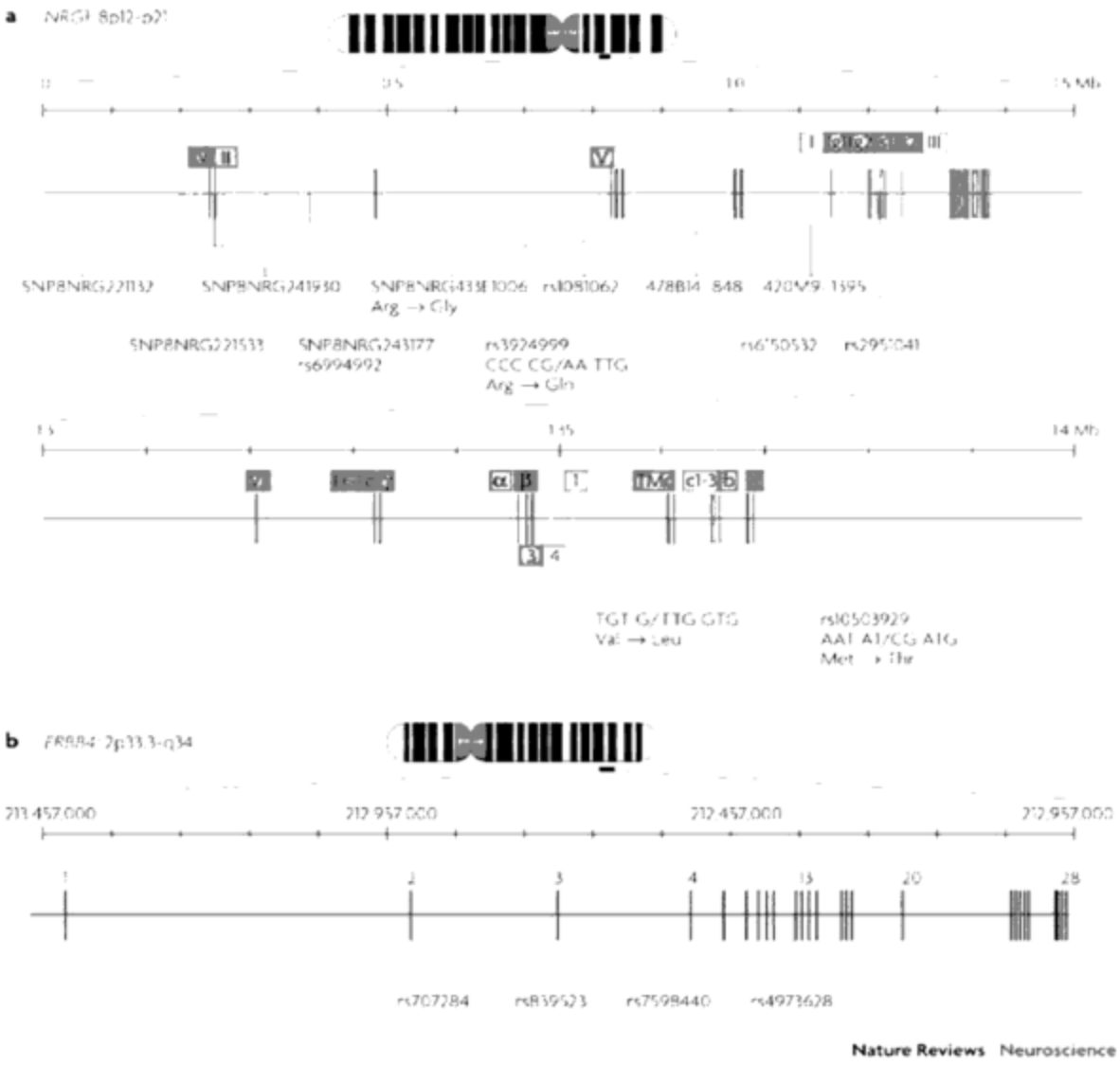

Figure 1. (a)The structure of NRG1 and ErbB4 and their associated single nucleotide polymorphisms(SNPs). The neuroligin 1(NRG1) gene is located in a 1.5 Mb region of DNA, at 8p12-8p21. Roman numerals indicate the type-specific exons.(b)The 1.15 Mb region of the ErbB4 gene, at 2q33.3-2q34.The SNPs are mainly clustered around exon 3 and in front of exon 13

A genome-wide scan of Iceland's population provided scientists with an advantage due to their extensive pedigree information and genetic isolation. Genome -wide scanning is 'linkage analysis' involving a comparative study of genomic sequences in families with schizophrenia with genomes of non schizophrenic individuals. As a result they were able to discover a useful so-called 'linkage signal', a region of the short arm of the eighth chromosome, exactly where NRG1 is situated. And when scientists looked specifically at NRG1 they found distinct variations in sequences present in schizophrenia patients. Similar studies have been replicated around the world including with Scottish and Chinese populations. This provided enough evidence to consider NRG1 as a functional candidate gene for schizophrenia. Empowered with the ability to scrutinize a single gene, scientists obtained solid evidence that because of the gene-poor location of NRG1, it was unlikely that the

malfunction could have been affected by other closely situated genes. (Corfas, Roy & Buxbaum, 2004, p. 576). On the other hand, there is no mutation on the NRG1 gene to suggest that the dysfunction was due to amino acid replacement. Subsequently, the only possible explanation was an occurrence of polymorphism. Since polymorphism does not change the NRG1's bioactivity, the idea of "the NRG1 gene expression" became the prevailing hypothesis. (Corfas, Roy & Buxbaum, 2004, p. 576). In support of this hypothesis, scientists recently found that "the ratios of three NRG1 mRNA isoforms are altered in the dorsolateral prefrontal cortex of schizophrenia patients".

"While NRG1 is not the only candidate gene that can predispose an individual to schizophrenia, extensive knowledge of the biological roles of NRG1-ErbB pathway provides an opportunity to

gain new insight into the molecular and cellular mechanisms of the disease". (Corfas, Roy & Buxbaum, 2004: p.575-576).

A number of genetic association studies within several populations confirmed that NRG1-ErbB4 signaling pathways play a key role in diverse neurodevelopmental processes and neurotransmitter signaling pathways; areas involved in schizophrenia. Future studies of postmortem brains taken from schizophrenia individuals revealed high gene expressions of NRG1 and ErbB4 and high NRG1-ErbB4 signaling but low NMDAR activity which is known to reduce synaptic plasticity (Corfas, Roy & Buxbaum, 2004: p.575). This occurred as a discrepancy with an early study of mice lacking one copy of NRG1 ($NRG^{-/+}$) gene and who displayed behavioral symptoms pertaining to schizophrenia including hyperactivity, deficiencies in prepulse inhibition, and measures of sensory gaining. Such a discrepancy was resolved by the work of two scientists: Michael Salter and Graham Pitcher who previously have been jointly working on protein -protein interactions and protein intracellular domain of NMDA channels; specifically how these channels regulate the function of NMDA receptor.

In their article "*Schizophrenia susceptibility pathway neuregulin 1 - ErbB4 suppresses Src upregulation of NMDA receptors"* published in "*Nature Medicine"* they investigated a potential link between glutamatergic dysfunction and the candidate schizophrenia genes NRG1 and ErbB4. Their study of mouse models revealed that mice are either heterozygous for one of the susceptibility genes (NRG1 or ErbB4), whereas mice with overexpression of NRG1 displayed the same schizophrenic phenotype. Respectively, both overexpression and underexpression of one of these genes or altered signaling between NRG1 gene and ErbB4 receptor can result in schizophrenia pathology. Furthermore, their study reveals that excessive NRG1β-ErbB4

signaling has no direct impact on NMDAR function. Instead, the synaptic NMDAR function is suppressed via Src kinase activity which is induced by the NRG1β-ErbB4 signaling. They provide evidence by illustrating three experiments where they manipulated the following variables:

IV. Introduction to Scientific Method

Traditional proteomic studies represent a complex structure of the brain synapse with more than thousand different proteins being associated with the postsynaptic density. Yet, the function of about 80% of these proteins is not well comprehended. Thus, new electrophysiological methods offer a quantitative way to assess consequences of the loss, mutation or overexpression of a particular protein since many of the neuron-specific proteins are often important for synaptic transmission. Brain slice preparation is a powerful tool for studying the fundamentals of neurophysiology at the molecular and cellular levels. While the neuronal membrane properties can be performed using intracellular recording, such as ion channels and putative neurotransmitters, the study of synaptic activity can be studied with extracellular recordings and specific stimuli. Different synaptic connections are studied by evoking excitatory. Extracellular response recording is a common method used to measure frequently from the hippocampal slice is the field excitatory postsynaptic potential (EPSP). There are number of advantages of using a brain slice preparation over in vivo approaches to the study of the central nervous system (CNS). This includes rapid preparation, use of relatively inexpensive and accessible animals (mice, rats, guinea pigs) where anesthetics are not necessary; mechanical stability of the preparation (due to lack of heartbeat and respiration pulsations) which permits intracellular

recordings for long periods and ability to control and manipulate variables over the preparation conditions, such as use of animals with knock out, knock in and deletion of certain genetic information. Because magnitude of signalling between neurons is mostly an activity-dependent variable, in vitro models recapitulating short- and long-term plastic properties of synaptic transmission have become an extremely popular way to assess protein function following their pharmacological and/or genetic manipulation. Long-term potentiation (LTP) of synaptic transmission which is discussed in this paper evoked by trains of patterned stimulation. LTP represents one of the most widely used models to study plastic properties of the synapse that aimed to elucidate functional roles of brain proteins. (https://www.genes2cognition.org/research/electrophysiology/)

Experiment 1. Is SRC needed for the NRG1 and NMDA Connection?

For this experiment Pitcher and Salter made a whole- cell recordings in hippocampal slices from adult wild type mice($Src^{+/+}$)and mice lacking Src ($Src^{-/-}$) (**Figure 2&3**.) Pharmacologically isolated NMDA-mediated excitatory postsynaptic currents (EPSCs) to prevent any potential effect on $GABA_A$-mediated inhibition, they used the phosphopeptide EPQ(pY)EIPIA, to activate Src. First they made a recording of NMDAR EPSCs from Src wild- type mice as a standard marker(mice in control) then they recorded the same wild type mice with Src activator (e.i EPQ(pY)EEIPIA) and found that within 10-15 min NMDAR EPSC amplitude progressively increased. Whereas, NMDAR EPSCs from mice in control remained stable without Src activator. Further, they bath-applied wild type mice in a soluble form of NRG1, NRG1β 20 min before recordings in which EPQ(pY)EEIPIA was intracellularly present and detected that NMDAR

EPSCs remained stable during 30 min of whole -cell recording. This means that NRG1 was able to prevent NMDAR enhancement by suppressing Src. Interestingly, they also discovered that, EPQ(pY)EEIPIA did not potentiated NMDAR EPSCs in Src knockout mice, compared to wild type mice. This experiment confirmed that NMDAR potentiation is Src-mediated and with the presence of NRG1 the enhancement of NMDAR is suppressed. Thus, both Src and NRG1 are needed to downstream the effect of effects of signaling pathogenesis found in schizophrenic individuals.

Table1. Experimental conditions and results of NMDAR EPSCs.

Genotype	Cell Phenotype: NMDAR Phosphorylation EPSCs: Electrical Signal in vitro brain slices
1)Wild type (Scr+/ Scr+)	Wild type EPSCs
2)Wild type (Scr+/ Scr+) + SCR ACTIVATOR	Enhanced EPSCs
3)Wild type mice (Src +/+) + SRC ACTIVATOR + NRG1β 20 min before recording	Wild type EPSCs
4) Knock out (Scr-/Scr-) + SRC ACTIVATOR	Wild type EPSCs

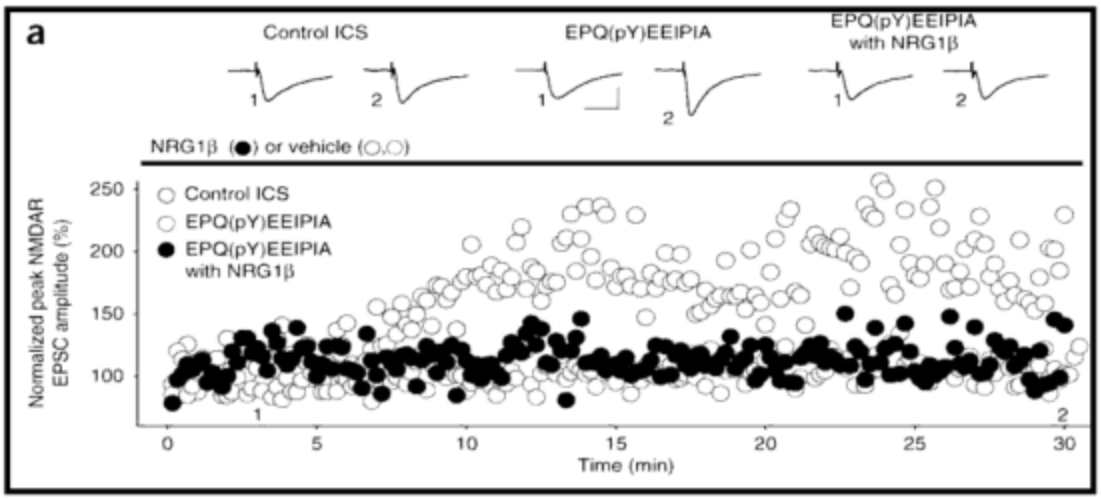

Figure 2. NRG1 prevents Src- mediated NMDAR phosphorylation

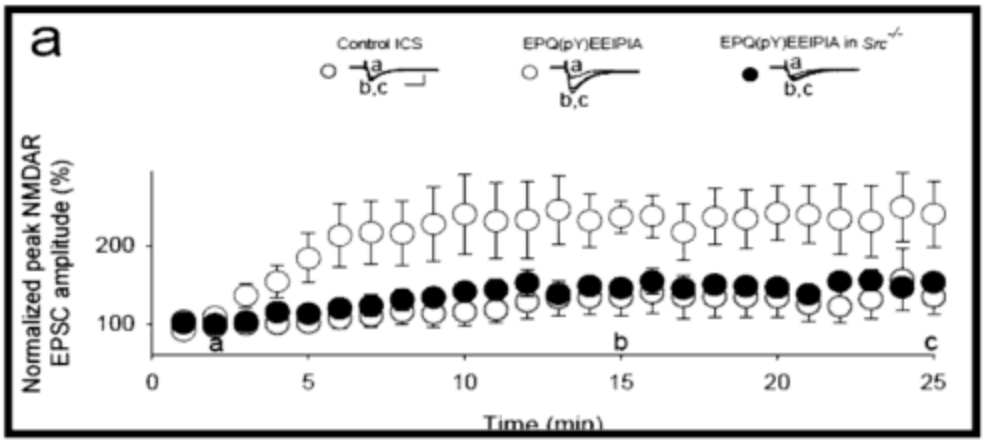

Figure 3. EPQ(pY)EEIPIA does not potentiate NMDAR EPSCs in Src-null mice

Experiment 2 . Is ErbB4 needed?

To determine whether NRG1 requires ErbB4 in suppressing Src-mediated enhancement of NMDAR currents this experiment was investigating the role of ErbB4 in the signaling pathology implicated in schizophrenia. Here Pitcher et al. tested brain slices of knockout mouse models-mutant ErbB4 homozygous mouse (ErbB4 $^{-/-}$) and wild-type mice(ErbB4 $^{+/+}$). Both slices were previously bath-applied with NRG1 β and recorded with intracellular administration of

EPQ(pY)E IPA and found that hippocampal neurons lacking ErbB4 have no effect on EPQ(pY)EEIPIA-induced potentiation of NMDAR EPSCs **(Figure 4)**.Whereas, NMDAR EPSC remained monotonous in hippocampal slices from WT mice. Thus, it allowed them to conclude that ErbB4 is needed for NRG1 -mediated suppression of Src. To confirm this findings, they prevented ErbB4 signaling in slices of wild type mice by using ErbB4 inhibitor, AG1478 and the outcomes confirmed that ErbB4 is needed for NRG1β to downstream effects of signaling pathogenesis found in schizophrenic individuals.

Table 2. Experimental conditions and results of NMDAR EPSCs.

Genotype	In vitro slices cell signaling: EPSCs via NMDAR
1)Wild type mice (ErbB4+/+) + *SCR ACTIVATOR* + NRG1β	Wild type
2)Knockout mice (ErbB4 -/-) +*SCR ACTIVATOR* + NRG1β	Enhanced
3) Wild type mice (ErbB4+/+) + ErbB4 inhibitor	Enhanced

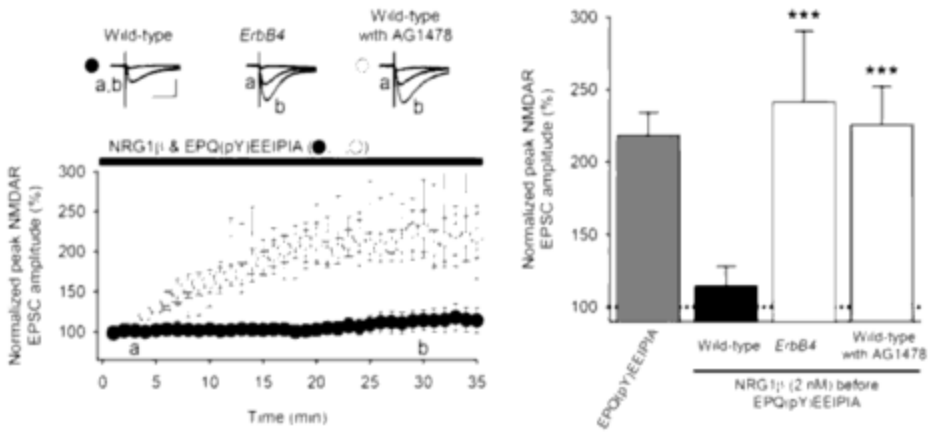

Figure 4. ErbB4 mediates NRG1β suppression of Src potentiation of NMDAR EPSCs in CA1

Experiment 3 Can NRG1B reverse the Src mediated effect (inhibit)

After scientists observed that the enhancement of basel's or long- term potentiation(LTP) and the ability of NRG1β to inhibit long-term potentiation is dependent upon ErbB kinases they started to consider other possibilities such as whether NRG1β has an effect on NMDAR function. Therefore, at this time they applied NRG1β to an entire slice of hippocampus a few minutes before conditional stimulus; in this case theta burst stimulation (TBS). By doing so they blocked the production of LTP. But when they applied NRG1β after potentiation developed for approximately 30 minutes, there was no change in amplitude of synaptic currents or field excitatory postsynaptic potentials (EPSPs). The interpretation is that NRG1β- ErbB4 signaling is inhibiting induction of activity-dependant potentiation of NMDAR synaptic transmission via Src but not reverse stimulation of a long- term potentiation of this synapsis. During this induction time NMDAR gets activated by chemical and psychological stimulations. Therefore, one

important thing they discovered is that NRG1β can prevent but not reverse the Src-mediated suppression of NMDAR function (**Figure 5**)

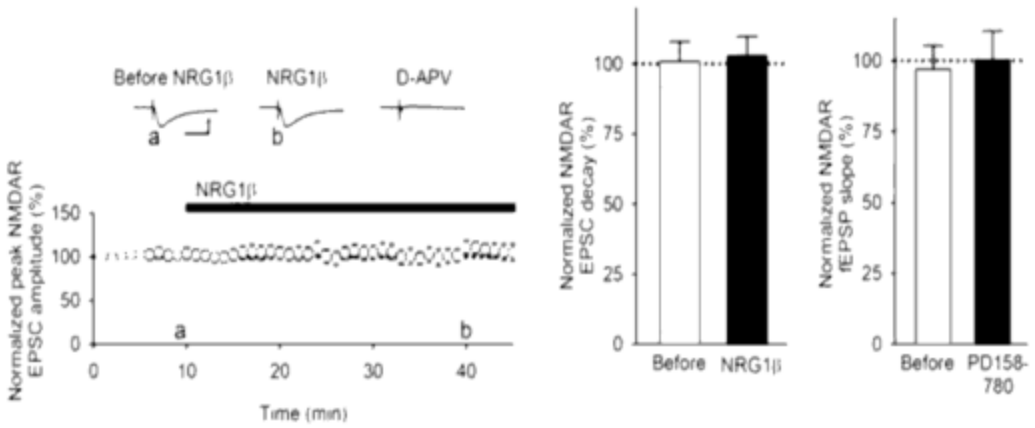

Figure 5. NRG1β has no effect on basal NMDAR EPSCs in CA1. The graph shows that during induction of postsynaptic electrical signals(EPSCs)NMDAR resistant to NRG1β or PD 158-780 (a potent ErbB receptor tyrosine kinase inhibitor)

This evidence disproved the previous hypothesis, that NRG1β was downregulating NMDA function, which eventually meant that there was something else involved in induction of long -term potentiation.

To ascertain whether NRG1β-ErbB4 signaling blocks Src enhancement of NMDAR EPSCs in CA1, they made whole-cell recordings of neurons in the CA1- pyramidal layer in acute hippocampal slices taken from adult mice. In order to induce synaptic response they used EPQ(pY)EEIPIA as an activator for Src and recorded hippocampal slices from CA1 neurons infused in EPQ(pY)EEIPIA. They found that the amplitude of the NMDA component of synaptic currents increased but in cells pretreated with NRG1β no escalation was found. To put it simply, a pretreatment application of NRG1β was able to prevent the enhancement that otherwise would have been mediated by Src and Src family activators. Essentially cutting off Src family kinases'

ability to increase NMDA receptor function, they determined the effect of NRG1β in suppression of Src enhancement as mediated by ErbB4 receptors.

Table 3. Experimental conditions and results of NMDAR EPSCs.

Genotype	In vitro a whole cell level LTP	In vitro slices cell signaling: EPSCs via NMDAR
1) Wild type mice with EPQ(pY) EEIPIA peptide & NRGβ	No change	Monotonous
1)Wild type mice (ErbB4 +/+) with NRGβ before	Prevented	Reduced
2) Wild type mice (ErbB4 +/+) with NRGβ after TBS (~30min)	No change	Monotonous
3)Wild type mice	No change	Monotonous
4)Wild type mice with EPQ(pY) EEIPIA peptide	Increased	Enhanced

In regards to schizophrenia these findings did not provide adequate evidence as it was known that in schizophrenic individuals two brain areas, the hippocampus and prefrontal cortex, are affected. Accordingly, Graham and Pitcher executed new recordings using the same method, this time involving the prefrontal cortex. Just like in CA1 synapses, NRG1β has been able to prevent enhancement of NMDA by using the peptide. In short, they received the same results for hippocampus and prefrontal cortex. (**Figure 4)**

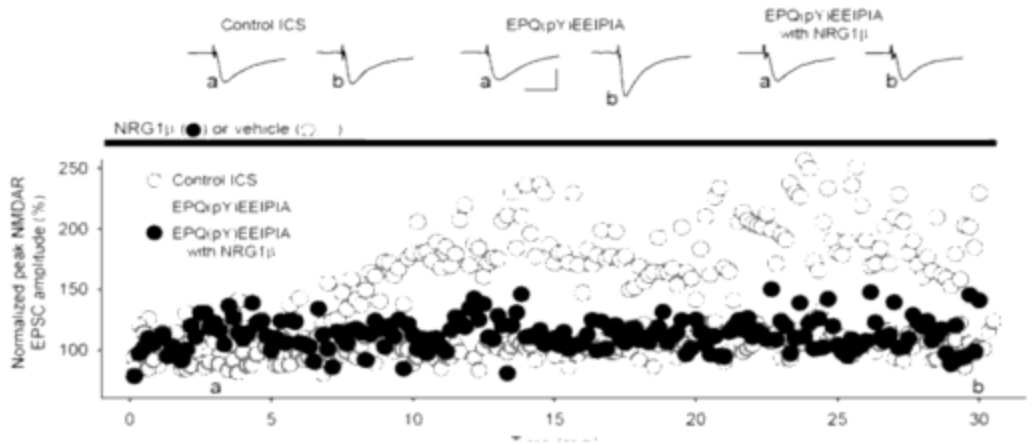

Figure 2. NRG1β prevents endogenous Src- activation -induced potentiation of NMDAR's EPSCs in CA1. This schematic graph shows an ability of NRG1β to suppress an enhancement by EPQ(pY)EEIPIA peptide prevented in animals lacking ErbB4.

ErbB4 signaling causes basel ongoing partial suppression of long-term potentiation of induction. Enhancing NRG1β-ErbB4 signaling can essentially shut off or dramatically suppress synaptic plasticity in this case long-term potentiation. Conversely, to explain what may be going on in certain hyperexcitability situations such as

chronic pain or epilepsy is that there is enhanced synaptic plasticity. Moving to NRG1β-ErbB4 signaling either up or down then can have these effects of suppression when NRG1β-ErbB4 signaling increases, or inhibit further enhancement of synaptic plasticity when NRG1β-ErbB4 signaling decreases. The idea in terms of schizophrenia is that there is no effect of NRG1β-ErbB4 signaling on basel permeable synaptic transmission or basal signaling through NMDA signal inputs; schizophrenia is a result of a hypofunction of NMDAR signaling. The predominant take away of this last experiment is that schizophrenia might not be a hypofunction of NMDAR per se but rather a loss of Src- mediated enhancement so hypoplasticity or hypofunction of NMDAR in the context of whether it is upregulated by synaptic transmission or not.

V. Critics of the experiment

One of the prominent achievements in the past ten years of SCHZ research has been the discovery of multiple candidate susceptibility genes, including NRG1. Due to complexity of SCHZ and its vulnerability to multifactorial influences the pathophysiology of the disease is still bluer. Thereof, Michael Salter and Graham Pitcher's study represents is a new promising avenue for effective therapies and medications. Nevertheless, there are few nuances in their study that did not make me fully convinced that this molecular mechanism is applicable for humans. One consideration is that they never specified how many mice they used in their experiments. It's true that mice are an accurate animal model for scientific studies to mimic human disease involving particular brain functioning but I wonder if more robust animal models could have been used in their study? For example, there are different responses can be produced, depending on the brain

structure under study, placement of electrodes and the type of recording (extracellular or intracellular). Therefore, it's not certain that human brain would have exactly the same neuron responses as was recorded in the brains of mice. Another aspect that did not convince me is the study method that was used in their experiment. Although brain slice preparation is a common method for studying synaptic plasticity and other neurophysiological functions of the human brain at the molecular and cellular levels, this method has serious limitations which I believe should be taken more seriously by scientists. For instance, there is a lack of certain inputs and outputs normally existing in the intact brain because certain portions of the sliced tissue tend to be damaged by the slicing action. The lifespan of brain slices are limited and the tissue gets "older" at a much faster rate than if they had used the whole animal. Vitally, an artificial bathing medium of brain slices cannot retain an optimal composition of human brain since blood-borne factors may be missing. (A. Schurr et al, 1985)

VI. Genes, environment and schizophrenia

Scientists have long known that schizophrenia runs in families but they couldn't explain how it develops in families without a history of the illness. Taking the "Gene, Environment and Behavior" course I became versed in how the environment is likely to be a triggering factor in the disruption of gene regulation. Understanding the relation between genes and environment are crucial for scientists and the general public in preventing and predicting many mental diseases. Although incidences of SCHZ are higher among children whose biological parents had the disease, adoption studies confirmed that some adopted children (genetically not predisposed) raised in a hostile environment also develop SCHZ. Interestingly, twins studies have also shown that schizophrenia must also have a prominent nongenetic component. For example, if

one monozygotic twin develops the condition, the risk that the other will is 30-50 percent regardless of the fact that they share 100% of their genes. Accordingly, dizygotic twins sharing only 50% of genes are less likely to develop the disease (~12-18%). Family studies have shown that even with the first degree relativeness to the affected person the likelihood for SCHZ is only 6-9%. Respectively, the lesser degree, the smaller probability (2-nd degree- 2.6 %; 3-rd degree-2.0%). Therefor the affected genetic risk in developing SCHZ depends on both genetics and environment

There are a variety of other nongenetic factors such as exposure to an infection during fetal development or shortly after birth, maternal stress, and socio-economic status that may lead to the development of SCHZ. Various studies searching for "schizophrenia genes" suggest that the illness is caused by more than one gene, and that other factors must also have a role. These statistics are a clear indication that environment is an equally important factor whether a person will develop the disease or not.

VII. Policy and Politics Around Mental Illnesses

Social stigmas are an inseparable part of human society, affecting many people's personal, social and professional parts of life. When someone tells you that his or her relative is mentally ill how do you approach this information? How do you view this person?

It has been always unclear to me why an antagonistic approach for mental illnesses seem to be a more common way for people to deal with the issue than compassion and sympathy. In Russia mentally ill people, including schizophrenic individuals, were always viewed as a threat for society.Correspondingly, the first compulsory medical treatment legislation of mental illnesses

was developed in 1926. Since criminal responsibility in relation to people with mental disorders in those days were not used as "social protection measures of a medical field" it suggested forcibly isolating patients in hospital wards rather than in prison cells. Fundamental changes have occurred only in 1961, with the advent of the new Criminal Code of the RSFSR. This new legislation enabled the USSR (Soviet Union) government to use psychiatric diagnoses including schizophrenia on non mentally ill people for political purposes.Thus, credentials of the Russian health system started further due to the “default” practices of the government which unleashed many social and political issues in the country. Even Russian literature of the nineteenth century is a veiled interpretation of fallacy, politics and the backstabbing of Russian society. Recalling one of the fragments of Mikhail Bulgakov’s nove*l The Master and Margarit*a when the Master, a Peterburg writer, was committed to psychiatric clinic for writing a novel that was in clash with the Soviet literary bureaucracy, it seems clear to me now how medical examination is deeply rooted in politics. Particularly, the diagnosis of co-called “sluggish schizophrenia” was most frequently used in the mid-1970 to facilitate the stifling of dissidents and used as a tool of oppression in the name of a political system As a result, the reported incidence of schizophrenia in the Russian population was, at the time, highly elevated.

Almost a century later the credentials of the Russian health system is still disintegrating. Today the trend is quite the opposite; there is a significant drop in schizophrenia diagnosis. The 2007 WHO Global Burden of Disease study has also identified that the isolation of Russia during Soviet times and economic stagnation significantly affected the health care system and limited its findings, including psychiatry. Today most psychiatric practitioners lack the knowledge and skills required to deliver a range of effective medical and psychosocial treatments necessary for

community-based care. A comparative study of diagnostic practices in psychiatry in Northern Norway and Northwest Russia were made by Russian and Norwegian specialists in psychiatry. Their comparative analysis once again confirms that the limited knowledge and skills of Russian practitioners in identifying schizophrenia result in poor diagnostic quality. http://link.springer.com/article/10.1007%2Fs00127-005-0894-1

Approaches to psychiatric medication differ too. For example, the Russian classification and treatment of schizophrenia allows for non-psychotic forms of the illness, and for non-psychotic patients to be treated with neuroleptic drugs. Which drugs are used to treat schizophrenia varies internationally, partly because first-generation antipsychotic medication is cheaper than second-generation or atypical antipsychotic medication.*(https://www.sharecare.com/health/schizophrenia/how-does-schizophrenia-treatment-differ*).

In similar fashion mentally ill people in many third world countries such as Benin (West Africa) and Indonesia are often at risk of being overmedicated. This often occurs due to the absence of proper medical facilities and professional psychiatrists who would be able to correctly identify a disease before treating it with heavy drugs.

New York Times article *The Chains of Mental Illness in West Africa* by Benedict Carey (provides shocking insight into a hard lot of people with mental disabilities. In poor countries such as Benin, the government spends minimally on health care and the funding of mental illnesses are non-existent. Therefore, families of affected people with no other options use praying centers as the only hope for cure. The appalling part is that in these centers people are held like dogs in chains around trees and left to pray for weeks months or years without any

diagnosis.

(http://www.nytimes.com/2015/10/12/health/the-chains-of-mental-illness-in-west-africa.html?smprod=nytcore-iphone&smid=nytcore-iphone-share)

Another similar and heartbreaking article, *Caged and Chained in the Philippines,* illustrates inhumanity towards people with mental disorders by their own families. (http://vishvasamani.com/caged-and-chained-in-the-philippines/). In reference to both articles it's clear that mental disorders are not well documented in many third world countries as they don't have the psychiatric and financial resources to handle them. These inhuman acts towards their own children and family members are compulsory actions due to poverty, lack of resources, and the knowledge on how to care for them. From my perspective, it's not simply poverty that forces families to cage their loved ones but the stigma and fear surrounding mental illnesses that are deeply rooted in these parts of the world. Similarly to Russia, these nations believe that mentally ill people are victims of witchcraft that must be kept detached from general society for safety purposes. But even in many wealthy developed countries a large number of people with psychosis or other severe mental health problems instead of being send to mental clinic are imprisoned. As of today, in the U.S alone, there are more than hundreds of thousands of people that remaining in prisons after having been diagnosed with a mental disorder. Interestingly *most o*f them are African American men believed to be schizophrenics which also points towards a secondary social stigma based on racial prejudice.

VIII. Social and Economic Aspects

According to the 2016 International Society of Pharmacoeconomics and Outcomes Research, annual costs for SHZ health services for the U.S range from $94 million to $102 billion. Despite tremendous spending the American mental health care system is far from perfect. So it is understandable why third world nations such West African countries including Benin and Cape Verde along with the Philippines are lagging behind when it comes to addressing mental health care issues. It is not just a matter of ignorance and neglect but also a lack of financial capabilities. To investigate budgeting into the research of SCHZ and other mental illnesses in the U.S I inspected the estimated data from previous, current and future years provided by National Institute of Health (https://report.nih.gov/PFSummaryTable.aspx).

In the graph below, which was modified for this comparative review, it is clearly illustrated that mental health is not a priority of current scientific research.

Research/Disease Areas (Dollars in millions and rounded)	FY 2012 Actual	FY 2013 Actual	FY 2014 Actual	FY 2015 Actual	FY 2016 Estimated	FY 2017 Estimated
Alzheimer's Disease	$503	$504	$562	$589	$910	$910
Bipolar Disorder	+	+	+	$80	$83	$83
Cystic Fibrosis	$86	$78	$77	$80	$83	$83
Cancer	$5,621	$5,274	$5,392	$5,389	$5,652	$6,332
Huntington's Disease	$65	$55	$50	$39	$39	$39
Malaria	$152	$147	$169	$163	$171	$171
Schizophrenia	$268	$232	$253	$241	$251	$251
Sickle Cell Disease	$65	$70	$75	$75	$78	$78
Obesity	$836	$812	$857	$900	$931	$931
HIV/AIDS 9/	$3,074	$2,898	$2,978	$3,000	$3,000	$3,000
Alcoholism, Alcohol Use and Health1/	$455	$437	$475	$473	$494	$494
Vaccine Related	$1,691	$1,608	$1,573	$1,585	$1,653	$1,653
Pediatric	$3,612	$3,266	$3,486	$3,632	$3,766	$3,766
Stem Cell	$1,374	$1,273	$1,391	$1,429	$1,495	$1,495

The main problem is that research is often funded by drug companies who devote most of investment into illnesses that most frequent, thus financially beneficial for them. For example, depression is one of the most common illnesses, especially in the U.S. As a result, there is a plenty of research on depression due to the size of the market.

There is a need for realization that more copious investments into scientific research concerning mental illnesses are a potential avenue for development of preventive or curable measures for mental diseases. Unlike existing life-long drug therapies, these new measures could be more cost-effective and beneficial in a long run. The main point here is that funding research should not be limited to drug development and funding by pharmaceutical companies per se but an issue that needs to be prioritized by individual countries NGOs.

On a larger scale the question of medication affordability is as vital as the research behind it. The primary reason why incidences of HIV/AIDS still remain outrageous in third world countries despite the extensivity of research and drug availability is a financial one.

IX. Conclusion

Currently SCHZ is considered to be an incurable disease; I as a sister of a brother, who suffers from schizophrenia and a student who had an opportunity to learn about the number of new impressive discoveries and studies regarding SCHZ, truly believe in a bright future for my brother and other people with mental illnesses. The growing number of new discoveries and studies made including Pitcher et al. are remarkable advances that allow for a more extensive understanding of the many implications of SCHZ. This new knowledge in combination with

biotech discoveries provide hope that in the next decade or two we will be able to prevent or cure people with schizophrenia. Before these new treatments are developed perhaps we as a society can at least change attitudes towards people with mental illnesses and mental health in general. As was mentioned earlier there is a large gap of research funding between communicable and mental diseases.

It is equally essential to realize that the growing number of people with mental disease are not a problem of one single nation. It's no one's choice to be born in a country who has no financial means to support their citizens. Prioritizing and handling mental illnesses collaboratively as a global society can have a very positive impact.Even though I am thrilled by the idea of new therapies, techniques, and the development of more effective medications, there is no guarantee that these advances will be implemented in third world nations. Although the *2005 Declaration and Action Plan* that prioritizes mental health has been endorsed by most WHO European Member State post-communist countries such as Russia they have yet to introduce reforms that would enable innovative treatments to be embedded in routine care (http://www.who.int/bulletin/volumes/85/11/06-039156/en/). And even if these treatments will be available in other parts of the world, the question is who will have access to the presumably expensive medications?

Historically mental diseases were neglected from global health priorities and left far behind other disease such as malaria, measles and HIV. Because of the high burden of mental illnesses globally, last year for the first time the United Nations included a commitment to promote mental health and well-being into a new Sustainable Development Goal (SDG) Agenda. According to SDG, every country- member of the U.N is responsible to reduce premature death

from non -communicable disease, including mental disorders by one- third by 2030. Despite the compellingness of these goals, they do not directly include targets for mental disorders; consequently, it is most likely that these illnesses will attract meagre investment by international donors. And often times these types of donor investments for health services are sparse, short-term and intersectoral. Therefore, to make the U.N agenda successful in addressing mental health these goals should be revised in such a way that they directly address the need for improving the mental health system. Because the enormous economic burden of mental health is suggestive of the inadequate provision of health care services I believe increasing recognition among the public and policymakers will aid in more thoughtful and careful decision-making of how much and where financial resources should be allocated.

X. Bibliography

1. Corfas,Gabriel; Roy, Kristine; Buxbaum, Joseph D. *Neuregulin 1-erbB signaling and the molecular/cellular basis of schizophrenia.* Nat.Neurosci., 2004, 7, 6, 575-580, Nature Publishing Group, United States
2. Pitcher G, Kalia L, Salter M, et al. *Schizophrenia susceptibility pathway neuregulin 1-ErbB4 suppresses Src upregulation of NMDA receptors.* Nature Medicine [serial online]. April 2011;17(4):470-478
3. Harrison,Paul J.; Law,Amanda J.. *Neuregulin 1 and schizophrenia: genetics, gene expression, and neurobiology.* Biol Psychiatry. 2006 Jul 15;60(2):132-140, Elsevier, United States

4. Hahn,Chang-Gyu. *A Src link in schizophrenia.* Nat.Med., 2011, 17, 4, 425-427, Nature Publishing Company, United States
5. Schurr A, Reid KH, Tseng MT, Edmonds HL Jr, and Rigor BM: A dual chamber for comparative studies using brain slice preparation. Comp Biochem Physiol 82A(3): 701-704, 1985
6. http://www.schizophrenia.com/sznews/archives/002562.html#
7. https://www.dnalc.org/view/2226-Schizophrenia-.html
8. https://www.genes2cognition.org/research/electrophysiology/
9. http://bmcmededuc.biomedcentral.com/articles/10.1186/1472-6920-8-15
10. https://www.sharecare.com/health/schizophrenia/how-does-schizophrenia-treatment-diffr
11. https://en.wikipedia.org/wiki/Sluggish_schizophrenia#Recurrence_in_post-Soviet_Russia
12. http://www.psychiatrictimes.com/special-reports/state-psychiatry-russia
13. http://www.who.int/bulletin/volumes/85/11/06-039156/en/
14. http://vishvasamani.com/caged-and-chained-in-the-philippines/
15. http://www.nytimes.com/2015/10/12/health/the-chains-of-mental-illness-in-west-africa.html?smprod=nytcore-iphone&smid=nytcore-iphone-sharehttps:/study.com/academy/lesson/ray-tracing-with-mirrors-reflected-images.html&_r=2
16. https://report.nih.gov/PFSummaryTable.aspx