2005

Neurodevelopmental Models of the Heterogeneous Syndrome of Schizophrenia

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ROCHESTER INSTITUTE OF TECHNOLOGY

A Thesis Submitted to the Faculty of:

The College of Imaging Arts and Sciences

In Candidacy for the Degree of:

Master of Fine Arts

Neurodevelopmental Models of the Heterogeneous Syndrome of Schizophrenia

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Date: July 5, 2005

Signature Page for the Master of Fine Arts Degree
School of Art
College of Imaging Arts and Sciences
Rochester Institute of Technology

Title: **Neurodevelopmental Models of the Heterogeneous Syndrome of Schizophrenia**

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I. Introduction:

1. Motivation and target audience:

The neurodevelopmental theories of the pathogenesis of schizophrenia are a popular subject among many writers and researchers. The majority of articles written, however, are rarely if ever illustrated. Instead, spaces within the articles that could be occupied by colorful and informative illustrations are filled with sterile, often ambiguous diagrams. While it seems a daunting task to create visual aids to explain unproven theories, this author was not deterred. This concept was the basis of this thesis: to create illustrative, informative artwork that visually explains selected neurodevelopmental theories of the syndrome of schizophrenia.

The intended audience for this thesis was undergraduate college-educated viewers, preferably neuroanatomy or psychology students. Although the concepts were simplified to a certain degree, the learner who would most readily absorb the subject matter would be one with a fair amount of background knowledge of the subject. This is due to terminology prevalent throughout the thesis including phrases such as "negative symptoms" and "active phase."

The motivation behind this thesis was a personal one. Schizophrenia is thought to be multifactorial in its origin, but due to its possible heterogeneity, it could easily be either genetic, environmental or both, depending on the specific type of schizophrenic disease. In the case of this author's family, schizophrenia is found throughout the family tree on both sides. This leads her to believe that the type or types of schizophrenia that run rampant in her family are genetic in origin. This thesis was the author's attempt to become more familiar with the subject of schizophrenia and to gain an understanding of contemporary scientific literature and research about this nebulous syndrome.

II. Research:

1. Psychological categorization: *The Diagnostic and Statistical Manual of Mental Disorders* categorization of schizophrenia.

Definition of schizophrenia:

The diagnostic criteria for schizophrenia are defined in the *Diagnostic and statistical manual of mental disorders (DSM IV TR)*[1] by five distinctive symptoms. These symptoms are delusions, hallucinations, disorganized speech, disorganized or catatonic behavior, and negative symptoms that include features such as flattened affect, and a lack of goal oriented behavior.[2] To be diagnosed as schizophrenic, a person must present two or more or these symptoms "each present for a significant portion of time during a 1 month period[3]." If the delusions or hallucinations are severe enough, however, only one of these characteristic symptoms is required for a diagnosis of schizophrenia. The duration of signs for schizophrenia must persist for a period of six months and include a period of symptoms lasting at least one month. An individual must display a marked diminution in interpersonal relationships, academic and or occupational abilities, and a decreased concern for self-hygiene and general self-care. Substance abuse, medication, and medical conditions including other mental disorders must be ruled out as a cause. Mental disorders to be eliminated include autism, pervasive developmental disorder, schizoaffective disorder, and mood disorder with psychotic features.

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[1] American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders* (text revision). Washington, D.C.

[2] These symptoms are of what the DSM IV TR calls the "active phase" of schizophrenia

[3] Or less if treated successfully.

Schizophrenia Subtypes:

The DSM IV TR[4] divides schizophrenia into five distinctive types including paranoid, disorganized, catatonic, residual, and undifferentiated. The characteristic symptoms of paranoid schizophrenia are primarily delusions and hallucinations. There is a substantial amount of cognitive functionality and normal affect presented, as well as a lack of catatonic and disorganized behavior, thus ruling out these two subtypes. Hallucinations in paranoid types are usually the product of delusions, which are typified by persecutory and grandiose themes, although other delusional themes may occur as well. Delusions and associated hallucinations usually occur around a consistent subject. The onset of paranoid schizophrenia usually happens later in life and typically, individuals show little cognitive impairment. Due to these two factors, prognosis for paranoid schizophrenics may be more hopeful than for other types.

The symptoms of disorganized types are disorganized behavior, speech, and blunted or inappropriate affect. Avolition, or lack of goal-oriented behavior, may cause dysfunction in daily abilities including personal hygiene and nutrition. Verbal communication may be impaired due to disorganized speech patterns. Cognitive dysfunction may also be present due to a disorganization of thoughts. Disorganized schizophrenics typically display poor premorbid adjustment[5] and the onset of this illness appears to be early and chronic. Other subtypes must be ruled out to determine a diagnosis of disorganized schizophrenia. Hallucinations may be present, but they should not be prominent.

The catatonic subtype is defined by an impairment and or dysfunction in motor activity. This includes postural rigidity, excess in motor activity, bizarre posturing, or repetitive simulations of movement or speech from another person. Persistent imitation of another person's movements is known as echopraxia and

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[4] American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders* (text revision). Washington, D.C. p. 303.

[5] Ibid.

echolalia is the repetition of speech from another person[6]. Excessive motor activity exhibited by the catatonic subtype appears nonsensical and is not affected by surrounding stimuli. Inappropriate movements and/or facial expressions characterize bizarre posturing. Postural rigidity or extreme negativism is defined by a physical refusal to be moved. Catalepsy[7] or waxy flexibility is the ability of another person to "mold" a catatonic type into a position, which the catatonic will maintain for an extended period of time. The catatonic subtype is at risk for injury to self or to others, malnutrition and physical exhaustion. Thus, this type may require constant supervision to avoid such trauma.

A diagnosis of undifferentiated type requires that an individual does not meet the requirements for the Paranoid, Disorganized, or Catatonic types. Delusions, hallucinations, disorganized speech, catatonic behavior and negative symptoms may be present for a one-month period, but the symptoms cannot be differentiated. The prominent features of residual types are the absence of delusions, disorganized speech and behavior, and catatonia, but there still is a presentation of negative symptoms. There may be positive symptoms but they are less severe and usually transitory. Residual symptoms are typically chronic and exist with or without acute aggravation.

Schizophrenia Statistics:

The age of onset of schizophrenia is between 15 and 35 years of age. Onset in childhood is rare and occurs in only 1% of cases. Late onset, after the age of 45 years, is also unusual and occurs in less than 10% of cases, mostly in women. Average age of onset is 21 to 27 years and usually occurs earlier in men.[8]

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[6] American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders* (text revision). Washington, D.C. p. 315.

[7] Ibid.

[8] Ibid.

Many schizophrenics are not able to perform everyday activities, and thus are unable to establish and keep consistent employment. Without sufficient income, many schizophrenics find themselves homeless. One third of Americans who are homeless are mentally ill, and the majority of this population is schizophrenic.[9] Due to characteristic social withdrawal, many with this illness do not marry (60-70%) and live a relatively isolated existence. Among schizophrenics, suicide is the number one cause of premature death. Factors that increase the risk of suicide in schizophrenics include recent hospital discharge, being younger than 45 years and being male[10]. 10% to 13% will commit suicide, while 20%-40% will attempt it at least once during the course of their illness. Nicotine abuse is prevalent in schizophrenia as well; 80% to 90% of schizophrenics smoke cigarettes. Because of this, along with a typically poor diet, many suffer health problems and/or early death due to diabetes, cardiovascular disorders, and obesity.[11]

Due to the variability of the disease, there is no ascertainable outcome of schizophrenia. Full remission is rare, although many schizophrenics are capable of living a functional life. Factors affecting a good prognosis include acute onset of the disease, insight into the disease, being female, early and consistent treatment, minimal residual symptoms, a brief course of active symptoms, and the ability to function well between episodes. Also affecting a good prognosis are a family history of mood disorders, and no family history of schizophrenia.

Signs and Symptoms:

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[9] Andreasen, Nancy C. (1994.) *Schizophrenia, from mind to molecule.* American Psychiatric Press, Washington D.C. p.44.

[10] American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders* (text revision). Washington, D.C. pp. 306-311.

[11] Stefan, M, Murray, R (2002). *An Atlas of Schizophrenia.* New York, NY: Parthenon Publishing.

The symptoms of schizophrenia vary from person to person. Although many symptoms exist under the category of schizophrenia, every individual afflicted with the disease displays different symptoms. A single pathognomic symptom of schizophrenia does not exist; instead, every individual afflicted with the disease presents unique symptoms.

The essential features of schizophrenia are a combination of both negative and positive symptoms, which reflect a person's diminished capacity to carry on functional interpersonal and occupational relationships. These two types of symptoms also reflect a reduction in cognitive[12], motor, emotional, and verbal abilities[13].

Positive symptoms are considered to be a distortion of normal functioning and include hallucinations, delusions, positive thought disorder, disorganized and/or catatonic behavior and, inappropriate affect[14]. These symptoms are frequently the most recognizable qualities of schizophrenia. They are also the most responsive to antipsychotic medications[15]. Hallucinations are fictitious perceptions of non-existent sensory stimuli. They include auditory, visual, and in some cases, olfactory and tactile hallucinations. Auditory hallucinations are the most common, which occur in 60-70% of patients.[16] Delusions are illogical beliefs that are true only to the person who is having them. Primary delusions originate seemingly from

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[12] Deficits in cognitive abilities include a marked decline in memory, psychomotor abilities, and attention.

[13] The terms negative and positive symptoms are not meant to denote quality or type. The terms indicate characteristics that are presented (positive) and those that are absent (negative) as compared to normal subjects.

[14]Andreasen, Nancy C. (1994.) *Schizophrenia, from mind to molecule.* American Psychiatric Press, Washington D.C. p.44. .

[15] Ibid.

[16] Stefan, M, Murray, R (2002). *An Atlas of Schizophrenia.* New York, NY: Parthenon Publishing.

out of nowhere. There is no connection or logical association as to when or why a delusion develops. Secondary delusions arise from other positive symptoms, primarily from hallucinations.

Delusions vary in terms of content. Different types of delusions include persecutory, referential, somatic, grandiose, and religious. Persecutory delusions are the conviction that a person is being watched, followed, or ridiculed. Referential delusions are marked by the belief that an individual can receive specific messages for him/herself through newspaper articles, shows on television, song lyrics, or other modes of communication. Somatic delusions include the belief that a person is afflicted with bizarre bodily abnormalities. For example, an individual may believe that his/her organs have vanished. Grandiose delusions, or delusions of grandeur are an exaggerated conviction in one's power or personal identity. Religious delusions are those with religious undertones.

Disorganized thought processing (positive thought disorder), another component of positive symptoms, is often reflected in speech and is characterized by a loosening of associations. Disorganized speech presents itself in various ways. It is distinguished by unintelligible speech patterns, which reflect in turn, a disorganization of thoughts. Types of disorganized speech include incoherence, tangentiality, and derailments. Derailments are patterns of speech that change subject mid-sentence. Tangentiality is when a person replies to a question with an irrelevant answer.[17] Incoherent speech is when patterns of speech change subject so often that it is indecipherable[18]. The disorganized nature of schizophrenic symptoms manifests itself through behavior and motor movements as well.

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[17] American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders* (text revision). Washington, D.C. pp. 297-317.

[18] Andreasen, Nancy C. (1994). *Schizophrenia, from mind to molecule.* American Psychiatric Press, Washington D.C. Press. 57.

Behavior that is disorganized includes inappropriate sexual behavior, unpredictable agitation, and trouble maintaining good hygiene.

Grossly abnormal movements characterize catatonic behavior, a dysfunction of movement. Various types of catatonic motor behaviors[19] include stupor[20], posturing[21], excitement,[22] and negativism[23]. Another positive symptom, inappropriate affect, is exemplified by an inappropriate emotional reaction. An example of this is when a schizophrenic laughs in response to a situation where one more appropriately cries. Positive symptoms are thought to have two separate entities: those that involve distorted beliefs and perceptions (delusions and hallucinations), and those that involve a disorganization of speech and behavior. These two entities are thought to be related to two separate neural mechanisms.[24]

Negative symptoms can be described as normal human characteristics that are absent in schizophrenia. The onset of negative symptoms may also precede the presentation of positive symptoms in prodromal (unusual behavior that precedes the onset of the disease) schizophrenia[25]. Negative or deficit symptoms are generally more difficult to treat and diagnose than positive symptoms. This is because they may be due to other factors: depression, positive symptoms; the potential side effects of anti-psychotics, and/or self-imposed isolation.[26] They are more debilitating than positive symptoms in that schizophrenics who display

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[19] American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders* (text revision). Washington, D.C. pp. 297-317

[20] Characterized by complete unawareness.

[21] The assumption of strange postures.

[22] Marked by unstimulated movement.

[23] When an individual displays a resistance to be moved.

[24] Ibid.

[25] Ibid.

[26] Ibid.

negative symptoms appear to lack the very characteristics that define a functional human being. These include poverty of speech (alogia), absence of emotional expression (flattened affect), social withdrawal (anhedonia, asociality), reduced initiative (avolition), and attentional impairments[27].

Prodromal Phase, Prognosis:

The prognosis of schizophrenia is variable and depends on many factors including age of onset, and the severity of prodromal symptoms. If the onset is early (i.e. childhood or adolescence) then there may be a failure to finish school, resulting in an inability to establish a foundation necessary for finding future employment. Without education, they may be at higher risk for unemployment than those who develop the disease later in life. Another factor that appears to worsen the course of schizophrenia is the use of elicit drugs and/or a family history of the disease[28]. Prodromal symptoms are those that are typically presented before the onset of the active phase. They consist of unusual behavior and beliefs and are generally mild, but digressive. Prodromal symptoms mirror those of positive and negative symptoms, but are not severe enough to be labeled as such. Individuals may exhibit an array of strange behaviors such as talking to themselves or believe that they possess magical powers. Nonetheless, these behaviors are not of "delusional proportions"[29] and may appear to be a consequence of imagination.

Negative symptoms are particularly characteristic in the prodromal phase. Individuals who are usually social may begin to isolate themselves from others and

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[27] Andreasen, Nancy C. (1994.) *Schizophrenia, from mind to molecule*. American Psychiatric Press, Washington D.C. Press.

[28] First-degree biological relatives of individuals with schizophrenia have 10 times greater chance than general population.

[29] American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders* (text revision). Washington, D.C. p. 302.

may lose interest in activities they once enjoyed. They also may appear to be less adept at holding a conversation. Other factors affecting prognosis are low I.Q., a history of psychiatric problems before the onset of the illness, lower social class, male gender, and negative symptoms[30]

An important issue in treating schizophrenia is that negative and positive symptoms are accompanied by other more insidious characteristics. As previously mentioned, schizophrenics display an increase in cognitive impairments during the progression of their disease. These cognitive deficits appear to be independent of other symptoms and usually precede the onset of active phase symptoms. These cognitive impairments include a marked decline in the ability to think abstractly and to learn new skills. There may also be a diminution in the ability to concentrate or solve problems that may arise in everyday activities. When taking an I.Q. test, schizophrenics score up to 10 points lower than they did before the onset of their illness[31]. This lack of ability to problem solve, attentional impairments and the inability to think abstractly may prevent a schizophrenic from living a productive life.

Another more insidious characteristic among schizophrenics is their apparent lack of insight into their disease. An individual's inability to recognize his/her own illness is known as anosognosia, and is often misinterpreted by others as a purposeful refusal to cooperate. This anosognosia is in fact another symptom that contributes to the difficulty of successful treatment and the ultimate prognosis of the disease. A schizophrenic individual may unequivocally believe that he/she is not ill. This conviction may lead to a refusal to take antipsychotic medications, medications that, ironically, could alleviate some if not all symptoms. This

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[30] Johnstone, E.C., Frith, C.D., Crow, T.J. (1992). **Functional psychoses study: diagnosis and outcome.** *Psychol Med,* 22: pp. 331-46.

[31] Andreasen, Nancy C. (1994). *Schizophrenia, from mind to molecule.* American Psychiatric Press, Washington D.C. Press.

apparent lack of insight, as well as cognitive deficits serve only to exacerbate an already seemingly hopeless prognosis. Lack of insight is not the only factor contributing to the general reluctance by schizophrenics to take medications. There are also unpleasant side effects that schizophrenics suffer when taking antipsychotic medication. These include extrapyramidal symptoms (Parkinsonian-like movement as a result of the blockade of D2 receptors in the substantia nigra), weight gain, and sexual dysfunction. With all of these factors, it is no wonder that the majority of patients admit to stopping medication at least once in the course of their disease[32].

Schizophrenia is like any other complex disorder in that it does not appear to have a single mode of causality, but is instead considered by most to be multifactorial. It is believed that many factors increase the risk of schizophrenia including both environmental and genetic mechanisms. The genetic modalities behind schizophrenia are most likely polygenic, meaning that a number of different genes are involved in its pathogenesis. As far as environmental factors, many now believe that environmental insults might act concurrently with any number of genes helping to contribute to the disorder.

2. Scientific Categorization of Schizophrenia:

Heterogeneity and Subtypes:

When considering all of the information presented in this paper, one must keep in mind the possibility that schizophrenia is a heterogeneous syndrome and not a disease. Bleuler[33] recognized the heterogeneity of schizophrenia and used the terms "disease group" and the "schizophrenias" to refer to what he theorized were different subtypes of a larger syndrome. This hypothetical syndrome would mean

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[32] Stefan, M, Murray, R. (2002). *An Atlas of Schizophrenia*. New York, NY: Parthenon Publishing.

[33] Bleuler, Eugene. (1950). *Dementia Praecox; or the group of schizophrenias*. International Universities Press. Inc.

that there might be common underlying neuroanatomical changes with several different pathological origins. This is not unlike pneumonia; the diagnosis is the same but the pathogenesis could be viral, bacterial, fungal, or mycoplasmic in origin. This heterogeneity of a larger syndrome would explain the lack of consistent findings in fMRI, PET scans, and post-mortem studies.

If schizophrenia is indeed a syndrome then it is necessary to identify the specific diseases (and their individual pathological processes) within it for the advancement of more specific treatments according to subtypes. The following is a collection of recent data summarizing many different research topics within the study of the pathogenesis of schizophrenia. The reader must approach the following material with the understanding that it is most likely multifactorial, and that the term schizophrenia probably encompasses an array of discreet diseases or risk being over whelmed and frustrated by the conflicting data and inconclusive results presented by each study.

Deficit and Non-Deficit Schizophrenia:

Many researchers have attempted to identify and categorize these theoretical subtypes of schizophrenia. For example, Kirkpatrick, et al,[34] proposed a subtype of schizophrenia defined by negative symptoms. This subcategory, known as deficit schizophrenia, is characterized by primary, persistent, enduring negative symptoms including flattened affect, poverty of emotion and speech, curbing of interests, decreased or lack of initiative and social withdrawal[35]. Kirkpatrick, et al[36],

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[34] Kirkpatrick, Brian, Buchanan, Robert, W., Ross, David E., Carpenter, William T. Jr. (2001). **A separate disease within the syndrome of schizophrenia.** *Arch Gen Psychiatry*, Vol. 58: pp.165-171.

[35] Carpenter, W.T. Jr. **Deficit and non-deficit forms of schizophrenia: the concept.** (1988). *Am J Psychiatry*, 145: pp. 578-583.

[36] Kirkpatrick, Brian, Buchanan, Robert W., Ross, David E., Carpenter, William T. Jr., **A separate disease within the syndrome of schizophrenia.** *Arch Gen Psychiatry* Vol. 58: pp.165-171.

proposed that the variety of signs and symptoms presented by deficit schizophrenics are markedly different from their non-deficit counterparts. Non-deficit schizophrenics present mainly positive symptoms and are better socially adapted than deficit schizophrenics. Deficit and non-deficit subtypes appear to differ in other ways as well. For example, even though schizophrenia has generally been associated with winter birth, deficit schizophrenics appear to be associated with summer birth[37]. Deficit schizophrenics have a lower frequency of depression as well as less anxiety, drug abuse, and hostility and display fewer suicidal tendencies, as compared to non-deficit schizophrenics[38]. There is also evidence that environmental exposure to elements such as the Borna virus may contribute to the pathogenesis of the deficit subtype.[39]. In a study by Arango, et al,[40] deficit subtypes were less aware of the dyskinetic movements they presented because of their illness. Heredity also seems to play a role in deficit schizophrenia as indicated by evidence that the relatives of these individuals show an increased risk of developing the disease.[41]

According to theorists, positive symptoms are still exhibited by deficit schizophrenics, but these symptoms do no appear to be any more ominous than the non-deficit sub-types. Obviously, since there appear to be symptomatic

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[37] Kirkpatrick, B. (1998) **Summer birth and the deficit syndrome of schizophrenia**. *Am J Psychiatry*, 155: pp.1221-1226.

[38] Kirkpatrick, B. (1994). **Depressive symptoms and the deficit syndrome of schizophrenia.** *J Nerv Ment Dis*, 182: pp. 452-455.

[39] Iwahashi, K. (1998). **Positive and Negative syndromes and Borna disease virus infection in schizophrenia.** *Neuropsychobiology*, 37: pp.59-64.

[40] Arango, C. (1999). **Awareness of dyskinesia in schizophrenia: relationship to insight into mental illness.** *Am J Psychiatry*, 156: pp. 1097-1099.

[41] Dollfus, S. (1996). **Family history and deficit form in schizophrenia.** *Eur Psychiatry*, 11: pp. 260-267.

variations between deficit and nondeficit individuals, there must also be structural differences between the two groups. Carpenter, et al, [42] suggests that nondeficit symptoms arise because of abnormal circuits in the limbic system, whereas the deficit syndrome is due to abnormal circuits in both the limbic system and the prefrontal cortex. This theory is supported by another study, which demonstrates that nondeficit schizophrenics displayed very little parietal and frontal lobe dysfunction, as compared to deficit schizophrenics who showed increased impairment[43] in these areas. In the temporal region, deficits and nondeficits could not be differentiated: both groups showed impairment in this area.

This attempt to sub-categorize schizophrenia into individual disease entities is important in the search for the variety of pathogenic mechanisms behind the schizophrenic syndrome. What Carpenter, Buchanan, Kirkpatrick, and colleagues [44]are attempting to do is to establish a dialogue that questions the common assumption that methods and standards used in research studies of schizophrenics are infallible. By proposing this deficit subtype, the authors are challenging others to consider the possibility that in order to obtain consistent findings in neuroanatomical studies a more concrete division of the schizophrenias must first be established. Additionally, this information and the proposals put forth by its authors serves to substantiate the theory that different schizophrenics suffer from different afflictions.

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[42] Carpenter, W.T. (1993). **Strong inference, theory, testing, and neuroanatomy of schizophrenia.** *Arch Gen Psychiatry*, Vol. 50: pp. 825-831.

[43] Buchanan, R.W., Strauss M.D., Breier A, Carpenter W.T. Jr, (1994). **Attentional impairments in deficit and nondeficit forms of schizophrenia.** *Arch Gen Psychiatry*, 51: pp.804-811.

[44] Kirkpatrick, Brian, Buchanan, Robert W., Ross, David E., Carpenter William T. Jr., **A separate disease within the syndrome of schizophrenia.** *Arch Gen Psychiatry* Vol. 58: pp.165-171.

3. Pathogenesis:

Lack of Gliosis:

Early theories regarding the pathogenesis of schizophrenia were that it is a neurodegenerative disease of the brain not unlike Alzheimer's or Parkinson's disease. Recent evidence, however, seems to show that it is a neurodevelopmental disorder with a continuous loss of brain tissue volume happening even before birth[45]. Many researchers have ruled out a degenerative hypothesis because gliosis, a sign of degeneration in the brain, has not been present in the majority of post mortem studies.

Physical Brain Abnormalities in Schizophrenia:

The physical features of the brain are of great interest in the study of how schizophrenia develops and progresses. Researchers now are commonly using brain imaging techniques such as PET scans, fMRIs, and post mortem studies in an attempt to identify portions of the brain showing abnormalities in schizophrenic patients. One of the most common observations made when studying the physical features of a schizophrenic brain is ventriculomegaly of the lateral and third ventricles. Perhaps because of this, brain imaging commonly shows subtle decreases in overall brain volume and enlarged CSF fluid volumes in the schizophrenic[46]. A lack of white matter expansion in the cortices could contribute to this volumetric enlargement of CSF, meaning that there is a decreased amount of white matter and thus a dysfunction in cortical communication.

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[45] Bartzokis, G. (2002). **Schizophrenia: Breakdown in the Well-regulated Lifelong Process of Brain development and maturation.** *Neuropsychopharmacology,* New York, NY: Elsevier Science Inc.

[46] Ibid.

In a quantitative MRI study by Harvard Medical School students[47], researchers concluded that a gray matter volume deficit occurred in the left lateral temporal lobe in schizophrenics. This left-lateralized temporal lobe deficit and the abnormalities of the superior temporal gyri in this particular study suggest a temporal lobe pathology, particularly on the left side, which contains the planum temporale, a structure responsible for language. The superior temporal gyrus (STG), is essential for auditory associative memory. Damage to this interconnected network of the STG and other structures of the temporal lobe could result in difficulties in auditory and language storage and retrieval. During this study a new clinical correlation was made: "the total amount of thought disorder increased exponentially as a function of volume reductions in the left posterior superior temporal gyrus." Also found in this MRI study were gray matter reductions in the amygdala[48], hippocampus, and parahippocampal gyrus[49] as compared to normal controls.

In another research project, headed by Lawrie, it was similarly found that the temporal lobes were often smaller in schizophrenics. The thalamic nuclei and the amygdala-hippocampal complex were also found to be significantly smaller.[50] Also discovered was a reduction of hippocampal volume in schizophrenic subjects,

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[47] Shenton, M.E. (1992). **Left Temporal Lobe Abnormalities in Schizophrenia and Thought disorder: A quantitative MRI study.** *New England Journal of Medicine*, 327: pp. 604 -12.

[48] The amygdala is thought to be responsible for the emotions involved in behavior, memory, and learning.

[49] It is worthy to note that these structures are of the medial temporal lobe. They are believed to be responsible for establishing and retrieving memories as well as aiding in long- term memory storage through reciprocal connections with areas of the neocortex.

[50] Some studies have reported smaller thalamic volumes (Andreasen et al.1994); others have not (Portas et al. 1998). Morphometric studies of the thalamus suggest that this reduction indicates cell loss. (Pakkenburg 1990).

although reduced amygdala volumes were only found in males[51]. It has also been found that schizophrenics often have both reduced hippocampal[52] volume and hippocampal hyperactivity. In post mortem studies, slight structural irregularities have been noted when examining the schizophrenic brain. These include smaller hippocampal and parahippocampal volumes, cytoarchitectural changes in the hippocampus and enlarged temporal horns.[53] Also found were alterations in the cell density of the frontal and entorhinal cortex and cingulate gyrus. Lim, et al, found that in first episode schizophrenics there was a reduction of cortical gray matter and enlarged ventricles without a reduction in white matter at or near the onset of the illness.[54] R.E. Gur found a reduction of gray matter in the dorsal prefrontal cortex of neuroleptic naïve schizophrenics and also discovered that there was a reduction in cortical gray matter in the lateral and medial orbital volume specific to the female subjects only.[55] The author attributes this gender- based difference to the fact that female schizophrenics are more likely to display negative symptoms. Despite this discovery, in males, the negative symptoms are typically more severe.

Notwithstanding these studies, most investigations examining volume deficits in the schizophrenic brain are conflicting. For almost every positive

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[51] Gur, Raquel E. (2000). **Temporolimbic volume reductions in Schizophrenia.** *Arch Gen Psych,* 57: pp. 769-775.

[52] Shenton, M.E. (1992). **Left Temporal Lobe Abnormalities in Schizophrenia and Thought disorder: A quantitative MRI study.** *New England Journal of Medicine,* 327: 604 –12.

[53] Weinberger, D.R. (1999). **Cell Biology of the Hippocampal formation in schizophrenia.** *Biological Psychiatry,* 45: pp. 395-402.

[54] Lim, Kelvin O. (1996). **Cortical Gray Matter Volume Deficit in Patients with First-Episode Schizophrenia.** *American Journal of Psychiatry,* 153:12.

[55] Gur, R.E. (2000). **Reduced Dorsal and Orbital prefrontal gray matter volumes in schizophrenia.** *Archives of General Psychiatry,* 57: pp. 761-768.

finding, there are multiple negative ones to contradict it. While total gray matter volume decreases are frequently detected,[56] but it is not a consistent discovery[57]. This irregularity may be due to inconsistencies in measuring techniques, or the heterogeneity of the samples. (Differences in ventricular sizes, the varying pathological mechanisms behind different symptoms and duration of antipsychotic administration or lack thereof.) Several negative and/or non-replicating studies have contradicted findings of temporal lobe reductions. Even though discoveries of temporal lobe reductions have been reported,[58] Zipursky [59] and Marsh, et al, [60] conducted studies unable to replicate positive findings.

It is thought that positive psychotic symptoms of schizophrenia (delusions and hallucinations) result from hyperactivity in the medial temporal lobe especially in the amygdala and/or hippocampus.[61] Negative symptoms (flattened affect, social withdrawal, lack of initiative) are attributed to hypometabolism of the frontal

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[56] Zipursky, R.B., (1992): **Widespread cerebral gray matter volume deficits in schizophrenia.** *Arch Gen Psychiatry*, 49: pp. 195-205.

[57] Pearlson, G.D. (1997a): **Schizophrenia.** *Int J Psychiatry*, 9: pp. 317-319.

[58] Shenton, Martha E. (1992) **Left Temporal Lobe Abnormalities in Schizophrenia and Thought disorder: A quantitative MRI study.** *New England Journal of Medicine*, 327: pp. 604 -12.

[59] Zipursky, R.B., Marsh, L, Lim, KO, DeMent, S, Shear, P.K., Sullivan, E.V., et al (1994). **Volumetric MRI assessment of temporal lobe structures in schizophrenia.** *Biol Psychiatry*, 35: pp. 501-516.

[60] Marsh, L, Harris, D Lim, K.O., Beal, M, Hoff, A.L., Minn, K, (1997) **Structural magnetic resonance imaging abnormalities in men with severe chronic schizophrenia and an early age at clinical onset.** *Arch Gen Psychiatry*, 54: pp. 1104-1112.

[61] Bogerts, B. (1997). **The Temporolimbic System Theory of Positive Schizophrenic Symptoms.** *Schiz Bull*, pp.423-435.

cortex. Along with these positive and negative symptoms of schizophrenia, there is also cognitive impairment. This cognitive impairment is thought to be due to a hypofrontality in the cortex of the schizophrenic brain, and is known to exist long before either positive or negative symptoms appear.

RCBF: Relative Cerebral Blood Flow:

In 1986 DR Weinberger and associates[62] completed an innovative experiment where it was discovered that during the administration of the Wisconsin Card Sorting Test there was a failure of relative cerebral blood flow (rCBF) activation to the dorsolateral prefrontal cortex (DLPFC) in schizophrenic subjects. This evidence suggests that frontal lobe mechanisms are dysfunctional in schizophrenics. While controls showed a substantial increased amount of rCBF to the DLPFC, the schizophrenics did not, leading many to conclude that there is a cognitive impairment in schizophrenics (due to frontal lobe dysfunction) preventing an increase in rCBF. However, the 2000 study in the *British Journal of Psychiatry* failed to replicate Weinberger's findings.

4. Neurodevelopmental Models of Schizophrenia:

Early Developmental Model:

Woods[63] describes neurodevelopment as "brain development and maturation that occurs as a consequence of an early process that begins *in utero*

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[62] Weinberger, D.R. (1986) **Physiology, Dysfunction of dorsolateral prefrontal cortex in schizophrenia. Regional cerebral blood flow evidence.** *Archives of General Psychiatry*, Vol. 43: 114-124.

[63] Woods, Bryan T., (1998). **Is Schizophrenia a progressive neurodevelopmental disorder? Toward a Unitary Pathogenic Mechanism**. *The American Journal of Psychiatry*, Washington: pp. 1661-1671.

and continues into the early 20's." In the normal maturity of the brain, the synaptogenesis of the occipital cortex is established by two years of age, but is not complete in the temporal and parietal areas (the prefrontal and association areas) until mid puberty. Some researchers believe that schizophrenia is a congenital lesion that an individual grows into over time. This is known as the "early developmental model" hypothesis. Thus, since the parietal and temporal lobes are not fully developed until adolescence to early adulthood, (and it is commonly thought that these areas contribute to the symptoms of psychosis) it can be surmised that schizophrenics "grow into" their lesions as soon as the affected area with the lesion has fully established its synaptic connections, if one believes this model. A child may not show signs of psychosis until adolescence because the lesion is dormant and the brain structures that would potentially be affected by it are not fully functioning yet[64]. This theory supports the idea of delayed expression of psychotic behavior until early adulthood.

The Reduction of Gray Matter without Gliosis:

Recent evidence indicates that there is a natural progressive loss of brain tissue volume that occurs some time during postnatal maturation. Findings published in the September 25, 2001 issue of the *Proceedings of the National Academy of Sciences* describe an abnormal amount of tissue loss in the brains of schizophrenics during their teenage years. According to its authors, loss of gray matter first occurs in the parietal cortex[65] and outer regions of the brain. This loss will engulf the rest of the brain in a period of approximately 5 years. [66]The deficit

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[64] Weinberger, Daniel R. (1987). **Implications of Normal Brain Development for the Pathogenesis of Schizophrenia.** *Archives of General Psychiatry*, Vol. 44, pp. 660-669.

[65] Stefan, M, Murray, R (2002). *An Atlas of Schizophrenia.* New York, NY: Parthenon Publishing.

[66] In this article, it is also noted that the patients with the worst loss of tissue also had the worst schizophrenic symptoms.

however, is unusual due to an absence of gliosis[67]. This indicates that the process involving cell loss is not degenerative. Bartzokis, et al, describe this cell-loss without gliosis as "an arrest in the developmental process of myelination." According to Bartzokis, there is a reduction of gray matter yet very little neuronal loss. The author[68] discusses the progressive loss of brain tissue occurring in the schizophrenic after birth. In normal brains, gray matter naturally decreases as we age and white matter volume increases. This means our brains make more synaptic connections as we grow older. These two processes "volumetrically cancel each other out" in normal brains, showing no indication of loss of brain volume. In schizophrenics, he argues, there is both a loss of gray matter (as a natural part of maturation) and white matter (reduced neuropil). Thus, the schizophrenic would have a smaller brain volume, and in many cases this has been found, though not all.

DLPFC-the Dorsolateral Prefrontal Cortex:

It should be noted that in the plight to discover the pathogenesis of schizophrenia, the dorsolateral prefrontal cortex[69] is a region of great importance and investigation. It shares connections with the brain stem, hypothalamus, the limbic system, and the thalamus.[70] This structure is the last area to begin myelination and is thought to be the only area that continues myelination throughout life.

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[67] Gliosis is the synthesis of a dense fibrous network of neuroglia around a degenerative lesion.

[68] Bartzokis, George (2002). **Schizophrenia: Breakdown in the Well-regulated Lifelong process of Brain development and maturation.** *Neuropsychopharmacology*, New York, NY: Elsevier Science Inc.

[69] The D.L.P.F.C. consists of the dorsolateral prefrontal cortex, the parietal cortices, the head, and body of the caudate and specific nuclei of the thalamus.

[70] The D.L.P.F.C. is part of the association cortex

White matter of the prefrontal cortex, specifically, is of great interest because it is thought to be a major contributor to the brain's synchrony. It exhibits the greatest interconnectivity of all the neocortical regions. If there is a lower amount of white matter, the areas of the brain that it communicates with might be prevented from doing so adequately. This line of reasoning has lead to the reduced neuropil hypothesis.

The Reduced Neuropil Hypothesis (The Late Developmental Model):

Many theorists believe that there is a reduction of neuronal processes in the prefrontal cortex of the schizophrenic brain. In theory, this faulty connectivity results in cognitive impairment in schizophrenics. These neuronal processes are referred to as neuropil. Neuropil is generally made of the dendritic branchings of neurons of the cortex and/or presynaptic terminal input onto cortical neurons. The dysfunction in prefrontal cognition may involve the deterioration of these neuropil, without the loss of actual neurons. This process may be due to a dysfunction in normal synaptic pruning that occurs around adolescence, which would eliminate all seemingly unnecessary connections. It has been theorized that instead of being an early developmental pathology (involving a model of a fixed lesion from early development) schizophrenia is perhaps a "late neurodevelopmental" dysfunction. This model, proposed by Feinburg, et al, [71] states that schizophrenia might be a result of an abnormality in normal developmental processes of the cerebral cortex occurring during postnatal maturation. These processes involve large-scale synaptic overproductions during the first years of life followed by an extensive synaptic eradication of neurons in areas of the brain essential for cognitive development. *In vivo* imaging studies support a large-scale synaptic pruning that occurs in normal adolescence. Feinburg proposes that a defect in this programmed synaptic eradication might lead to schizophrenia. Even a small alteration in the

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[71] Feinburg, I. (1990). **Cortical pruning and the development of schizophrenia.** *Schizophrenia Bulletin*, 16: pp. 567-568.

dendritic branches, especially at the susceptible distal portions would be detrimental to a neuron's encoding of a sensory event. This elimination of neuropil in normal cases is thought to be necessary to allow for a more effective use of neuronal connections for continued logical thought. In abnormal cases such as schizophrenia, this pruning may be faulty and eliminate necessary cortical connections, perhaps even those utilized in sustained logical thought processing.

Obstetric complications:

Environmental insults are a subject of intense scrutiny in the field of schizophre research. One type of insult is obstetric complication endured during pregnancy such as maternal malnutrition, fetal hypoxia, or prolonged labor. Some researchers also include in this category an occurrence of maternal influenza during the second trimester of gestation. In a series of studies performed from the late 1960's to the early 1980's, it was consistently found that obstetric complications were more frequent in schizophrenics than in controls.[72] These obstetric complications have been closely correlated with subsequent ventricular enlargement, a characteristic common among many schizophrenics[73]. In a study conducted by Lewis and Murray[74], researchers discovered that, within their samples, obstetric complications were more likely to have occurred in patients without a family history of schizophrenia. This evidence points to the conclusion that environmental insults are more detrimental to those without genetic

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[72] Pollack et al 1966, Woerner et al 1973, McNeil and Kaij 1978, Jacobson and Kinney, 1980, and Parnas et al 1982, from Lewis and Murray, 1987.

[73] Turner, S, Toone B, Brett-Jones, J. (1986). **Computerised tomographic scan changes in early schizophrenia.** *Psychol Med,* 16: 219-225.

[74] Lewis, S.W., Murray, R. (1987). **Obstetric complications, neurodevelopmental deviance, and risk of schizophrenia.** *Journal of Psychiatric Research,* 21: 413-421.

predisposition of schizophrenia. Dalen[75] observes "if we believe that some cases of so-called schizophrenia develop on the basis of perinatal damage...one would then expect the non-familial group to contain an excess of patients with a history of adverse perinatal circumstances or signs of brain damage."

Maternal Influenza:

In an article published in the *Archives of General Psychiatry*[76], researchers were interested in finding out whether or not individuals who were exposed to a 1957 influenza epidemic had a substantial incidence of schizophrenia. This study lasted 24 years, and observed citizens from the city of Helsinki who had been exposed *in utero* to a type A2 influenza epidemic during their second or third trimester of gestation. In a previously published study, Mednick, et al, [77]noted a prevalence of perinatal complications including viral exposure and birth during winter months among the schizophrenic cohorts. In the study, researchers were hoping to find a correlation between influenza exposure and insidious CNS damage that might subsequently manifest itself as schizophrenia. The researchers were in fact able to make this correlation but other arguments remained. Although there was a higher incidence of schizophrenia among patients than controls, there were still other factors to be considered. The authors speculate that perhaps OTC or prescription drugs administered to the pregnant mothers may have had teratogenic properties contributing to the later development of schizophrenia. Another argument is that not all women who contracted A2 influenza during their

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[75] Dalen, P. (1972). *One, two or many? Genetic factors of schizophrenia.* (Edited by Kaplan, A.R.) pp. 478-489 Springfield Illinois: Charles C. Thomas.

[76] Mednick, S.A., Machon, R.A., Huttunen, M.O., Bonett, D. (1988). **Adult schizophrenia following prenatal exposure to an influenza epidemic.** *Arch Gen Psych,* 45: pp.189-192.

[77] Machon, RA, Mednick, S.A., (1983). **The interaction of seasonality, place of birth, genetic risk and subsequent schizophrenia in a high risk population.** *Br J Psychiatry,* 143: pp. 383-388.

second trimester in 1957 gave birth to subsequently schizophrenic offspring. The authors go on to speculate that perhaps only those who were genetically vulnerable from the beginning were affected by this *in utero* viral exposure. There is also the issue that schizophrenia had existed in Helsinki long before 1957: Thus, they note: "If fetal viral infection is a critical factor in the etiology of schizophrenia then a broad spectrum of virus types must be involved." The formation of significant cortical structures occurs at around the 16th to 24th week of gestation with the migration of neuroblasts from the ventricular zone to the neocortex. The authors hypothesize that if, during this time, a fetus that is not only genetically predisposed to schizophrenia is also exposed to teratogenic factors such as a virus, the possibility of cortical maldevelopment along with risk of the later development of schizophrenia may be greatly increased.

Twin Studies:

In a study published in the *American Journal of Psychiatry*, led by Thomas F. McNeil[78], researchers investigated the structural anatomical differences in the brains of 22 monozygotic twins discordant for schizophrenia. Compared to the well twin of the discordant pair, the ill twin consistently showed smaller left and right hippocampi as well as larger left lateral and third ventricles. Also discovered were differences in dermatoglyphics, differences thought to be established during the second trimester of gestation. In a study published in the *New England Journal of Medicine*, Suddath, et al, [79] also reported anatomical changes in the brains of

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[78] McNeil, T.R, Cantor Graae, E, Weinberger, D.R. (2000). **Relationship of obstetric complications and differences in size of brain structures in monozygotic twin pairs discordant for schizophrenia.** *The American Journal of Psychiatry,* Washington. Vol. 157, Iss.2; p. 203, 10 pgs.

[79] Suddath, R.L., Christison, G.W., Torrey, E.F., Casanova, M.F., Weinberger, D.R. (1990). **Anatomical abnormalities in the brains of monozygotic twins discordant for schizophrenia.** *New England Journal of Medicine,* pp. 789-94.

monozygotic twins discordant for schizophrenia. Using magnetic resonance imaging, researchers discovered smaller left temporal lobes, (including a reduction in both sides of the anterior hippocampus) in 13 of the 15 ill co-twins as compared to their well twins. Also found was enlarged lateral and third ventricles in most of the ill twins as compared to their well co-twins.

MPA's: Minor Physical Anomalies:

Minor physical anomalies (MPA's) have been found more often among schizophrenics than controls, although they are not unique to the disorder. These MPA's include the ears, hands, mouth, head, and feet and tend to be ectodermic in origin. This may indicate first or second trimester maldevelopment and may also imply brain malformation, since the CNS is ectodermal in origin as well. Therefore, some researchers [80] believe that MPA's may be external representations of prenatal maldevelopment of the ectodermal layer during the first or second trimester of gestation. Thus, they may provide insight into schizophrenia spectrum disorders from a neurodevelopmental point of view. Because these morphologies are permanent, (in that they are not affected by medication, substance abuse or other minor environmental trauma) they serve as dependable, unbiased physical markers of prenatal insult.

Even though most organogenesis is finalized by the first trimester, the second trimester is critical for a large- scale neuronal movement towards the cortex. Migration of these ectodermal cells from the periventricular germinal matrix to the cortex happens simultaneously with the migration of ectodermal cells to the skin of the distal upper limb. In monozygotic twins discordant for schizophrenia, there is a within-pair variation in the morphology of the dermal layer on the skin of the hand. Some researchers believe that this morphology occurs because of prenatal insults occurring *in utero* during the 2nd trimester.

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[80] Murphy, K.C., Owen, M.J., (1996). **Minor Physical Anomalies and their relationship to the aetiology of schizophrenia.** *British Journal of Psychiatry*, 168: pp. 139-142.

Dermal cell migration is both genetically and environmentally affected, making the distinction of whether MPA's and subsequently schizophrenia are genetically or environmentally caused even more perplexing. Firestone, et al,[81] advocate a genetic causality in the etiology of MPA's. This is supported by the fact that other types of physical anomalies exist in chromosomal disorders such as Down's syndrome[82]. One theory is that MPA's may stem from the same aberrant gene/genes responsible for the pathogenesis involved in schizophrenia.

Arguments for an environmental etiology of MPA's are just as robust, however. In fact, most advocates of the neurodevelopmental model prefer to concentrate their efforts on an environmental modality rather than a genetic one to explain the presence of MPA's in schizophrenics. Some of these speculated environmental insults are suspected to occur as a result of pre- or perinatal or labor/delivery complications including hypoxic ischemia[83], maternal malnutrition, and *in utero* viral infection[84]. These pre- or perinatal insults do not always affect monozygotic twins in the same manner. This is revealed by the fact that there is a 50% chance of discordance among monozygotic twins, if one chooses to believe this school of thought. Perinatal hypoxia can lead to intraventricular bleeding which may result in enlarged ventricles. It is speculated that this may account for the ventriculomegaly in some schizophrenic individuals.[85] Although it has been

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[81] Firestone, P, (1978) **Minor Physical anomalies in hyperactive, retarded, and normal children, and their families.** *Journal of Child Psychology and Psychiatry*, 19: pp.155-160.

[82] Smith, D. W. (1976). *Recognisable patterns of human malformation: Genetic, Embryologic and Clinical Aspects.* Philadelphia: W.B. Saunders.

[83] Hamilton, W.J. (1972). *Human Embryology: Prenatal Development of form and function.* Cambridge England: Heffer.

[84] Achs, R.S. (1966). **Unusual dermatoglyphics findings associated with rubella embryopathy**. *New England Journal of Medicine*. 274: pp. 148-150.

[85] Stefan, M, Murray, R (2002). *An Atlas of Schizophrenia.* New York, NY: Parthenon Publishing.

reported that *in utero* viral infection during the second trimester is associated with the later affliction of schizophrenia[86], no correlation between maternal influenza and the development of MPA's in schizophrenia has been made. The most plausible explanation for the cause of MPA's is that they may come from both factors. Perhaps, due to the heterogeneity of the syndrome, MPA's may be attributed to environmental modalities in some cases, and in others, genetics may be to blame. It seems most logical however, that MPA's reflect the two factors working in tandem to create ectodermal malformations during the second trimester.

5. Summary of Research:

The search for the underlying pathogenesis of schizophrenia is daunting. Researchers are faced with numerous obstacles to overcome. Perhaps the largest of these obstacles is the fact that schizophrenia appears to be a term used to describe a variety of discreet pathological processes that may or may not be related. There are no conclusive studies. For every positive finding, there is usually a negative one to contradict it. Perhaps if better standards of measurement were used in these studies, i.e. a uniform standard to which all studies adhere, there would be less inconclusive conflicting data. Along with a standard, more attempts should be made at delineating separate schizophrenias within the syndrome and creating a diagnostic criterion for each one. This way, inconclusive studies can be looked at again from a perspective that they are measuring more than one disease at a time. The neurodevelopmental hypothesis seems quite possible, due to overwhelming evidence, i.e., lack of gliosis and other neurodegenerative histological findings. What researchers need to do now is to find out if the late developmental model, and early developmental model are potential subcategories within the syndrome of schizophrenia and research each one not as though they are separate theories of

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[86] Mednick, S.A., Machon, R.A., Huttunen, M.O., Bonett, D. (1988). **Adult Schizophrenia following prenatal exposure to an influenza epidemic.** *Arch Gen Psychiatry*, 45: pp. 189-192.

one disease, but two possible disease mechanisms within the syndrome of schizophrenia.

III. Methods of Execution of Artwork:

Platform:

The factors that determined the platform on which to present this project included how readily the information could be accessed and how easily the information could be transported. The information of this thesis was too substantial to put into an informational brochure, and although a book seemed more logical a platform than a brochure, a website seemed most appropriate, given the amount of space needed, and ease of transport. The only limiting factor in a web-based platform is access to a computer. The target audience was however, intended to be those with a college level degree. It is probably safe to assume that most individuals from this population have access to a computer. Another crucial factor in this decision was the number of viewers who could access the information. A book limits the number of viewers for obvious reasons, while the web allows for universal access for all who seek it. Therefore, the internet was the most logical platform for this thesis.

Subject Matter:

Subject matter for this project was selected by first sketching out a visual response to the research paper. The necessity for a number of portraits was evident immediately. In order for a user to understand the location of certain structures in the brain, a human orientation was needed. To vary the artwork, portraiture was done from different angles and from several subjects varying in age, ethnicity, and gender. Numerous structures of the brain were also illustrated including the limbic system, the cortex, and the ventricles. On a microscopic level, it was determined that illustrations of neurons and their associated neuropil were needed to visually explain the reduced neuropil hypothesis.

In some cases, static illustrations were not explanatory enough. In these instances, animation was employed. For example, to explain the migration of the neuroblasts and what it might look like if it were dysfunctional, it was necessary to show the actual direction and fluidity of the migration, something that could not be conveyed through a static image. Another illustration that required animation was the progression of a latent lesion in the dorsolateral prefrontal cortex in the brain of a nine -year- old girl into a crippling lesion in the brain of a twenty one year old woman.

Artistic technique:

Each static image was created in Photoshop® from an initial hand drawn sketch rendered in graphite. The sketch was imported into Photoshop®. First, "washes" of transparent yellow ochre[87] and burnt sienna were used to block off plane changes in the subject matter. A naples yellow hue served as a soft light on the areas of highlight .The values were blended and the layers were merged. Then came the assessment of temperature. Where it was warm, a cadmium red hue was painted semi-opaquely. For cool areas, a deep warm purple was applied semi transparently. Washes of a yellow ochre hue emphasized the warm shades, and the under planes were described with washes of crimson red. The final touches were applied and the Photoshop® document was placed into Illustrator® and exported to Flash® as a Swf® file.

Each bitmap was converted into a symbol according to its use. For example, an image used in an animation was key-framed into a movie clip. An illustration used for a static image was changed into a graphic. For the sepia toned

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[87] There are not actual names to the RGB colors used in Photoshop. Each color described, is meant to describe the RGB equivalent of the color, i.e. crimson red is meant to denote the RGB equivalent of crimson red. A crimson red hue in Photoshop is denoted as approximately: R: 167, G: 0, B: 57. A yellow ochre hue is denoted as approximately: R: 221, G: 155, B: 0.

images at the introduction of each chapter, each full-color RGB Photoshop® document was converted to grayscale. Then it was changed back to an RGB color space and photo-filtered with sepia tone.

The decision for this method of artwork comes from a general comfort level with Photoshop® software as well as the desire to create digital static images that were easily accessible and easy to manipulate. This author found Adobe Photoshop® more intuitive and thus easier to use than a vector program such as Adobe Illustrator®. The reason for the use of Macromedia® Flash® as opposed to Macromedia® Dreamweaver® or another HTML program was also due to the author's ease of use. The focus of this project was not to become distracted by learning new programs, but to make a functional website with as much ease and intuition as possible. The primary emphasis of this project was on the illustrations placed within the website. The site itself, although initially ancillary, was also something to consider. In the end, the design of the website became as important to the success of the project as the artwork placed inside of it.

Artistic License:

In many instances, artistic license came into play. There were very few if any visual references of abnormal neuroblast migration, so this particular animation was created through artistic interpretation of the research material. Another similar animation, the progression of a latent lesion over a period of ten years, was also rendered based on written description found through research and without photographic reference. An illustration of the brain inside the head of a fetus during the 13th week of gestation was also approximated, for only a few meager visual aides were found that showed what it actually looked like.

The Design of the Website:

As previously stated, the construction of the website was initially assumed to be secondary to the illustrations in this project. As time progressed however, and the site came into fruition, this author realized the importance of the organization

of the platform on which she placed her images. Specifically, purposeful orderliness became a major concern.

The actual graphics in association with the website were thoroughly planned out. The author wanted to create an environment in which to hold the static images, one that would convey a mood of psychosis, isolation, and disorder. For the backdrop of the website a piece of notebook paper was soaked in tea overnight and dried. Then the paper was scanned into Photoshop® and pasted on top of a brown, rustic background. This background was made with Photoshop® filters and antique photographs of mental asylums. Then a warm, yellow lighting filter was applied. The image was brought into Flash® as a Swf™ file.

Initial Design for the Site

The initial design for the site included six topic chapters with three subtopics within each chapter. Each chapter would correspond to a different topic within the research section of this paper. Each page would contain a forward and backward button as well as a home button to allow the user to return to the table of contents. Within each chapter there would be an introduction page with text, an explanation page with illustrations to help explain the subject, and an animation page to supplement the explanation and introduction pages.

Trials and Navigational Issues:

Even though the research, static images, and animations were sufficiently planned and thoroughly executed, the navigational aspects of this site were initially lacking. Although in the end they were a relative success, in the beginning, the navigation of the site was ambiguous at best.

The original idea for the layout was that there would be six topic chapters (later changed to seven) with individual pages explaining separate subtopics within each chapter. This idea was not obvious to the trial users, which meant that the hierarchy of the website needed to be explained more succinctly. The solution was to place a navigational bar, or "breadcrumbs," at the bottom of each page. This

bar included the name of the chapter that the user was currently in, as well as the page and section number. Also included in this navigational bar was a link to the last page that the user was on, as well as a link to go to the next page within the chapter. As an additional aid, the navigational bar offered the user two more options as well: to go back to the previous chapter or skip ahead to the next one.

As the trials continued, constraints and affordances[88] became another consideration. Previously, for the sake of consistency the amount of buttons on each page stayed the same. Each button that was not in use on a certain page was rendered inoperable by deleting the hit key-framed for it. This had negative consequences. The hand icon of the mouse still appeared on roll over, leaving the user to believe that it was a functional button. Eliminating the button on the pages where it was not used repaired this problem.

Another problem encountered by trial users was that the play buttons for the animations were not consistent in placement and therefore the user often overlooked them. The remedy for this problem was to place all of the play buttons within the entire project in the same location.

There were other problems encountered when gauging the usability of this website. These included drop down menus that were not obviously menus as well as the option to roll over insets for a more detailed description of an illustration. After consideration, many of these rollover options were deemed superfluous and were eliminated from the website. The rollover options deemed necessary were labeled with instructions. One feature that was not eliminated was the group of rollovers in the summary chapter. These rollovers were originally buttons without a "hit" or "activation" state. They acted as buttons when moused over. During the trials, many users tried to "hit" these rollovers in anticipation of being directed to a new page. To get rid of any confusion, the rollovers were given a "hit" state and were linked back to the page that they referred to. This created a pathway from the summary page back into the heart of the material. The summary buttons, though

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[88] Norman, D. A. (2002) *The Design of Everyday Things,* New York: Basic Books; 1st Basic edition.

not originally intended to do so, served as a quick reminder of each chapter and section with the option for the viewer to go to where it referred.

Changes and Revisions:

The focus of this project was primarily research based. In retrospect, more preparation should have been done in terms of the architecture of the website. The exorbitant amount of scientific research that was completed, though comprehensive, often bordered on superfluous, while the artistic planning seemed at times insufficient. As the project progressed however, revisions were made accordingly, and the structure of the site vastly improved in terms of the user's ease of navigation and understanding of the subject matter.

The illustrations and animations were well planned, with sketches, revisions and final product carefully thought out and executed. In hindsight, perhaps the animations would have been more successful if they were created with vector images instead of raster ones but the matter of ease of creation far outweighed the risk of experimentation.

The project improved as time progressed. A determining factor in the overall functionality of the website came from constructive criticism offered by trial users, the most helpful of them being the idea of the navigation bar.

If changes were to be made, it would be that the information on the website would go into more depth than it did. The subject covered would be more narrow than broad and discuss the specifics of one of the neurodevelopmental models as opposed to three or four. The animations would more abundant, for users seemed to understand concepts better with the animations than with the static images. Formatting within the website could be improved as well. The actual space within the site would be larger and more open than the present one, and allow for more breathing room for the text, illustrations, and buttons. In addition, the technical detail of each illustration would be greater, warranted by a more narrow specificity of subject matter.

The final version of this project was generally well received by the audience at the graduate thesis exhibition, which was held April 22, 2005 in the Bevier Gallery of the Art Building on the R.I.T. campus. Some viewers asked simple navigation questions, indicating that more work remains to be done to increase the level of usability. The comments on the actual design of the website (not the architecture) were generally positive, as well as those made in reference to the illustrations and animations.

IV. Concluding Statements:

The primary goal of this project was to create a functional interactive website that was informative, academic and thought provoking. It was the intention of this author to generate a large amount of colorful illustrations and animations that would help to supplement the thick, sometimes dry information of the research. The design of the website was intended to serve as a quasi-environment in which the user experienced the information. Many aspects of this project, though initially overlooked, were adequate in the end including navigational issues that were solved after trial users overwhelmingly agreed that the navigation was difficult to understand. The creative journey that this author traveled was an arduous one. It was a journey of exploration of her intellectual and artistic capabilities, as well as one of exploration of the syndrome that has devastated her family for generations. The creation and completion of this paper and website have given the author invaluable insight into herself and from whom she came.

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Gwen DeCelles Thesis
Summer 2005