Understanding the Brain of an Adolescent with Schizophrenia

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This paper aims to summarize current research on the schizophrenic brain to describe the abnormalities seen in patients with schizophrenia at the cellular and gross anatomical level. The symptoms of this disorder are diverse in both manifestation and severity from person to person, which is reflected in the heterogeneity of brain abnormalities cited in the scientific literature. First, a description of schizophrenia and its implications will be addressed, especially in special education. The structure of the brain and schizophrenia's impact will be discussed.

In the film *A Beautiful Mind (2001)*, Russell Crowe plays the role of John Nash, a mathematical genius with schizophrenia. Nash shifts between madness and genius as he experiences delusions and extreme paranoia while simultaneously developing an economic theory that catapults him into the scientific world stage. Many others with schizophrenia experience a hybrid world where they are torn between reality and the paranoia and delusions their brains create. Among the many challenges of experiencing delusions, one of the most isolating is that other people reject part of their experience as imaginary though to them it is real. Though Hollywood captures this reality, schizophrenia itself is different between individuals. The *Diagnostic and Statistical Manual of Mental Disorders (DSM)* characterizes schizophrenia by the presence of delusions or false beliefs, hallucinations, or disorganized thinking, though abnormal motor behavior and negative symptoms may also be present (5th ed.; DSM–5; American Psychiatric Association, 2013). Negative symptoms refer to diminished qualities, such as decreases in emotional expression or goal-directed behavior. In contrast, delusions and hallucinations are examples of positive symptoms, which refer to the appearance of symptoms such as suddenly hearing voices where none exist or developing intricate theories or ideas that have no logical basis. To expand this, the term psychosis is the condition of losing touch with reality due to the workings of the mind. The symptoms of schizophrenia are broad, as each person experiences the disorder differently (van Erp, Hibar, Rasmussen, Glahn, Pearlson, Andreassen, 2015). This paper aims to summarize symptoms commonly experienced by individuals

with schizophrenia and describe the heterogeneity of brain abnormalities associated with the array of symptoms, particularly those common in adolescents.

Schizophrenia and Special Education Law

According to Hill and colleagues (2017), studying youth is important because schizophrenia appears most often in the transition from late adolescence to early adulthood. Therefore, by studying youth at risk for schizophrenia, more insight can be applied to preventative and early care. When an adolescent begins acting erratically or begins to say they are seeing objects and hearing voices, it is common to assume drugs are the cause. Psychosis can be induced by drug use, particularly during adolescence when many youths begin to experiment with illicit drugs. Some adolescents who hear voices, hallucinate, or have a break with reality may be beginning to experience symptoms of schizophrenia. Hallucinations and delusions are common symptoms of schizophrenia, but other symptoms include cognitive deficits such as impaired memory and attention or negative symptoms such as social withdrawal (Hill et al, 2017), which can also appear in the classroom and be grossly misinterpreted as signs of other problems, including drug use. Rae and colleagues (2017) use both participants with schizophrenia and those with drug-induced psychosis to explore mechanisms of hallucinations. Through that, they found out that abnormalities in the neurite structure appear in both types of participants. Thus, their brains are aberrant in similar ways, and the symptoms of schizophrenia present similarly to the symptoms of drug-induced states. Shared symptoms between these two conditions include paranoia, erratic behavior, and visual or auditory hallucinations.

The Individuals with Disabilities Education Act (IDEA) is the federal special education law that governs the education and treatment of students with disabilities in the US ("About IDEA", n.d.). IDEA defines emotional disturbance as:

> (i) A condition exhibiting one or more of the following characteristics over a long period of time and to a marked degree that adversely affects a child's educational performance:
> (A) An inability to learn that cannot be explained by intellectual, sensory, or health factors.
> (B) An inability to build or maintain satisfactory interpersonal relationships with peers and teachers.
> (C) Inappropriate types of behavior or feelings under normal circumstances.
> (D) A general pervasive mood of unhappiness or depression.
> (E) A tendency to develop physical symptoms or fears associated with personal or school problems.
> (ii) Emotional disturbance includes schizophrenia. The term does not apply to children who are socially maladjusted, unless it is determined that they have an emotional disturbance under paragraph I(4)(i).

IDEA ensures that individuals with disabilities, including schizophrenia, have access to education and individualized treatment for their symptoms. Therefore, the difference between schizophrenia and drug induced states are important for the layperson and education systems to understand. If a student in a high school class begins hearing voices, their teachers, counselors, parents, or

other caretakers may mistake it for drug-induced psychosis, and therefore, disciplinary actions could be taken against the student. This could include suspension, expulsion, or, in extreme cases, moving to a rehabilitation center or incarceration. Removing a student from the classroom could effectively deny the student access to an important learning environment. However, if the possibility that this individual suffers from schizophrenia is considered, a vastly different course of action will likely be undertaken. The student would have access to counselors, treatment, and adjusted learning environments, which are vital to improving the quality of life for a person with a mental disorder. Misunderstanding the signs of schizophrenia could not only deny a student proper treatment but could also remove them from their basic learning environment. This could unintentionally lead to a progression of the symptoms of the disorder. It is important that teachers know the symptoms of schizophrenia, so that a student with this neurological disorder can receive the care needed to improve their quality of life.

Whole Brain Networks in Schizophrenic Individuals

Schizophrenia is the result of miscommunication within the entire brain. Research on patients at risk for psychosis, such as that of Amico and colleagues (2017), suggests wide scale brain network dysfunction, showing that certain brain regions of schizophrenic patients are unable to communicate properly. Brains are complex in that no region is isolated to a single function; areas work together to form networks. Three specific networks have been implicated in schizophrenia and are known as the "Triple Network Model" (Menon, 2011; Amico et al, 2017). This suggests a mechanism for how the combination of abnormalities identified in research produces dysfunctional behavior. These three networks consist of the default mode network (DMN), the salience network (SN), and the central executive network (CEN) (Menon and Uddin, 2010; in Amico et al, 2017).

Disruptions within these three networks may explain how hallucinations manifest in schizophrenic individuals. Individuals who experience hallucinations have been shown to have overactive auditory cortices, an area of the brain that receives and processes sound. In the DMN, aberrant connections from the auditory cortex to the anterior cingulate gyrus are known to lead to a reduced ability of the brain to differentiate between signals coming from the auditory cortex. Furthermore, disruptions of the SN may lead to a decreased ability to differentiate between external stimulation and internal responses, which could lead to a focus on internal brain activity over external stimuli. According to many researchers, this may be due to disruptions between the insula and prefrontal cortex (Palaniyappan, Simmonite, White, Liddle, Liddle, 2013). Because of these disruptions, if the brain incorrectly focuses on internal brain activity over activation of the auditory cortex, the individual may consciously perceive this extra activity as sound. In this way, over-activation of one area, such as the auditory cortex, becomes perceived as an external stimulus, which is a hallucination, experienced as hearing sounds that are not present.

Gross Anatomy

Although an important feature of schizophrenia is disruptions between brain regions, many studies

of schizophrenia have thoroughly demonstrated abnormalities of gross anatomical brain structures, consistently in frontotemporal areas. In a sample of patients with schizophrenia (n=2028) from many different countries, volumetric reductions were seen in the hippocampus, amygdala, thalamus, accumbens, and of total intracranial volume. These are all areas of the limbic system, which as a whole is responsible for emotion processing, learning, and memory (van Erp et al, 2015). Furthermore, it is important to note that greater hippocampal reductions were found in unmedicated patients, which suggests that treatment affects this area of the brain. In contrast, volumetric increases were seen in the pallidum and lateral ventricles when compared to controls. The brain ventricles are four fluid-filled cavities located throughout the brain. They are worthy of mention since the larger a brain cavity is, the less grey matter the surrounding structures possess. Of these observations, reduction of the hippocampus and increases in the lateral ventricles were the most significant results, which is widely replicated in the neurological literature (van Erp et al, 2015). Other studies have also demonstrated increased ventricle size in schizophrenic patients. A study (Cuesta, Lecumberri, Cabada, Moreno-Izco, Ribeiro, Lopez-Ilundain, Gomez, 2017) showed that patients with schizophrenia have increased third ventricle volume when compared to controls and increased lateral ventricle volume when compared to their healthy siblings. Patients with schizophrenia that had enlarged ventricles were shown to experience more negative symptoms.

Though not as prominent, changes in other limbic areas have been observed across studies, specifically in parts of the basal ganglia. The basal ganglia consist of a group of largely dopaminergic neurons in the limbic system that are also associated with emotion and learning but play important roles in other functions such as voluntary motor control. For example, the pallidum, a region of the basal ganglia, was found to be larger the longer an individual had schizophrenia (van Erp et al, 2015). This effect was also seen in the putamen, though initial measurements by van Erp et al. (2015) did not show the volume to be different from controls. One study observed slight caudate reductions in schizophrenic patients (Haijma, van Haren, Cahn, Koolscijn, Pol, Kahn 2012), though Cuesta et al. (2017) found larger right caudate volumes when comparing these patients to controls. These conflicting results suggest that volumetric changes to these regions of the basal ganglia are not as significant to the pathology of schizophrenia as abnormalities of the hippocampus and brain ventricles. Therefore, further research into this claim is necessary.

Another area of the brain identified as abnormal across schizophrenic patients is the superior temporal gyrus (STG). This is the region of the brain that contains the auditory cortex, which in schizophrenia patients has faulty connections to the wide scale brain networks. This results in symptoms such as hallucinations. To further support that the STG is key in producing these hallucinations, one can look at studies using patients with epilepsy that have demonstrated that electrical stimulation of the superior temporal gyrus results in illusions and hallucinations (Elliott, Joyce, Shorvon, 2009). A study by Walton and colleagues (2017) further explored this relationship and found that increased positive symptoms in

schizophrenic patients correlate with decreased cortical thickness of the STG in both hemispheres. This was regardless of other factors such as age, sex, handedness, or medication use. The duration of illness was also negatively correlated to cortical thickness of the STG. This is important because numerous studies cannot find relationships between cortical thickness of the STG and positive symptoms in new patients, which were patients that experienced symptoms for less than a year at the time of the study. This supports the theory that as schizophrenia progresses, the superior temporal gyrus loses grey matter, leading to hallmark symptoms of schizophrenia, such as hallucinations.

A different subset of brain regions may be connected to negative symptoms such as cognitive impairments. A study by Gay and colleagues (2016) investigated four brain markers that each suggested executive dysfunction and found that executive dysfunction stems from brain abnormalities even before signs of schizophrenia begin to appear. This study examined neurological soft signs (including sensory integration, motor integration, and motor coordination), handedness, anterior cingulate cortex morphology, and cerebrospinal fluid volume. For these four categories, patients with schizophrenia that also had the lowest cognitive functioning levels had more neurological soft signs, symmetric anterior cingulate cortex sulci, and mixed handedness. Gay found that the presence of two of these signs correlated with neurodevelopmental aberrations and thus a decrease in cognitive abilities. Cognitive dysfunction within schizophrenic patients is then likely to be the result of multiple instances of early damage to the brain (Gay, Plaze, Oppenheim, Gaillard, Olie, Krebs, Cachia, 2016).

Neural Underpinnings of Schizophrenia

Neuronal abnormalities are proving to be a key component of the biology of schizophrenia. According to one experiment, measurements of cortical thickness of each brain region are not correlated with neurite density in the same region, suggesting the two variables are unrelated (Nazeri, Rajji, Levesque, Pipitone, Stafanik, Voineskos, 2016). Since both are predictors of a diagnosis of schizophrenia, it is important to characterize abnormalities at the neuron level. However, it should be noted that further experimentation is needed to better describe the relationship between neurite density of the neurons themselves and the irregularities of whole brain structures if a relationship even exists.

Postmortem studies have established abnormalities of neuron microstructure in the prefrontal and temporal brain regions including reduced microtubule-associated protein 2 marker, reduced dendritic arborization, and reduced dendritic spine density (Nazeri et al, 2016), structures which are responsible for creating connections with surrounding neurons. In fact, experimentation by Nazeri determined that using grey matter microstructure, which refers to the dendrites and cell bodies of neurons that receive signals from other neurons, was a better differentiator of schizophrenia from healthy controls compared to utilizing measurements of cortical thickness alone. As such, researchers have developed neuroimaging techniques to study grey matter microstructure in vivo in schizophrenia patients. Using these techniques, Nazeri found that patients

with schizophrenia have a lower grey matter neurite density index (GM-NDI) in frontotemporal structures, including the temporal pole, hippocampus and parahippocampus. Furthermore, cognitive performance was tested between groups with schizophrenia and healthy controls. It was found that better spatial span performance was associated with higher GM-NDI in several areas throughout the brain, including the temporal pole and hippocampus (Nazeri et al, 2016). These results suggest that reduced GM-NDI contributes to the cognitive deficits observed in these patients, a symptom of schizophrenia that is in direct contrast to Hollywood portrayals of the disorder, such as in *A Beautiful Mind*. Though cognitive deficits are not a hallmark symptom of schizophrenia in the way delusions and hallucinations are, it is important to note they can occur with the disorder, since the genius of John Nash is the exception and not the rule.

Aside from grey matter alone, other studies suggest reduced neurite density of white matter may contribute to psychosis, a symptom of schizophrenia. Researchers have experimented with patients that have experienced psychosis, though not all the patients had psychosis as a result of schizophrenia. Patients that experience this symptom show reduced fractional anisotropy scores and greater mean diffusivity scores compared to controls in multiple white matter tracts throughout the brain (Rae et al, 2017), which describes how the neurons of someone that experiences psychosis have diffused around the brain differently from controlsas their brains were forming. These tracts of neurons occur through all four lobes of the brain. Furthermore, these tracts showed decreased axonal number and a decrease in the myelination of axons (Zhang, Schneider, Wheeler-Kingshott, Alexander, 2012). Rae suggests this reduction of axon density might contribute to the symptoms of psychosis more so than abnormalities in location of the neurons themselves as described earlier. However, both differences from controls suggest that abnormalities in neurons themselves contribute to psychosis, which is an important component of schizophrenia.

High Risk Youth Compared to Schizophrenia Patients

Youth at high risk for developing schizophrenia have been shown to have deficits in sustained attention, executive functioning, and verbal memory. Research suggests these symptoms have a biological basis and that these high-risk youths have brain abnormalities reflective of schizophrenic brains. For example, Amico and colleagues (2017) report that in a sample of adolescents that experienced subclinical psychosis, such that psychosis that did not warrant a diagnosis of schizophrenia, auditory verbal hallucinations were the most commonly reported symptom. It is important to note that the term individuals with auditory verbal hallucinations in this paper refers to a group of youth that experience auditory hallucinations, but this does not represent a group of patients that received a clinical diagnosis. Another component of research finds that even before these preliminary symptoms of psychosis appear, the brains of these youth show aberrant connectivity similar to the brains of patients with clinical schizophrenia, indicating that the brain is already wired to experience symptoms of the disorder.

Amico and colleagues (2017) demonstrated that patients with schizophrenia showed aberrant

connectivity in auditory networks, specifically in temporal and limbic areas, as well as alterations in the primary auditory cortex. This is consistent with other literature on the schizophrenic brain. They found the same results in the brains of high-risk subjects, in which schizophrenia was a part of their genetic family history. For example, some juveniles with auditory verbal hallucinations demonstrated weaker connectivity between the left anterior cingulate cortex and left inferior temporal cortex, between the right anterior cingulate cortex and right superior medial frontal cortex, and between the right dorsal anterior cingulate cortex and the left precentral gyrus when compared to controls (Amico et al, 2017).

Another finding is that youth with subclinical psychotic symptoms have stronger connections between the anterior cingulate cortex and the putamen, a region of the basal ganglia. Amico and colleagues (2017) suggest this leads to aberrant functioning of the dopaminergic neurons of this region, resulting in disrupted salience detection, and thus disrupting whole brain networks similar to disruptions observed in schizophrenia patients. Thus, it can be argued that this stronger connection is a mechanism for delusions, seen in both subclinical patients with psychosis and those with diagnosed schizophrenia.

The auditory cortex itself is also a noteworthy region in individuals with auditory verbal hallucinations. Both A1 and A2, regions of the brain corresponding to auditory processing, were found to have greater connectivity to frontal regions when compared to controls according to Amico. It was previously discussed that research shows over-activation of the auditory cortex contributes to hallucinations, and this research supports this assertion. This information supports that abnormalities of the brain accumulate to build symptoms that in some cases lead to clinical diagnosis of a disorder. However, if not enough changes occur, the individual remains high-risk with a brain that is intermediate between neurotypical and aberrant.

Apart from functional connectivity aberrations, brains of high-risk youth also show gross anatomical differences. A study by Hill and colleagues (2017) revealed significant inward displacements of regions of the right hippocampus and right amygdala of individuals that had a sibling or parent with schizophrenia but did not have the disorder themselves. The hippocampus and amygdala are two structures that have been found to be volumetrically reduced in patients with schizophrenia (van Erp et al, 2015). It is important to note that while inward displacements of these structures were found, there were no volumetric reductions in these regions in the family members of schizophrenic patients. Although significant anatomical abnormalities of the thalamus were not found in high-risk individuals, a correlation was established between sustained attention scores and thalamic inward displacement. This increased displacement in high-risk youth correlated to reduced attention, as well as increased schizotypy scores (Hill et al, 2017). Another important finding from the same study determined correlations between shape displacements of these subcortical structures and attention and executive functioning skills in control subjects (Hill et al, 2017). However, these correlations were lacking in high-risk groups. This suggests a fundamental rewiring of the brain in high-risk youth in regions known to be affected

in patients with schizophrenia, which should be explored further in future research.

Conclusion

The brains of patients with schizophrenia show plenty of variety, which is reflected in the vast differences and severity of symptoms seen in patients with schizophrenia and those that are high-risk with executive functioning and attention impairments. Unfortunately, this can cause confusion and appear to be symptoms of drug-induced psychosis, which can result in disciplinary action for special education students. Instituting disciplinary action, especially repeatedly, takes the student out of the classroom and puts them at a disadvantage in both abilities to complete work and opportunities to socialize. This is in addition to the negative consequence of punishment itself. This is why characterizing schizophrenia is important, especially for the layperson to understand. This variety can be characterized at three levels. At the most fundamental level of brain organization, deficits of neurite density are seen in both white and grey matter. At the gross anatomical level, frontotemporal regions show volumetric deficits and shape irregularities, such as the hippocampus, amygdala, STG, and lateral ventricles. These lead to symptoms such as an inability to process facial emotion or reduced attention and executive function. Finally, widespread connectivity aberrations between brain networks such as the DMN, SN, and CEN are thought to contribute to positive symptoms such as auditory verbal hallucinations. Though much longitudinal research remains to be undertaken to determine when and why these abnormalities arise, descriptions characterizing the schizophrenic brain are vital in better understanding the biology behind the symptoms.

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