The dopamine, glutamate, and GABA hypotheses of schizophrenia: Glutamate may be the key

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Abstract

This essay explores hypotheses postulating that the neurotransmitters dopamine, glutamate, and gamma-aminobutyric acid (GABA) cause schizophrenia, and reaches the conclusion that a joint model where glutamate affects dopamine and GABA is the most plausible explanatory mechanism. The dopamine hypothesis is supported by evidence that patients with schizophrenia have marked dopamine receptor and neurotransmitter increases and decreases in specific brain areas. Furthermore, drugs targeting dopamine receptors have been successful in reducing schizophrenic symptoms. The glutamate hypothesis proposes that the neurotransmitter glutamate is the basis of the disorder, as affecting NMDA (glutamate) receptors has been shown to cause positive and negative schizophrenic symptoms, including visual and auditory symptoms only ever seen in schizophrenia. Further, there are genetic associations with several genes associated with NMDA receptors and schizophrenia. The GABA model is also explored, as tampering with cells related to GABA has been shown to induce schizophrenic symptoms, though this can be explained as being in conjunction, not opposition, with the glutamate model. The hypotheses are flawed when considered in isolation. The dopamine model cannot explain negative schizophrenic symptoms, and drugs targeting dopamine receptors are still unable to completely reduce self-reported symptoms. Similarly, the glutamate model could be caused by irregular amounts of GABA, and the glutamate hypothesis may also explain the positive effects of treatments targeting dopamine. Evidence shows that drugs causing reduced functioning of NMDA receptors cause dopamine dysfunction. Pairing this with strong evidence of both dopamine and glutamate involvement, the most plausible model is one where NMDA dysfunction causes GABA and dopamine receptor issues.

Introduction

Schizophrenia is a mental disorder that affects approximately 1 per cent of the population, commonly emerging around early adulthood. The disorder is thought to cost the United States more than US$150 billion each year, and gravely affects sufferers who face long-term employment and social issues and deeply reduced quality of life. Those with schizophrenia have a mean life expectancy 15 years shorter than the rest of the population, and 5–10 per cent of people with the disorder are estimated to die via suicide (McCutcheon, Reis Marques, & Howes, 2019). This makes research into the causative elements of schizophrenia invaluable as it may provide preventative insights and/or help formulate life-changing medical treatments. The criteria of schizophrenia is defined by the DSM-V as sufferers having at least one positive symptom—best thought of as an addition of a damaging symptom—which can include hallucinations, delusions, and disorganised thinking. Patients also have negative symptoms—best thought of as the lack of a characteristic that a neurotypical person would have—which can include listlessness and lack of motivation. Cognitive symptoms—alterations in cognition—such as disorganisation and poor attention are also characteristic of schizophrenia (Kantrowitz & Javitt, 2012; McCutcheon et al., 2019).

The dopamine hypothesis and glutamate hypothesis of schizophrenia are the two most popular proposed theoretical explanations for the disorder. Dopamine and glutamate are two different types of neurotransmitters which are used to send signals between neurons, the signalling cells in the brain and nervous system. The GABA (gamma-aminobutyric acid) hypothesis is less popular but also explored

in this paper due to its connection with the glutamate model as glutamate and GABA neurotransmitters are closely related. These hypotheses are similar in that they involve neurotransmitter receptors and were developed by observing that certain drugs cause schizophrenic symptoms, but differ in the type of neurotransmitter receptor they deem responsible for the illness. There are other neurotransmitter hypotheses, including the serotonin hypothesis, and the acetylcholine hypothesis. The serotonin hypothesis is not examined as there is little to no direct evidence of serotonin receptor or neurotransmitter differences in schizophrenia, save the correlation that drugs affecting serotonin can cause similar symptoms (Yang & Tsai, 2017). The acetylcholine hypothesis was first hypothesised as there is a high rate of smoking—which affects the acetylcholine system—in those with schizophrenia, which has been linked in schizophrenia to a specific gene (alpha-7 nicotinic receptor) (Yang & Tsai, 2017). These theories are not explored in this paper as there is comparatively little evidence to support them compared to the dopamine and glutamate hypotheses.

This essay first explores how the dopamine model plausibly explains positive but not negative symptoms, before an examination of the aspects of schizophrenia explainable by the glutamate model. This is followed by a discussion on how the glutamate hypothesis may only be associated through the GABAergic model, which is explored but dismissed due to evidence suggesting the GABA involvement in schizophrenia is caused by glutamate dysfunction. This essay ultimately argues that the strongest explanatory approach for schizophrenia is a combination of the dopamine and glutamate (and GABA) models, due to evidence that suggests NMDA (glutamate) receptors affect dopamine and GABA.

The dopamine hypothesis explains positive but not negative symptoms

The dopamine hypothesis was the first suggested neurotransmitter model. It proposes that excess sensitivity to dopamine in patients with schizophrenia results in positive symptoms and thus the disorder. Dopamine is an inhibitory and excitatory neurotransmitter that works by being released from a neuron into a synapse (gap between neurons), where it is received by the post-synaptic neuron by one of five main receptors on the neuron's surface; D1, D2, D3, D4, and D5 (Eisenstein et al., 2017). D2 receptors are the specific dopamine receptor implicated with schizophrenia, as they have an association with symptom-causing drugs. Indeed, the dopamine hypothesis was first postulated after it was observed that amphetamines, which are dopamine agonists—drugs that cause the receptor to act as though there is an increase in neurotransmitter—caused positive schizophrenic symptoms in non-schizophrenic drug abusers. This evidence demonstrates how a flaw in the dopamine neurotransmitter system, through excess sensitivity to dopamine, can affect the system and thus result in the symptoms displayed in schizophrenia (Toda & Abi-Dargham, 2007).

An additional argument for the dopamine hypothesis is the evidence for the involvement of D2 receptors in antipsychotics: drugs used to reduce symptoms and attacks in those with schizophrenia. Studies on antipsychotics have found that all effective antipsychotics produced until 2007 work via antagonism of D2 receptors; antagonism causes the receptor to act as though there is a decrease in neurotransmitter (Toda & Abi-Dargham, 2007). In a study of 498 schizophrenic participants, self-reported symptom reduction across all dopamine-targeting antipsychotic drugs was approximately 60 per cent, showing that there is a correlation between dopamine antagonism and improved schizophrenic symptoms (Kahn et al., 2018). Furthermore, psychostimulant drugs specifically targeting D2 receptors in doses that were low enough to produce no reported change in healthy controls, were found to produce worse symptoms in actively schizophrenic patients. Of the schizophrenic patients, sufferers who were more likely to relapse were also affected more by the same low amount of psychostimulant drugs. Patients who were less likely to relapse were less affected by this low dose of psychostimulants (Kahn et al., 2018; Toda & Abi-Dargham, 2007). Therefore, the unique D2 receptor brain chemistry in patients correlates to the severity of symptoms and likelihood of relapse. These findings imply that D2 receptors have a causal role in schizophrenia, as manipulating them can increase or decrease positive schizophrenia symptoms.

The characteristic amount of D2 receptors in specific brain areas, and the positive correlation between receptor numbers and the strength of positive symptoms is another argument for the involvement of

dopamine in schizophrenia. In the brain, schizophrenic patients have significant differences in the number of D2 receptors compared to healthy controls, implying a connection between the receptors (and thus dopamine) and the disorder. It has been found that schizophrenic patients have lower D2 neurotransmitter binding in certain areas of the brain—extrastriatal regions and the thalamus—and multiple studies found that schizophrenic patients had reduced D2 receptors in other brain regions: the thalamus and anterior cingulate cortex (Toda & Abi-Dargham, 2007). Further research found that not only were the number of extrastriatal D2 receptors correlated with patients who had schizophrenia, but there is a relationship between the number of frontal D2 receptors and severity of the disorder: the number of frontal D2 receptors could predict the severity of positive symptoms, showing a direct link between dopamine involvement and schizophrenia (Toda & Abi-Dargham, 2007).

Further evidence also shows that the characteristic levels of D2 receptors function differently in patients with schizophrenia compared to neurotypical patients, which shows how these different receptor numbers act to produce a different effect on the brain. In some brain areas—striatal regions—multiple imaging studies have found an increase of D2 receptors by approximately 12 per cent in untreated chronic and newly onset schizophrenic patients compared to healthy controls (Toda & Abi-Dargham, 2007). These receptors have also been found to be definitively active: one study compared never-medicated schizophrenia patients to healthy controls in an amphetamine challenge, testing the effect on schizophrenic symptoms after administering amphetamine, a psychostimulant. When dopamine transmission was measured, it was found there was dysregulation of dopamine in schizophrenic patients compared to the healthy controls, shown by a dopamine antagonist having increased binding during the challenge in those with the disorder compared to healthy controls. The addition of amphetamine also worsened schizophrenic symptoms, and further this dysfunction was only found in actively schizophrenic patients, not in those in remission (Laruelle, Abi-Darghum, Gil, Kegeles, & Innis, 1999). Overall this evidence shows a direct correlation between unique D2 receptor levels and dopamine dysfunction, which appears to be causing schizophrenic symptoms.

Despite the aforementioned evidence about D2 receptors supporting the dopamine hypothesis—including the correlation between dopamine and positive symptoms, the helpful effects of dopamine-affecting antipsychotics, and unique receptor numbers and D2 activity in those with schizophrenia—there are several unanswered questions, which all concern how dopamine is related to negative symptoms. Studies of both D2 and D3 receptors have reached very different conclusions on whether the receptors are associated with negative symptoms. Thus far, there is no common underlying dopaminergic explanation (Eisenstein et al., 2017). Further, antipsychotic drugs targeting dopamine receptors, though effective, only reduce symptoms by 60 per cent, implying there may be significant symptoms involved in the disorder unexplainable by this hypothesis (Kahn et al., 2018). This suggests that while the dopamine hypothesis can explain and is responsible for producing parts of the disorder, there may be an even larger causal mechanism. This mechanism may be dysregulating the effects of dopamine and its associated receptors, while also producing other effects that can explain schizophrenia-associated negative symptoms. An alternative hypothesis explores how glutamate may be responsible for negative symptoms and disturbing the dopaminergic system, which then results in the dopamine-associated positive symptoms.

The glutamate hypothesis is strongly implicated in schizophrenia

The second major hypothesis explored, the glutamate hypothesis, postulates that glutamate is the sole neurotransmitter with a causal role in schizophrenia. The hypothesis is derived from unique schizophrenic symptoms only associated with glutamate treatments, genetic association with glutamate dysregulation, and glutamate-associated poor sensory abilities, which are hypothesised to cause positive symptoms. Glutamate is the most common excitatory (stimulating) neurotransmitter. It works similarly to dopamine by crossing synapses, and binding to its primary receptor, N-methyl-d-aspartate (NMDA) (Kantrowitz & Javitt, 2012). The glutamate hypothesis of schizophrenia was developed after the observation that two NMDA receptor antagonists, phencyclidine (PCP) and ketamine, caused healthy

patients to develop a range of symptoms associated with schizophrenia from all three of the positive, negative, and cognitive symptom categories. This finding is especially noteworthy as dopamine has only been associated with positive symptoms, as discussed above (Poels et al., 2013).

Many unique features of schizophrenia have been noted to be similar to NMDA receptor antagonism, implying an association between schizophrenia and a systematic glutamate dysregulation. Schizophrenic patients have difficulty learning new things but are easily able to recall this information once learned, which is not observed in healthy patients and those suffering memory conditions. The same symptoms have been noted in NMDA receptor antagonism after administration of PCP and ketamine (Kantrowitz & Javitt, 2012). This shows how NMDA dysfunction may be causing this symptom and thus may be involved in the disorder, as NMDA receptors are located throughout the brain cortex and are linked to uniquely schizophrenic symptoms in areas where dopamine receptors are not present. Thus, this symptom cannot be explained by the dopaminergic hypothesis in isolation, highlighting that the glutamate hypothesis can explain some symptoms the dopamine hypothesis cannot.

Schizophrenic patients display unique auditory defects, including difficulty matching tones, which has now been associated with glutamate and thus provides support for the glutamate model. Research has found that schizophrenic auditory defects have been observed after localised application of NMDA antagonistic drugs into the auditory cortex, but no defects were observed when dopamine and serotonin antagonists were applied. This result implies that this schizophrenic symptom is caused only by NMDA dysfunction and reduces the likelihood of the accuracy of the serotonin and dopamine hypotheses. However, it should also be noted that there was a strong correlation between patients presenting with severe auditory symptoms and having a structurally worse auditory cortex, so NMDA dysfunction may not be the only explanation for reduced hearing abilities in patients with schizophrenia (Leitman et al., 2007). Nonetheless, this association between glutamate and distinctive schizophrenia-associated hearing symptoms supports the likely interpretation of glutamate dysfunction involvement.

Further strong evidence for glutamate involvement in schizophrenia comes in the form of genetic association studies, as multiple genetic mutations in glutamate-associated proteins are highly common in schizophrenia. A gene associated with schizophrenia, Dysbindin, is known to cause cognitive impairment. It has also been found to reduce a subunit—part of the overall protein—of NMDA receptor proteins, thus changing the shape and function of the NMDA receptor. This has been found to result in reduced neuron firing in NMDA receptor–associated neurons, consequently conveying fewer signals around the brain (Kantrowitz & Javitt, 2012). Similarly, polymorphisms—specific mutations in DNA that can cause a change in the protein—have been found in sufferers of schizophrenia in a NMDA receptor subunit, GRIN2B (Kantrowitz & Javitt, 2010). This mutation could possibly cause a change in the utility of the protein, which could cause more or fewer signals to be sent. Furthermore, a particular protein known as DARP-332 has been found to be responsible for regulating NMDA and D1 receptors: dopamine receptors which so far have relatively little evidence for any symptomatic involvement in schizophrenia (Kantrowitz & Javitt, 2012). Post-mortem studies revealed that DARP-332 was under-expressed in schizophrenic patients in some brain areas (superior temporal gyrus and rostral agranular insular cortex). The rostral agranular insular cortex is associated with pain, and people with schizophrenia have reduced pain thresholds, showing that these polymorphic genetic changes are most likely related to the phenotypic expression—observable physical and behavioural characteristics—in people with schizophrenia (Cepeda, André, Jocoy, & Levine, 2009). This evidence that there are three different genes associated with both schizophrenic phenotype and NMDA receptors enforces the likelihood of the glutamate hypothesis.

A theoretical approach to the glutamate hypothesis postulates that large schizophrenic symptoms are based off glutamate dysregulation causing poor sensory discrimination. There is evidence for a link between NMDA receptors and schizophrenia, as the magnocellular visual system—which is responsible for giving basic information on the visual scene—has characteristic schizophrenic deficiencies. This system relies on the retina, which is reliant on NMDA receptors. Application of PCP and ketamine to this area produces similar symptoms to that of schizophrenia in healthy patients (Butler et al., 2005). Psychologists have thus used this auditory and visual evidence to propose a plausible theoretical mechanism on how schizophrenia and its more significant impacts, such as hallucination, occur. This basic NMDA dysfunction is stipulated to cause poor sensory discrimination, which is noted as there is

an auditory correlation between poor tone matching and poor auditory emotion, including sarcasm, and between the aforementioned visual defects, poor identification of objects, processing motion, and reading ability (Doniger, Foxe, Murray, & Javitt, 2002; Kantrowitz & Javitt, 2012). Hence, it is plausible that the poor sensory discrimination that has been found to be due to increased NMDA stimulation can potentially explain the larger hallucinogenic symptoms that may be happening due to a similar mechanism.

The GABA hypothesis contributes to but does not disprove the glutamate model

The glutamate hypothesis has a large potential flaw which must be discussed; the less studied, less plausible GABA hypothesis. Where there is near-indisputable evidence of the involvement of NMDA receptors, the GABAergic hypothesis—based around the neurotransmitter gamma-aminobutyric acid (GABA)—has been proposed and also involves NMDA receptors and glutamate. GABA and glutamate are made in similar pathways but have inverse effects; glutamate is excitatory and thus makes signals more likely to be sent, while GABA is inhibitory, making signals less likely to be sent (Hampe, Mitoma, & Manto, 2017).

The GABA hypothesis predicts that only GABA interneurons—nodes that connect neurons—have faulty NMDA receptors, as opposed to the glutamate hypothesis, which postulates that these changes to NMDA receptors are more widespread (Nakazawaka et al., 2018). This theory also postulates that there are reduced GABA levels and increased glutamate levels in schizophrenic patients, and that the effects noted by the glutamate hypothesis are all due to GABA, not glutamate itself. Followers of both the glutamate and GABA approaches involve and seek to find medicines to affect glutamate and GABA (Nakazawaka et al., 2018), but if the GABA hypothesis is true, treatments could be found that only influence GABA, which may reduce potential side effects. Though there is evidence that GABA is the responsible molecule for some symptoms, MRI and post-mortem studies found no GABA differences in healthy and schizophrenic participants, leading this author to conclude that glutamate is immensely likely to be involved beyond its association with GABA.

There is evidence that GABA may cause at least some symptoms and may be more likely than glutamate to be the main responsible neurotransmitter. For one, schizophrenic patients have reduced parvalbumin cells and GAD67 enzymes. These are both associated with the GABA hypothesis and have been found to cause the same schizophrenic symptoms on a molecular and behavioural basis as noted in rodents, after these rodents' genes were altered to disrupt NMDA receptors only on GABA interneurons. This result shows that at least in this symptom, GABA is needed for schizophrenic functioning, though it does not necessarily follow that these GABA interneurons are the only parts of the system that are responsible. Furthermore, the purpose of GAD67 is to catalyse (make happen) the reaction responsible for turning glutamate to GABA molecules, so glutamate and GABA are closely involved with each other. Thus, the GABA hypothesis postulates that NMDA antagonistic drugs only cause schizophrenic symptoms because they decrease the levels of GABA. Basically, this theory states that there is evidence for glutamate only because glutamate is interlinked with GABA, which the theory asserts is the real underlying mechanism for schizophrenia (Lazarus, Krishan, & Huang, 2013). As GAD67 is expressed in lower quantities in schizophrenia, this does provide evidence that there may be some part of the disorder directly affected by the levels of GABA. Thus, there is an association between GABA and schizophrenia which cannot be answered by the glutamate hypothesis alone.

The GABA hypothesis has not yet been disproved as it is still newly proposed, though recent research monitoring via MRI the levels of glutamate and GABA in an area of the brain—superior temporal gyrus—casts doubt on it. In those with schizophrenia there were increased levels of glutamate compared to controls, which also significantly predicted the severity of auditory hallucinations. The level of GABA, however, was found to be much the same in both healthy and schizophrenic participants and was not significantly associated with either severity or frequency of hallucinations. Though this study only measured one brain region (superior temporal gyrus), this region is one of the main areas associated with schizophrenia and thus it is clear from this study that the GABAergic hypothesis—that GABA is

reduced and glutamate is increased—does not apply at least in this key area (Hjelmervik et al., 2018). This shows that GABA cannot be solely responsible for this disorder.

Post-mortem studies have also revealed the frail nature of the GABA hypothesis. Within another schizophrenia-associated brain area—the prefrontal cortex, which has reduced activity in those with schizophrenia (Callicott, 2000)—certain cells associated with GABA (chandelier cells) have been found to have an unaltered ability to both create and discharge GABA. This makes it less likely therefore that GABA is associated with this change and thus wholly responsible for all of the symptoms associated with the disorder (Hjelmervik et al., 2018).

There is evidence that GABA is involved in schizophrenia to some degree, though most likely not to the extent proposed by the GABA hypothesis. The fact that tampering with GABAergic interneurons mimics schizophrenia, and the implications of reduced GAD67 in schizophrenia patients, indicates distinct GABA involvement beyond its connection with glutamate. However, the results of post-mortem and MRI studies that found no observable difference in GABA in those with schizophrenia suggests that glutamate still contributes to schizophrenia. Thus while the GABA hypothesis is partly correct in that GABA interneurons have some role to play in schizophrenia, this author concludes that the GABA hypothesis does not undermine the glutamate hypothesis as has been suggested.

NMDA abnormalities may cause dopamine and GABA dysfunction

Despite being different models, it is possible that all three hypotheses could work together, with NMDA dysfunction causing dysfunction of dopamine and GABA. This combined model acknowledges that dopamine, GABA, and glutamate all contribute in the causation of the many complicated symptoms of schizophrenia. All the aforementioned evidence shows it is likely that all are involved, which reflects most current approaches stating that multiple neurotransmitter pathways are dysregulated (Field, Walker, & Conn, 2011). However, this common approach does not propose that these multiple hypotheses are ultimately due to dysregulated glutamate causing a cascade of other neurotransmitter dysfunction.

As mentioned above, multiple studies have found that there are differently functioning D2 receptors in actively schizophrenic patients compared to healthy patients and those in remission: the glutamate system may cause this dopamine dysfunction (Laruelle et al., 1999). Evidence for this comes from studies in healthy patients and rodents which have shown the same characteristic dopamine dysfunction after participants were treated with ketamine, which has been associated with the glutamate hypothesis, as it is a NMDA receptor antagonist (Kantrowitz & Javitt, 2012). In research conducted using another NMDA antagonist (CPP) on the prefrontal cortex of rat brains, there was a noted increase in D2 receptors—detected through an increase of D2-associated mRNA, which is comparable to code that makes the D2 receptor—in the striatum. The striatum is the brain region associated with increased D2 receptors in the dopamine hypothesis. This shows a direct causal link between the NMDA receptors affecting the expression of the D2 dopamine receptors that are implicated in schizophrenia. Thus, it appears likely that NMDA receptors increase the production of dopamine receptors, which are then responsible for changes—like positive symptoms—associated with the dopamine hypothesis (Nair, Savelli, & Mishra, 1998). This of course explains how tampering with dopamine can reduce schizophrenia symptoms, while explaining how the dopamine itself is not directly associated with any negative symptoms and dopamine-affecting medications cannot completely eradicate symptoms, as these would be caused by glutamate.

I propose a similar argument that glutamate causes GABA dysregulation, as GABA and glutamate impact each other. GABA shows involvement in the disorder, as without GABA interneurons schizophrenic symptoms occur, and reduced levels of GAD67 show that there are likely warped amounts of GABA in the brain. But due to GABA's link with glutamate, and evidence including definitive glutamate involvement where there is no change in GABA, GABA is likely not to be the

main neurotransmitter responsible. This explains why there are no large-scale GABA defects, as it is likely to be due to its closely linked counterpart, glutamate (Nakazawaka et al., 2018).

The effect of dysregulated glutamate and NMDA receptors provides a plausible mechanism to explain the dysregulation of GABA and dopamine, whereas there is no evidence for the GABA hypothesis and dopamine hypothesis to explain the effects of the other. The intertwining pathways of GABA and glutamate show they are closely linked, and evidence shows they are both most likely involved, though glutamate is involved to a larger extent. The evidence showing dopamine receptors and how symptoms respond to changes in glutamate also provides evidence that the dopamine-associated symptoms are due to glutamate dysregulation. Therefore, this author believes that a combination of the dopamine and glutamate models, postulating that NMDA receptors affect dopamine and GABA, is the strongest theoretical approach.

Issues with this theory primarily lie not with its theoretical components, but with the treatments that it implies. Were glutamate dysregulation to be responsible for these other neurotransmitter dysfunctions, one would think that treating schizophrenia should be as easy as targeting the NMDA pathway. While in principle this would work, there are difficulties targeting the NMDA receptors or their glutamate components due to the widespread nature of these receptors in the body, including the central nervous system (brain, spine), which would cause drastic repercussions if targeted effectively. One such repercussion is excitotoxicity, where neuronal cell death occurs when NMDA receptors do not respond appropriately, so treatments would potentially drastically reduce the number of cells in the brain and spine. Unfortunately, even when NMDA receptor-targeting drugs have been viable for treatment in animals, side effects are severe, most likely due to NMDA receptors being used all over the body. Symptoms have included neuronal death, vomiting, nausea, memory impairment, and reduced functioning of the autonomic nervous system, affecting organs such as the heart, intestines, or bladder (Lynch & Guttmann, 2002).

However, this is not to say that drugs could not one day effectively target the glutamatergic system. As multiple drugs have been developed that impact different areas of the NMDA receptor—including the glutamate site, the glycine site, and the ion channel—these have produced different effects and side effects, meaning the NMDA receptors function variably in their sensitivity to diverse drugs. Therefore, the NMDA receptor could still function as an effective pharmaceutical target if an appropriate drug is developed (Lynch & Guttmann, 2002). Thus, on the postulated basis that NMDA dysregulation is the overarching cause in schizophrenia, this author recommends further research into the NMDA receptor, and developing NMDA receptor-targeted drugs as a priority for schizophrenia treatment.

Conclusion

A model that glutamate dysregulation impacts and causes dopamine and GABA dysfunction in schizophrenia is deemed the most likely model. Overall, the dopamine hypothesis can explain why some drugs like amphetamines cause schizophrenic symptoms and why antipsychotic drugs achieve some level of success through affecting D2 receptors. It also explains the unique pattern of D2 receptors in schizophrenic patients. Further, it explains that increased dopamine dysfunction is observed in actively schizophrenic patients (Toda & Abi-Dargham, 2007). However, it fails to explain schizophrenia's negative and cognitive symptoms, and why antipsychotic medications are only partly effective. The glutamate hypothesis can explain the positive, negative, and cognitive symptoms as these symptoms are recreated in NMDA receptor antagonistic drugs. It can also explain many niche symptoms of schizophrenia not found in any other symptoms for disorders or drug use, and provides many genetic associations, and sound theoretical reasoning on how NMDA dysfunction causes smaller symptoms that then cause larger symptoms and thus schizophrenia. GABA was proposed as a more specific alternative to the NMDA hypothesis, and while evidence shows it is involved, there is definitive glutamate involvement in the absence of GABA (Nakazawaka et al., 2018). Overall however, it is likely that NMDA dysfunction affects both dopamine and GABA. A combination model effectively explains why there is evidence of both glutamate and GABA involvement, and why glutamate changes D2 receptor numbers and replicates symptoms linked to dopamine dysregulation (Kantrowitz & Javitt, 2012).

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