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Imaging-Based Neurochemistry in Schizophrenia: A Systematic Review and Implications for Dysfunctional Long-Term Potentiation

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Cognitive deficits are commonly observed in patients with schizophrenia. Converging lines of evidence suggest that these deficits are associated with impaired long-term potentiation (LTP). In our systematic review, this hypothesis is evaluated using neuroimaging literature focused on proton magnetic resonance spectroscopy, positron emission tomography, and single-photon emission computed tomography. The review provides evidence for abnormal dopaminergic, GABAergic, and glutamatergic neurotransmission in antipsychotic-naive/free patients with schizophrenia compared with healthy controls. The review concludes with a model illustrating how these abnormalities could lead to impaired LTP in patients with schizophrenia and consequently cognitive deficits.

Key words: schizophrenia/long-term potentiation/glutamate/dopamine/GABA/MRS/PET/SPECT

Background

Schizophrenia is a psychiatric disorder that affects 1% of the world population.[1,2] Cognitive deficits such as learning and memory impairments are considered core features of the illness.[3,4] Long-term potentiation (LTP) is a key determinant of learning and memory function[5,6] and may be a key neurophysiological mechanism underlying cognitive impairment in schizophrenia.

LTP is defined as an activity dependent long lasting enhancement in synaptic efficacy.[7] LTP is typically dependent on the glutamatergic *N*-methyl-D-aspartate (NMDA) receptor.[8,9] Glutamate activates NMDA receptors allowing calcium (Ca^{+2}) entry, which in turn acts on calmodulin-dependent protein kinases (CaM Kinases) II and IV and leads to the upregulation of alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptors.[10]

LTP is modulated by the dopaminergic[11] and GABAergic systems.[12,13] Dopaminergic modulation of LTP depends on the type of receptors. Dopamine D_1 receptor activation enhances LTP,[14,15] while dopamine $D_{2/3}$ receptor activation suppresses NMDA activity and GABA activity.[16,17] GABAergic modulation of LTP also depends on the subtype of GABA receptor. Antagonism of $GABA_A$ receptor facilitates LTP.[18] Activation of $GABA_B$ receptor modulates $GABA_A$ receptor through presynaptic autoinhibition of interneurons which facilitates LTP.[19,20]

A number of imaging studies using proton magnetic resonance spectroscopy (^{1}H MRS), positron emission tomography (PET), and single-photon emission computed tomography (SPECT) assessed these systems (glutamatergic, dopaminergic, and GABAergic) in patients. To date, there has been 1 meta-analysis, and 1 review paper on glutamate ^{1}H MRS studies,[21,22] 2 meta-analyses on dopamine PET and SPECT studies,[23,24] and 1 narrative review on imaging studies assessing dopamine, serotonin, GABA, and glutamate systems in schizophrenia.[25] This last review was performed more than a decade ago and included patient with and without exposure to antipsychotic treatment. Thus, our aim was to perform a systematic review on imaging studies assessing these 3 neurotransmitter systems, focusing only on antipsychotic-naive or antipsychotic-free patients with schizophrenia. Assessing this subgroup helps to disentangle

changes in neurochemistry related to illness compared to changes related to medications. Differences between medicated and unmedicated patients are also highlighted throughout the review only for comparison purposes. Lastly, we present a model linking these systems to abnormal LTP and cognitive deficits associated with schizophrenia.

Methods

A literature search was performed on November 18, 2013 using PubMed with no date limits and the following terms were used: schizo* AND drug naiv* OR antipsychotic naiv* OR untreat* OR unmedicat* OR never treat* OR neuroleptic free OR antipsychotic free OR first episod* AND glutamate OR GABA OR dopamine. The inclusion criteria were determined a priori and were (1) in vivo human studies, (2) imaging studies, and (3) studies including antipsychotic-free and/or antipsychotic-naive patients with schizophrenia or schizoaffective disorder. In total, 2383 publications were identified. Articles were excluded after reviewing titles and abstracts, leaving 63 studies. Considering there was only one study for GABA, we summarized the characteristics and findings of each study into 2 separate tables: for dopamine and glutamate (See supplementary tables 1 and 2).

Results

Our search identified 16 studies on the glutamatergic system, 44 studies on the dopaminergic system, and 3 studies on the GABAergic system.

Glutamatergic System

Several ^{1}H MRS studies and one SPECT study demonstrated altered glutamatergic activity in antipsychotic-naive or antipsychotic-free patients. Changes were reported in the concentrations of glutamate, glutamine, a precursor of glutamate[26] and/or GLX, a combination of both. We summarize the findings below and have chosen to divide these findings based on various regions of the brain due to intrinsic variations that exist in the healthy brain.[27]

Medial Prefrontal Cortex. Two studies assessed glutamatergic activity in the medial prefrontal cortex (MPFC) of antipsychotic-free/naive patients with schizophrenia compared with healthy controls. One of these studies reported a 30% increase in GLX levels of 9 antipsychotic-naive and 7 antipsychotic-free patients (M = 11, F = 5) (mean age: 32 years) compared with 22 healthy controls (M = 14, F = 8) and 16 medicated patients (M = 11, F = 5).[28] The authors proposed that antipsychotics may have normalized GLX levels in the MPFC of medicated patients. Elevated GLX levels are also evident in the right MPFC of 20 adolescents (M = 7, F = 13) (mean age: 16.4 years), who are at high-risk for developing schizophrenia by having a parent with schizophrenia.[29] Since glutamine concentration is 40%–60% lower than that of glutamate,[30,31] it can be inferred that elevated GLX levels mostly reflect elevated glutamate concentrations.[32,33] These findings suggest that high-risk adolescents and young patients with schizophrenia have elevated levels of glutamate in the MPFC early in the illness. However, a study assessing both glutamine and glutamate levels independently reported an increase in only glutamine levels in the MPFC of 10 antipsychotic-naive patients (M = 8, F = 2).[34] The authors concluded that schizophrenia may be associated with an abnormal conversion of glutamine to glutamate, resulting in elevated glutamine levels.[34] Alternatively, this finding may be explained by experimental limitations. To accurately measure glutamate and glutamine levels separately, specialized ^{1}H MRS techniques (eg, high-magnetic field (>3 T) with short echo and long acquisition time) or editing techniques (eg, J-editing) are necessary due to glutamine and glutamate's analogous signals.[35–37] In this study, a 1.5 T magnetic field without editing techniques was used, which could be unreliable in distinguishing peaks arising from glutamine and glutamate independently, potentially confounding the results. While glutamine level in antipsychotic-free/naive patients might be still elusive, a meta-analysis including medicated and unmedicated patients indicated that glutamine is higher in patients than healthy controls.[21]

In contrast, a study comparing glutamate levels in the MPFC of older 12 patients with schizophrenia (M = 7, F = 5) (medication status unknown; mean age: 49.5 years) and their unaffected twin with healthy controls (M = 12, F = 9) found that both patients and their unaffected twins had decreased glutamate levels.[38] Taken together, these studies suggest that patients have elevated glutamate levels in the MPFC early in their illness but then experience a decline in glutamate concentrations as they age. This age-related change in glutamate levels in schizophrenia was shown by a recent meta-analysis describing a drop below healthy controls after the age of 35. Since some of the studies included in this meta-analysis include medicated patients, medication effects cannot be ruled out and therefore little is known about glutamate changes over the course of the illness in unmediated patients.[21]

Dorsolateral Prefrontal Cortex. Four studies assessed the dorsolateral prefrontal cortex (DLPFC) of antipsychotic-free/naive patients compared with healthy controls. A study using a 3 T MRS found no difference in GLX levels in the DLPFC of antipsychotic-free patients (M = 11, F = 5).[28] This finding is in line with other studies that reported similar results in antipsychotic-naive

patients,[39–41] high-risk individuals,[42] and childhood-onset patients.[43] However, a study that assessed 23 chronic antipsychotic-free patients using 1.5 T MRS found significantly greater combination of glutamate and GABA levels in patients than healthy controls.[44] Inconsistent results may be explained by the differences in acquisition and analysis techniques employed in these studies. In contrast, decrease in GLX levels were noted when 20 chronic medicated patients (M = 14, F = 6) were compared with 20 healthy controls (M = 13, F = 7),[41] suggesting either an aging or chronicity (including chronic exposure to antipsychotics) effect. As such, further studies using more specific ^{1}H MRS acquisition and quantification techniques are required.

Thalamus. Three different studies comparing antipsychotic-naive patients with healthy controls reported elevated glutamine levels in the thalamus of patients.[45–47] The first study assessed 21 antipsychotic-naive patients (M = 14, F = 7) and reported elevated glutamine levels in the left thalamus.[45] In contrast, a follow-up study conducted in 21 chronic medicated patients with schizophrenia (M = 20, F = 1) detected reduced glutamine levels in the left thalamus of patients.[48] This finding was replicated and extended in a cohort of 16 antipsychotic-naive patients (M = 14, F = 2), which included 12 patients from the earlier study.[46] Baseline glutamine levels in the left thalamus remained elevated until 30 months of antipsychotic treatment.[46] Another study also found high glutamine levels in antipsychotic-naive patients (M = 14, F = 3), which decreased over 80 months.[47] These findings may suggest an aging or treatment effect. In contrast, another study detected no difference in glutamine/glutamate (Gln/Glu) ratio between 14 (M = 12, F = 2) minimally treated patients and 10 healthy controls (M = 12, F = 2).[49] Medication effects could have played a role in this inconsistent finding, since these patients had some, albeit minimal exposure to antipsychotics, lasting less than 3 weeks. On the other hand, glutamate levels were found to be decreased in the thalamus of 27 high-risk adolescents (M = 14, F = 13).[50] However, recently Tandon et al (2013) reported increased GLX in the thalamus of 23 high-risk adolescents (M = 10, F = 13).[51]

These findings support a dysfunctional glutamate-glutamine cycle in the brains of patients. It is postulated that an abnormal conversion of glutamine to glutamate would result in high glutamine and low glutamate levels, consistent with the majority of the above-mentioned findings.

Basal Ganglia. Two studies assessed the basal ganglia (BG) in antipsychotic-naive/free patients compared to healthy controls. A study looking at the precommissural dorsal caudate (PCDC) of 14 antipsychotic-free patients detected elevated glutamate/creatine (Glu/Cr) ratio, suggesting elevated glutamate levels.[52] Another study that assessed the PCDC of first episodes antipsychotic-free (N = 18) (M = 10, F = 8) and ultra-high risk for psychosis patients (N = 18) (M = 14, F = 4) detected elevated glutamate levels in both groups.[53] A longitudinal study of 24 antipsychotic-naive patients (M = 13, F = 11) reported elevated glutamate in the PCDC of patients.[54] This study also showed that after 4 weeks of exposure to antipsychotics, glutamate levels in PCDC decreased to similar levels as controls. The same group followed 19 ultra-high-risk subjects for 2 years and showed that transition to psychosis was associated with higher glutamate levels in the PCDC. Another study including 23 ultra-high-risk subjects (M = 13, F = 10) reported increases in GLX in the caudate nucleus.[51] When 40 high-risk adolescents were assessed, a gender effect was noted, that is elevated glutamate and GLX levels was detected in the BG of only male adolescents (N = 18).[55] Overall, these results suggest that high glutamate and GLX levels in the BG precede the onset of schizophrenia, predict the onset of the first episode of psychosis, and remain elevated until patients are treated with antipsychotics.

Anterior Cingulate. Three publications reported increased glutamine levels in the anterior cingulate of high-risk adolescents (mean age: 16) or antipsychotic-naive first-episode patients (mean age: 21).[29,45,50] In contrast, a study assessing the anterior cingulate of 17 antipsychotic-naive patients found no difference in glutamate or glutamine levels.[47] Another group reported increased Gln/Glu ratio but did not find elevated glutamine levels in the anterior cingulate of 14 minimally treated patients (M = 12, F = 2) (mean age: 27).[49] A study assessing chronic medicated patients found decreased glutamate and glutamine levels in the anterior cingulate of patients.[46] Overall, these findings suggest that the levels of glutamine and glutamate are abnormal in the anterior cingulate of high-risk adolescents and first-episode antipsychotic-naive patients. Such findings suggest that the glutamate-glutamine cycle may be dysfunctional in anterior cingulate, resulting in excessive glutamine levels that decline as the disease progresses. The reason for the decline in glutamine level is still elusive.

Occipital, Parietal, and Hippocampal Regions. Several imaging studies have focused on glutamatergic activity in the occipital, parietal, and temporal regions of antipsychotic-naive or antipsychotic-free patients. A study looking at the hippocampus of 10 male patients (7 antipsychotic-free and 3 antipsychotic medicated) found elevated GLX/Cho levels in patients.[56] It is important to note that although in this study GLX is a combination of glutamate, glutamine, and GABA, the contribution of GABA and glutamine are almost negligible. A recent study assessing 27 patients (M = 20, F = 7) (11 antipsychotic-naive and 16 antipsychotic-free) found elevated GLX in the hippocampus of patients compared with healthy controls.[57] In contrast, no

differences in glutamate or glutamine were found in studies that assessed the medial temporal lobes of 11 antipsychotic-naive patients (M = 9, F = 2),[58] or glutamate in 14 twins discordant for schizophrenia..[38] It is important to note that the first study used a higher MRS field strength (3 T) and a larger sample size compared to the second study. No difference in GLX levels were reported when assessing the temporal gyri of 28 youths with childhood-onset schizophrenia (M = 15, F = 13).[43] Also, one study found elevated GLX levels in the inferior parietal lobe of only high-risk male adolescents (M = 18, F = 22).[55] In keeping with the glutamatergic dysfunction hypothesis, one SPECT study found reduced NMDA binding in the medial temporal lobe of antipsychotic-free patients, but not in antipsychotic medicated patients compared to healthy controls, suggesting that antipsychotic medication may have a normalizing effect.[59] Taken together, these studies suggest increased glutamatergic activity in the occipital and parietal region and in the medial temporal lobes of antipsychotic-naive or antipsychotic-free patients when compared with healthy controls.

Cerebellum. When assessing the cerebellum, 2 studies did not find difference in glutamatergic levels and 1 reported increased glutamate and GLX. The first negative study included first-episode antipsychotic-free patient and looked at the Glu/Cr ratio.[52] The second negative study included 18 antipsychotic-naive patients (M = 14, F = 4) and 18 patients with ultra-high risk for psychosis (M = 14, F = 4).[53] In contrast, a third study, which included only 24 antipsychotic-naive first-episode patients (M = 13, F = 11), reported increased glutamate and GLX levels. Interestingly, glutamate levels normalized after 4 weeks of antipsychotic treatment and GLX remained increased.[54] Glutamine could not be quantified to understand its contribution in the GLX signal.

Summary of Glutamatergic System Findings. The above sections evaluated studies that assessed glutamate, glutamine, or GLX levels in the brains of antipsychotic-free or antipsychotic-naive patients with schizophrenia and patients at high-risk of psychosis compared with healthy controls. Overall, our findings revealed the following: elevated GLX levels in the MPFC, parietal, anterior cingulate, thalamus, BG, and occipital region; elevated glutamine levels in the MPFC, thalamus, and anterior cingulate; elevated glutamate levels in the BG; decreased glutamate levels in the thalamus; and no differences or uncertainty in glutamatergic metabolites in the DLPFC and temporal and cerebellum regions. These results support the notion that the pathophysiology of schizophrenia may stem from dysfunctional glutamate and glutamine neurotransmission.

Dopaminergic System

Several PET and SPECT imaging studies assessed dopamine levels and receptors in different regions of the brains of antipsychotic-naive and antipsychotic-free patients with schizophrenia. This section will review the literature pertaining to abnormalities in the dopamine D_1 and $D_{2/3}$ receptors, because these dopamine receptors are highly relevant to LTP modulation,[60–62] as well as, dopamine synthesis, and release.

Dopamine D_1 Receptor Studies Four studies assessed dopamine D_1 receptor binding in the prefrontal cortex of patients. One of these studies using the PET radiotracer [^{11}C]-NNC112 reported greater dopamine D_1 receptor binding in 7 antipsychotic-naive and 9 antipsychotic-free patients (M = 13, F = 3).[63] In a follow-up study, an elevation in dopamine D_1 receptor binding was detected in the prefrontal cortex of only antipsychotic-naive patients (*N* = 12) (M = 5, F = 7), and not in that of antipsychotic-free patients (*N* = 13) (M = 11, F = 2) when compared with healthy controls (*N* = 24).[64] On the contrary, studies using the radiotracer [^{11}C]-SCH23390 reported decreased[65] or no change[66] in the dopamine D_1 receptor binding in the prefrontal cortex of antipsychotic-naive or antipsychotic-free patients. Discrepancies between studies might be accounted for by differences in demographic, clinical characteristics, previous antipsychotic exposure, and PET radiotracers ([^{11}C]-NNC112 vs [^{11}C]-SCH23390). Dopamine depletion studies in rodents showed increased [^{11}C]-NNC112 binding and decreased [^{11}C]-SCH23390 binding,[67] indicating opposite sensitivity for dopamine levels. In addition, 5-HT2A binding was shown to contribute to the cortical binding of both radiotracers in nonhuman primates[68] and in humans for [^{11}C]-NNC112 only.[69] As such, these limitations should be taken into consideration when evaluating the aforementioned studies. Regarding other brain regions, no difference in dopamine D_1 binding was found in the striatal, limbic, and thalamic regions when patients were compared with healthy controls.[63–65] Taken together, these results illustrate inconsistent differences in dopamine D_1 receptor binding in the DLPFC and no difference in D_1 receptor binding in the striatum, limbic, and thalamic regions of antipsychotic-naive/antipsychotic-free patient.

Dopamine $D_{2/3}$ Receptor Studies. Striatum and Substantia Nigra Studies Without Pharmacological Challenges Fourteen publications assessing dopamine $D_{2/3}$ receptor binding reported no difference between patients and healthy controls in the striatum.[65,70–85] In contrast, one study reported reduced $D_{2/3}$ binding in 23 acutely ill patients (M = 19; F = 4) compared with healthy controls.[86] In the above-mentioned studies, patients had in general mild to moderate symptoms. The mean scores on the Positive and Negative Symptom Scale (PANSS) positive subscale ranged from 18 to 21.9 and on the Brief

Psychiatric Rating Scale (BPRS) ranged from 28.8 to 60. One exception was a study in which patients had a mean PANSS positive subscale score of 30.92.[75] In contrast, the publication showing reduced $D_{2/3}$ binding in patients included patients with severe symptoms (PANSS positive score = 21.9; PANSS general score = 60.4; BPRS score = 73.6).[86] As such, lower dopamine $D_{2/3}$ receptor binding may be a result of greater endogenous dopamine concentrations which compete with the $D_{2/3}$ receptor ligand, resulting in reduced $D_{2/3}$ binding.[87] Thus, given that there is an inverse correlation between severity of psychosis and $D_{2/3}$ binding potential,[88] the differences in severity of patients' symptoms may account for the differences detected in $D_{2/3}$ binding among these studies.

On the contrary, 3 studies reported increased $D_{2/3}$ receptors binding in the striatal region.[89–92] Corripio et al (2011) found that $D_{2/3}$ striatal/frontal binding ratio was increased in 25 first-episode antipsychotic-naive patients (compared with 12 healthy controls and 12 patients with a psychotic disorder different to schizophrenia) using ^{123}I-IBZM SPECT.[90] Increased $D_{2/3}$ receptor binding was also reported in 11 patients (M = 6, F = 5) compared with 18 healthy controls (M = 10, F = 8) using ^{123}I-IBZM SPECT.[91] This finding is in line with an earlier study that reported increased $D_{2/3}$ receptor striatal binding in 25 antipsychotic-naive and antipsychotic-free chronic patients (M = 17, F = 8).[92] Notwithstanding, a meta-analysis by Laruelle reported approximately 12% elevation in D2/3 receptor binding in antipsychotic-free patients with schizophrenia compared to healthy controls.[24]

Studies that assessed the caudate or putamen independently reported inconsistent findings that seemed to be influenced by the radiotracer. For instance, when [^{11}C]-raclopride was used to separately assess the caudate and putamen of 18 antipsychotic-naive patients (M = 10, F = 8), elevation in $D_{2/3}$ receptor binding was not detected.[80] In contrast, 2 other studies that used [^{11}C]-methylspiperone reported greater $D_{2/3}$ receptor binding in the caudate nucleus of 10 antipsychotic-naive and antipsychotic-free patients (M = 8, F = 2)[93] and 22 antipsychotic-naive patients (M = 13, F = 9).[94] The radiotracer[^{11}C]-methylspiperone has been shown to be less sensitive to endogenous dopamine and binds to dopamine D_4 receptors unlike [^{11}C]-raclopride.[95,96] Therefore, considering that [^{11}C]-raclopride and [^{11}C]-methylspiperone have different pharmacological properties, it may be difficult to compare results obtained with these 2 radiotracers. Nevertheless, a study comparing antipsychotic-free (N = 16) (M = 13, F = 3) and antipsychotic-naive patients (N = 12) (M = 5, F = 7) detected no difference in $D_{2/3}$ receptor binding in the striatum between the 2 groups of patients.[97]

Lastly, 3 studies employing the dopamine $D_{2/3}$ receptor high affinity radiotracers [^{123}I]epidepride (SPECT)[98] and [^{18}F]fallypride (PET)[79] and the agonist [^{11}C]-(+)-PHNO[81] assessed the substantia nigra and reported inconsistent results. The study employing [^{123}I]epidepride detected decreased $D_{2/3}$ receptor binding, the study employing [^{18}F] fallypride detected greater $D_{2/3}$ receptor binding, and the study employing [^{11}C]-(+)-PHNO did not find any difference in antipsychotic-free patients with schizophrenia in comparison with controls. The reason for the discrepancy in results is still elusive and could be due to differences in the radiotracers employed and/or differences in the characteristics of the clinical population. Thus, the majority of the present results reveal no difference in $D_{2/3}$ receptor binding in the striatum, however a meta-analysis reported an elevation in D2 receptors[24] and the results in the substantia nigra require further exploration.

Studies Assessing Dopamine Synthesis Capacity In addition to changes in $D_{2/3}$ receptor, several PET studies performed on antipsychotic-naive and antipsychotic-free patients reported increased dopamine synthesis capacity in the striatum. Three studies found greater dopamine synthesis in the caudate nucleus and putamen of patients.[99–101] Specifically, Nozaki et al found significantly greater dopamine synthesis in only the left caudate of 14 antipsychotic-naive and 4 antipsychotic-free patients who were 3-month antipsychotic-free (M = 10, F = 3). Another study revealed increased dopamine synthesis in the striatum of 8 male antipsychotic-free/antipsychotic-naive patients (N = 3 antipsychotic-naive and N = 5 antipsychotic-free for at least 6 months).[102] This difference was nearly 2-fold, the greatest biochemical difference reported to date. In contrast, one study found no difference between 6 untreated male patients (2 antipsychotic-naive) and 7 male healthy controls.[103] Contradictory findings may be explained by age, type of schizophrenia, and gender, as patients in this study were generally younger (mean age: 26 years), more catatonic compared with the other studies (30+ years), and consisted exclusively of male patients. Comparable results were also evident in the high-risk individuals (N = 30) (M = 17, F = 13)[104] and dopamine synthesis in these individuals determined their clinical outcome 3 years later. The psychotic transition group (N = 9) had greater dopamine synthesis in the striatum (effect size = 1.18) compared with the healthy control (N = 29) (M = 20, F = 9) and the nontransition group (N = 15). This finding is consistent with another study that reported elevated dopamine levels in the striatum of high-risk individuals.[105] One study reported significantly higher dopamine synthesis in only the putamen, with no difference found in the caudate.[106] Overall, the evidence shows that patients with schizophrenia and individuals at high-risk for psychosis have increased dopamine release in the striatum and may be related to the illness severity.

Studies Under Dopamine Release Conditions To study dopamine release, investigators used the amphetamine-challenge method, as amphetamine has been shown to be linked to psychosis.[107] These studies reported elevated dopamine release in the striatum of antipsychotic-free

patients[71,108,109] and a sample of antipsychotic-naive and antipsychotic-free patients.[76] Overall, these results illustrate increased dopamine release in patients with schizophrenia.

Studies Under Dopamine Depletion Conditions To investigate indirectly the dopamine levels at the synaptic cleft, a few studies have used alpha-methyl-para-tyrosine (AMPT) to inhibit transiently the synthesis of dopamine. The first study compared 18 antipsychotic-naive and antipsychotic-free patients (M = 11, F = 7) to 18 healthy controls (M = 11, F = 7).[72] They demonstrated that patients have greater amounts of dopamine occupying the $D_{2/3}$ receptors in the striatum. In a follow-up study, the same group assessed only 6 antipsychotic-naive patients (M = 2, F = 4) with schizophrenia and demonstrated greater increase in dopamine $D_{2/3}$ binding in the striatum, suggesting greater dopamine levels at the synaptic cleft in the striatum compared to 8 healthy controls (M = 6, F = 2).[110]

Furthermore, another study that used [^{11}C]-raclopride after dopamine depletion with AMPT found greater $D_{2/3}$ receptor binding in the PCDC of 18 antipsychotic-naive and antipsychotic-free patients (M = 13, F = 5).[111] It is important to note that among the 18 patients assessed in this study, 12 were chronically ill and previously medicated.

In summary, based on the presented evidence, antipsychotic-naive and antipsychotic-free patients with schizophrenia present increased dopamine synthesis capacity, release after amphetamine challenge, and baseline dopamine levels in the striatum after dopamine depletion.

Thalamus Nine studies assessed the thalamus, one of these studies using [^{18}F]fallypride PET found increase binding in 6 antipsychotic-naive and 12 antipsychotic-free (M = 14, F = 7).[78] Another study using the same technique assessing 15 antipsychotic-naive patients (M = 10, F = 5), however, reported reduced $D_{2/3}$ receptor binding, with the greatest difference in the left medial dorsal nucleus and left pulvinar.[112] Several other studies also reported decreased $D_{2/3}$ receptor binding in the thalamus.[74,79,110,111] Talvik et al demonstrated decreased $D_{2/3}$ receptor binding in the right medial thalamus[113]; Yasuno et al., in the central medial[114] and posterior subregion of the thalamus; and Kessler et al, in the left medial thalamus.[79] A later study by Talvik and colleagues confirmed their earlier findings by demonstrating lower $D_{2/3}$ receptor binding in the right thalamus of patients compared with healthy controls, but they detected no difference in the left thalamus.[74] In contrast, 4 studies found no overall difference in $D_{2/3}$ receptor binding in the thalamus.[81,98,115,116] One assessed only 11 antipsychotic-naive male patients using [^{11}C]FLB 457 PET[115] and the other assessed 25 antipsychotic-naive patients (M = 2, F = 4) using ^{123}I-epidepride SPECT, the largest sample to date.[116] Although most of the evidence suggests reduced $D_{2/3}$ receptor binding in the thalamus of patients with schizophrenia, the only study that performed partial volume correction found increased D2/3 binding in this region.[78] As such, inconsistency in findings for the thalamus warrants further studies.

Temporal, Limbic, and Frontal Regions Studies comparing $D_{2/3}$ receptor binding between patients and healthy controls found patients had equal amounts of $D_{2/3}$ receptors in the limbic, sensorimotor, temporal, and frontal regions.[78,79,113] In contrast, a study specifically assessing the amygdala, cingulate gyrus, and temporal cortices reported reduced $D_{2/3}$ receptor binding in these regions.[112] Furthermore, a study that assessed the anterior cingulate of 11 antipsychotic-naive male patients reported a 12.5 % reduction in $D_{2/3}$ binding in patients.[115] As such, discrepancies may be attributed to sample and sex differences.

A study that assessed dopaminergic synthesis capacity in the limbic and temporal regions reported elevated dopamine levels.[102] In this study, a 50% increase in FDOPA clearance was detected in the amygdala of 8 male patients.[102] Greater dopamine synthesis capacity was also detected in the MPFC of 12 patients (M = 12, F = 2).[101] Thus, although further investigations are needed, preliminary results demonstrate reduced $D_{2/3}$ receptor binding and potentially elevated dopaminergic synthesis capacity in temporal and limbic regions of patients with schizophrenia compared with healthy controls.

In conclusion, evidence revealed no difference in $D_{2/3}$ receptor binding, increased dopamine synthesis capacity, increased dopamine release, increased dopamine occupying the $D_{2/3}$ receptors in the striatum, reduced $D_{2/3}$ receptor binding in the thalamus, and potentially increased dopamine synthesis capacity in the temporal and limbic regions. Inconsistent results were reported in the anterior cingulate and substantia nigra. The findings pertaining to D_1 receptor binding were inconsistent and further studies are needed to clarify inconclusive results.

GABAergic System

Presently, only one study has compared GABA levels independently between antipsychotic-free patients and healthy controls. The study reported elevated GABA concentrations in MPFC of 32 patients (M = 11, F = 5).[28] This study, albeit preliminary, suggests the involvement of the GABAergic anomalies in schizophrenia. MRS studies assessing medicated patients compared with healthy controls reported increased GABA/Cr in the medial frontal and parieto-occipital regions,[117] reduced GABA/Cr concentrations in the left BG but no difference in the frontal or occipital-parietal regions of early-stage patients with schizophrenia,[118] lower GABA/Cr levels in the occipital region of patients,[119] but no difference from the medial prefrontal and left BG,[120] and increased GABA/Cr in medial frontal and parieto-occipital regions.[121] Furthermore, as suggested by a recent study, GABA levels were elevated in younger patients compared with older

patients with schizophrenia, suggesting an association between the stage of illness and GABA levels.[122]

Discussion

A number of studies revealed abnormalities in the glutamatergic system in antipsychotic-naive or antipsychotic-free patients with schizophrenia. In brief, studies focusing on the glutamatergic system demonstrated that among individuals at high risk for psychosis or during the first-episode of schizophrenia, GLX, glutamine, and glutamate levels are elevated in most regions of the brain. In contrast, studies looking at patients who were older than 35 years of age or labeled as chronic showed low GLX levels, which may be a medication effect. In addition, one study reported decreased NMDA binding in the hippocampus of antipsychotic-free patients.[59]

Studies focusing on the dopaminergic system demonstrated a decrease in the dopamine $D_{2/3}$ receptor binding in the thalamus, an increase in dopamine synthesis capacity in the striatum, enhanced dopamine release, and increased dopamine at baseline. Lastly, one study reported elevation of GABA levels in MPFC of antipsychotic-free patients. Below we describe a model that could explain these various findings.

It has been proposed that at the onset of the disorder, hypofunctioning NMDA receptors on GABAergic interneurons lead to excessive release of glutamate from pyramidal neurons.[123] Excessive glutamate levels lead to excitotoxicity-mediated neuronal death.[124] As a precursor for glutamine, some of the glutamate is converted to glutamine within astrocytes[125] and result in high levels glutamine as demonstrated by in vivo imaging studies. Elevated glutamate levels may also over stimulate dopaminergic neurons resulting in high levels of dopamine, as suggested by striatal studies and yet to be confirmed in the cortex.[126,127] Further, given that glutamate is a precursor to GABA and that the current literature suggests high levels of GABA early in the course of the illness, our model proposes that high levels of GABA are driven by high levels of glutamate and that glutamate-to-GABA conversion is intact. Another possible scenario is that excessive glutamatergic activity stimulates interneurons to release more GABA. Finally, elevated GABA levels could be independent of high glutamate levels as they could reflect abnormal GABA reuptake by transporters. This finding is supported by postmortem studies that reported reduced presynaptic GAT1 transporters found in patients lead to increased GABAergic transmission at the synapse due to diminished reuptake.[128] As a compensatory measure, postsynaptic $GABA_A$ receptors are upregulated, followed by the downregulation of GAD67 and parvalbumin-positive interneurons,[13,117,129,130] eventually leading to reduced GABAergic activity. Irrespective of the underlying mechanism, high levels of GABA could be contributing to the relative stability of the excitation-inhibition system.

Dopamine effect on LTP facilitation depends on the concentration and activated subreceptors. Dopaminergic receptors are in close proximity to glutamatergic receptors and appear to have a major role in synaptic modulation, by affecting the phosphorylation of glutamatergic NMDA and AMPA receptors (figures 1 and 2).[131] The relationship between dopamine levels and LTP facilitation is reported as an inverted "U" shape dose-response curve.[132,133] Low levels of dopamine preferentially activate presynaptic $D_{2/3}$ receptors, which reduces the release of dopamine and essentially LTP facilitation. On the other hand, high levels equally activate postsynaptic D_1 and $D_{2/3}$ receptors, counteracting each other's effect. However, at optimal dopamine levels, D_1 postsynaptic receptors are stimulated and LTP facilitated. That is, insufficient or excessive dopamine levels impair LTP facilitation and optimal facilitation is achieved at moderate concentrations. Thus, high levels of dopamine in the striatum and potentially in the cortex of patients with schizophrenia likely result in impaired LTP because excessive dopamine may lead to the upregulation of the $D_{2/3}$ receptors[134] or the functional sensitization of the $D_{2/3}$ receptors.[135] Presynaptic $D_{2/3}$ receptors on interneurons enable LTP facilitation by suppressing GABAergic inhibition on pyramidal neurons.[60] Low levels of dopamine in the cortex can also result in impaired LTP. When $D_{2/3}$ receptors are hypofunctioning, understimulated pyramidal neurons are not sufficiently suppressed, thereby leading to excessive excitation. When D_1 receptors are stimulated, LTP activity is facilitated and resting glutamatergic neurons increase their production of neurotransmitters and receptors by stimulating the CAMP/protein-kinase

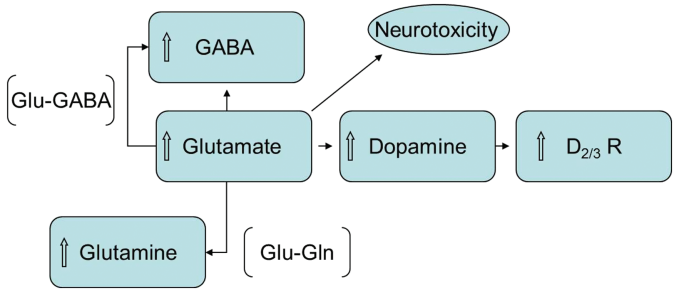

Fig. 1. Hypoactive NMDA receptor causes downstream hyperglutamatergic activity, which leads to the conversion of glutamate to glutamine by the enzyme glutaminase, as such increasing glutamine levels.[130] Glutamine is a molecule which cannot exert neurotoxic effects.[148] To balance out excitatory activity with inhibitory activity, glutamate is converted into GABA, the main inhibitory neurotransmitter. Extracellular dopamine is regulated by NMDA receptors located on the dopaminergic neuron. Hypoactive NMDA receptors on cortico-brainstem pathway reduce inhibition of tonic dopamine neurons of the mesocortical pathway, which leads to increase in DA release.[130,149] To attenuate the dopamine release, $D_{2/3}$ receptor density is upregulated.

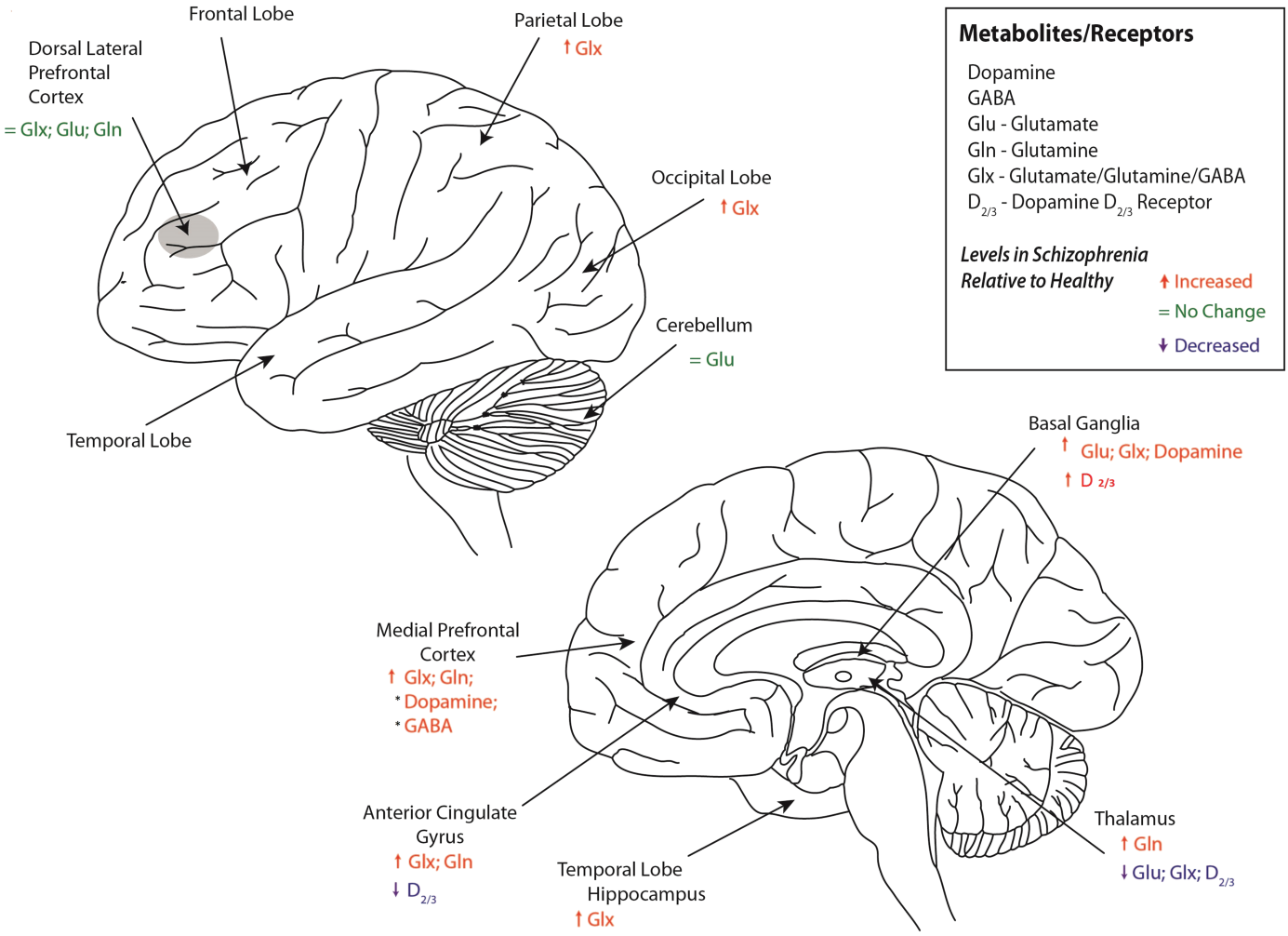

Fig. 2. Neurochemicals and receptors in patients with schizophrenia relative to healthy controls in different brain regions. *Evidence is based on one study.

A pathway.[62,136] As such, dopamine regulates both glutamatergic excitatory and GABAergic inhibitory circuits[137] and the balanced concentration of dopamine and interplay between excitation and inhibition facilitate the induction of LTP.[138] Several studies have demonstrated in vivo evidence for impaired LTP in patients with schizophrenia. Using transcranial direct current stimulation, Hasan et al (2011) showed that multiepisode patients had reduced LTP-like plasticity compared to healthy controls and recent-onset patients.[139] LTP impairments have also been revealed in the motor cortex and DLPFC of patients using paired associative stimulation.[140,141] LTP plasticity was also showed to be impaired in both medicated and unmedicated patients using transcranial magnetic stimulation.[142,143] Lastly, impaired LTP has been demonstrated in the visual cortex using high frequency stimulation.[144]

Limitations

First, discrepancies in findings may be accounted for by the difference in patient population, such as sex. Not all the studies included in this review assessed antipsychotic-naive patients, as some assessed antipsychotic-free; therefore, the effects of antipsychotics cannot be completely discounted, as studies in animals suggest that even minimal exposure to antipsychotics can modulate glutamatergic activity.[12] Second, the interpretations of GABA and GLX measurements present another limitation. The validity of early ^{1}H MRS studies may be less compared with recent studies, which employed better ^{1}H MRS technology including acquisition and quantification that allows the separation of overlapping resonance signals arising from glutamate, glutamine, and GABA. Third, MRS is capable of detecting total concentration of a neurochemical and currently cannot distinguish between intracellular and extracellular glutamate, glutamine, or GABA.[145] However, one study showed a relationship between MRS-derived measures of GABA and glutamate and behavior, suggesting that what is measured by MRS is associated with neurotransmission.[146] Fourth, discrepancies among PET studies may have resulted from the differences in the selectivity and affinity of the

radiotracers used. For instance, [^{11}C]-*N*-methylspiperone binds to $D_{2/3}$ receptors and 5-HT_2 serotonin receptors in vivo and has affinity for dopamine D4 receptors in vitro.[96] The increase in $D_{2/3}$ binding detected with this tracer may include the binding of serotonin receptors, which are not detected using other ligands.[147] Also, not all radioligands have the same affinity for $D_{2/3}$ receptors, presenting a major limitation when comparing one study to another. Lastly, since the sample size in most of the studies was small and heterogeneous, larger homogenous samples are needed to verify such findings. Therefore, future studies using better ^{1}H MRS technology, more selective PET ligands, and large homogenous samples are necessary in order to verify these observations.

Conclusion

LTP is a neuronal mechanism mediating learning and memory. This review presented evidence highlighting abnormal glutamatergic, dopaminergic, and GABAergic systems in antipsychotic-naive and antipsychotic-free patients with schizophrenia. As these systems are essential for LTP facilitation, cognitive impairments associated with schizophrenia may be explained by impaired LTP formation. This proposed model does not negate that these same systems could be mediating other dimensions of schizophrenia, eg, positive and negative symptoms, and not necessarily through LTP impairments. Lastly, it is important to note that medicated patients also experience cognitive deficits and that understanding the neurochemical abnormalities underlying these deficits among these patients could lead to better remediation interventions.

Supplementary Material

Supplementary material (reference 150 is cited in the supplementary material) is available at http://schizophreniabulletin.oxfordjournals.org.

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