Prog Neuropsychopharmacol Biol Psychiatry. Author manuscript; available in PMC 2017 February 23.

Published in final edited form as:

Prog Neuropsychopharmacol Biol Psychiatry. 2016 February 04; 65: 49–53. doi:10.1016/j.pnpbp.2015.08.013

The effect of striatal dopamine depletion on striatal and cortical glutamate: A mini-review

Fernando Caravaggio[a,b], **Shinichiro Nakajima**[a,c], **Eric Plitman**[a,b], **Philip Gerretsen**[a,b,c], **Jun Ku Chung**[a,b], **Yusuke Iwata**[a,b], and **Ariel Graff-Guerrero**[a,b,c,*]

[a]Research Imaging Centre, Centre for Addiction and Mental Health, 250 College Street, Toronto, Ontario M5T 1R8, Canada

[b]Institute of Medical Science, University of Toronto, 2374 Medical Sciences Building, 1 King's College Circle, Toronto, Ontario M5S 1A8, Canada

[c]Department of Psychiatry, University of Toronto, 250 College Street, Toronto, Ontario M5T 1R8, Canada

Abstract

Understanding the interplay between the neurotransmitters dopamine and glutamate in the striatum has become the highlight of several theories of neuropsychiatric illnesses, such as schizophrenia. Using in vivo brain imaging in humans, alterations in dopamine and glutamate concentrations have been observed in several neuropsychiatric disorders. However, it is unclear a priori how alterations in striatal dopamine should modulate glutamate concentrations in the basal ganglia. In this selective mini-review, we examine the consequence of reducing striatal dopamine functioning on glutamate concentrations in the striatum and cortex; regions of interest heavily examined in the human brain imaging studies. We examine the predictions of the classical model of the basal ganglia, and contrast it with findings in humans and animals. The review concludes that chronic dopamine depletion (>4 months) produces decreases in striatal glutamate levels which are consistent with the classical model of the basal ganglia. However, acute alterations in striatal dopamine functioning, specifically at the D2 receptors, may produce opposite affects. This has important implications for models of the basal ganglia and theorizing about neurochemical alterations in neuropsychiatric diseases. Moreover, these findings may help guide a priori hypotheses for 1H-MRS studies measuring glutamate changes given alterations in dopaminergic functioning in humans.

1. Introduction

Dopamine and glutamate interact with each other in the basal ganglia and prefrontal cortex, intimately regulating each other's function and release (David et al., 2005; Del Arco and Mora, 2008; Jones, 2012). Abnormalities in these dopaminergic and glutamatergic systems have been observed in numerous neuropsychiatric disorders, including Parkinson's disease (Griffith et al., 2008; Loane and Politis, 2011; Pavese et al., 2011), depression (Musazzi et al., 2012; Treadway and Zald, 2011), drug addiction (Martinez et al., 2009; Yang et al.,

*Corresponding author at: 250 College Street, Toronto, Ontario M5T 1R8, Canada. ariel.graff@camh.ca (A. Graff-Guerrero).

2009; Yucel et al., 2007), and schizophrenia (de la Fuente-Sandoval et al., 2013a,b; de la Fuente-Sandoval et al., 2011; Kegeles et al., 2010). The classical model of the basal ganglia developed in the 1980s (Obeso and Lanciego, 2011) predicts that loss of striatal dopamine will decrease extracellular levels of glutamate in the striatum and cortex (Albin et al., 1989, 1995; Jones, 2012). Similarly, it predicts that increasing levels of striatal dopamine should increase levels of glutamate in the striatum and cortex. However, the classical model of the basal ganglia is an incomplete one. For instance, it does not take into account the influence of the cholinergic system, and has been criticized for offering a better understanding of pathology rather than normal functioning (Obeso et al., 2008; Obeso et al., 2000). Undoubtedly, the in vivo environment in which dopamine–glutamate interactions take place in the basal ganglia is far more complex than suggested by the classical model.

Positron emission tomography (PET) and proton magnetic resonance spectroscopy (^{1}H-MRS) are two non-invasive brain-imaging techniques, which allow for quantification of biochemical information about the living human brain. PET employs the use of radio-labelled probes, termed radiotracers or radioisotopes (Baron, 2005; Das, 2015). These radiotracers are positron emitting isotopes which are chemically incorporated into a biologically active molecule (Das, 2015). For example, the accumulation of ^{18}F-labeled 3,4-dihydroxy-6-[18F]fluoro-L-phenylalanine ([^{18}F]F-DOPA) in the brain measured with PET can be used as a quantitative index of dopamine synthesis capacity (Nanni et al., 2007; Pretze et al., 2014). Moreover, dopamine$D_{2/3}$ receptor availability, as well as changes in dopamine concentrations at these receptors, can be measured with ^{11}C- and ^{18}F-labeled compounds such as [^{11}C]-raclopride, [^{11}C]-(+)-PHNO, and [^{18}F]-fallypride. ^{1}H-MRS allows for quantification of concentrations of several neurometabolites, which are characterized by their unique set of ^{1}H chemical shifts (Rae, 2014). These include glutamate, glutamine, glutamate + glutamine (Glx), creatine (Cr), myo-inositol (Myo), and N-acetyl-aspartate (NAA), among several others (Rae, 2014).

Findings from in vivo brain imaging in neuropsychiatric populations have largely supported the predictions of the basal ganglia model. For instance, Parkinson’s disease is a neurodegenerative disorder characterized by progressive loss of nigral-striatal dopamine, which has been supported by in vivo brain imaging using PET (Loane and Politis, 2011; Pavese et al., 2011). Using ^{1}H-MRS, it has been observed that patients with Parkinson’s disease have less glutamate-to-creatine ratios in the anterior cingulate gyrus compared to healthy controls (−46%; Cohen’s d=1) (Griffith et al., 2008). This is consistent with the predictions of the classical model: less striatal-nigral dopamine, less cortical glutamate. Notably, no studies have yet been published investigating glutamate concentrations in the striatum of persons with Parkinson’s disease with ^{1}H-MRS.

Using PET it has been demonstrated that persons with cocaine addiction have reduced dopamine $D_{2/3}$ receptor ($D_{2/3}$R) availability, reduced endogenous dopamine levels at $D_{2/3}$R, and reduced evoked dopamine release (Martinez et al., 2009). Consistent with the basal ganglia model, persons with cocaine addiction have also been observed to have less glutamate-to-creatine in the rostral anterior cingulate (Yang et al., 2009), and less glutamate-to-glutamine in the dorsal anterior cingulate (Yucel et al., 2007), compared to healthy

controls. Striatal concentrations of glutamate measured with ^{1}H-MRS have not yet been examined in persons with drug addiction.

In patients affected by schizophrenia, it has been demonstrated with PET that there is more endogenous dopamine occupying $D_{2/3}$R in the dorsal caudate (Caravaggio et al., 2015; Kegeles et al., 2010). In accordance with the classical model, it has been demonstrated with ^{1}HMRS that persons at ultra-high risk for psychosis (characterized by sub-threshold psychotic symptoms, a high likelihood of a family history of schizophrenia, and a decline in everyday functioning) and patients with a first episode of psychosis have increased glutamate levels in the dorsal caudate compared to healthy controls (de la Fuente-Sandoval et al., 2013a,b; de la Fuente-Sandoval et al., 2011). Note that ultra-high risk for psychosis was assessed using the Structured Interview for Prodromal Syndromes (SIPS) criteria (Miller et al., 2003). Moreover, it has been shown that four weeks of antipsychotic administration can reduce glutamate levels in the dorsal caudate of schizophrenia patients similar to the levels of healthy controls (de la Fuente-Sandoval et al., 2013a,b). Importantly, in ultra-high risk persons, higher glutamate levels in the striatum were predictive of transitioning into psychosis (de la Fuente-Sandoval et al., 2013a,b).

The aforementioned in vivo brain imaging findings in neurological and neuropsychiatric populations are notably prima facie observations. That is to say that the observed differences in dopamine and glutamate concentrations are correlational and presented as a point of reference to the predictions of the classical model of the basal ganglia. Undoubtedly the cause(s) of abnormal dopamine–glutamate interactions will differ across neurological and psychiatric disorders. For example, it has been proposed that hypofunctioning of the N-methyl-D-aspartate (NMDA) receptor may account for the increased glutamate and exacerbated psychostimulant-induced dopamine release observed in schizophrenia patients (Plitman et al., 2014; Poels et al., 2014). Like all working models, the NMDA receptor hypofunctioning model of schizophrenia requires further validation and support (Laruelle, 2014; Laruelle et al., 2005). Regardless of what the sine qua non may be for abnormal dopamine levels observed across neurological and neuropsychiatric populations, the in vivo brain imaging data suggests that decreased striatal dopamine is related to decreased striatal glutamate, and vice-versa. Future work is required to tease out the subtleties, causes, and consequences of these observed correlational changes in neurochemistry across disorders.

One study has simultaneously examined in healthy persons striatal dopamine synthesis capacity measured with [^{18}F]-DOPA and glutamate concentrations measured with ^{1}H-MRS (Gleich et al., 2015). Importantly, a positive correlation was observed between left ventral striatal glutamate concentrations and left ventral striatal dopamine synthesis capacity (r^2=. 17). This is at least prima facie consistent with the notion that increased dopaminergic activity in the striatum should also result in greater glutamatergic activity therein. This also mirrors the findings in persons with schizophrenia, wherein both increased striatal dopamine and striatal glutamate levels are observed compared to healthy controls; albeit in the dorsal striatum (Caravaggio et al., 2015; Kegeles et al., 2010). However, a negative correlation was observed between glutamate concentrations in the left prefrontal cortex and dopamine synthesis capacity in the left ventral striatum (r^2 = .17). Future PET studies examining dopamine synthesis capacity or endogenous dopaminergic tone (Caravaggio et al., 2014;

Laruelle et al., 1997; Verhoeff et al., 2001) should also examine glutamate concentrations measured with ^{1}H-MRS in the dorsal striatum and cortex; in healthy persons and persons with neuropsychiatric diseases.

The effect of dopamine depletion on the glutamatergic system has been extensively investigated in non-human primates and rodents, using a myriad of methods and techniques (David et al., 2005). However, these in vivo and ex vivo investigations have often not yielded consistent support for the classical model's predictions. The findings from these studies will be summarized below, separated by their respective method/technique.

2. Effects of dopamine depletion on tissue concentrations of free amino acids

Singh and Malhotra (1964) examined the effect of reserpine-induced (0.5 mg/kg, iv) dopamine depletion on brain tissue concentrations of numerous amino acids in adult Rhesus monkeys. They observed that reserpine significantly reduced glutamic acid/glutamate concentrations in the amygdala (390.9 ± 37.68 vs. 317.9 ± 11.4, $p < 0.001$), hippocampus (340.9±18.4 vs. 292.1±22.7, $p < 0.001$), and cerebellum (342.8 ± 20.38 vs. 315.2 ± 20.4, $p < 0.001$), with the largest effect observed in the cerebellum. However, concentrations in the midbrain significantly increased (155.3 ± 11.8 vs. 190.6 ± 19.7, $p < 0.001$), while there was no observed change in the frontal lobe and hypothalamus. Tanaka et al. (1986) examined the effect of unilateral 6-hydroxydopamine (6-OHDA) lesions (8 μg) in Wistar rats on striatal concentrations of glutamate. After 9 months of dopamine denervation, they observed that glutamate content was significantly decreased in the striatum (8.87 ± 0.48 vs 7.72 ± 0.76, $p < 0.05$). However, this study did not compare glutamate content between 6-OHDA treated rats and controls. Rather, they examined striatal tissue concentrations ipsilateral and contralateral to the 6-OHDA lesion in the same rats. Lindefors and Ungerstedt (1990) demonstrated, in Sprague-Dawley rats, that unilateral 6-OHDA lesions (2 μg/μl) caused a significant increase in tissue concentrations of glutamate both ipsilateral (45%) and contralateral (39%) to the lesion compared to controls. Thus, the lack of a proper sham-lesion control group poses a major flaw in interpreting the findings from Tanaka and colleagues. Collectively, these data suggests that dopamine depletion does not change tissue concentrations of glutamate in the cortex, increases concentrations in the striatum bilaterally, and decreases concentrations in the cerebellum.

3. Microdialysis of extracellular glutamate

Lindefors and Ungerstedt (1990) showed that unilateral 6-OHDA lesions in Sprague-Dawley rats resulted in increased extracellular release of glutamate in the striatum (by 107% ipsilateral to lesion, 94% contralateral). This is in accordance with their finding of increased striatal tissue concentrations of glutamate given the same administration of 6-OHDA. Biggs and Starr (1997) investigated how multiple dopaminergic manipulations affect extracellular glutamate release in the entopeduncular nucleus (globus pallidus in humans) in Wistar rats. They found that administration of the dopamine $D_{2/3}$ agonist LY171555 significantly decreased glutamate release (by 66.5%). Administration of the$D_{2/3}$ antagonist raclopride, however, had no effect. Reserpine (4 mg/kg, ip, 18 h) resulted in a significant increase in

glutamate release (341%), which was reversed by the $D_{2/3}$ agonist LY17155 but not the D_1 agonist SKF38393. Similarly, unilateral 6-OHDA lesions (8 μg/4 μl, 2 weeks) significantly increased glutamate release, both ipislateral (290%) and contralateral (165%) to the lesion. Finally, administration of L-DOPA (50 mg/kg, ip) had no effect on the increased glutamate release by 6-OHDA lesions.

Findings from Kalivas and Duffy (1997) in Sprague-Dawley rats further suggest a specific role of dopamine $D_{2/3}$ receptors in modulating striatal glutamate release in the nucleus accumbens. They found that perfusion with the indirect dopamine agonist amphetamine (1, 10, and 100 μM) and the $D_{2/3}$ agonist quinpirole (1, 10, and 100 μM) significantly decreased glutamate release in the nucleus accumbens (38% and 24.6%, respectively). Further, this amphetamine-induced decrease in glutamate was reversed by administration of the $D_{2/3}$ antagonist sulpiride (10 mg/kg, ip). Perfusion with the D_1 agonist SKF-82958 (1, 10, and 100 μM) had no effect on glutamate release. Collectively, the findings from Biggs and Starr and Kalivas and Duffy suggest that changes in extracellular levels of striatal glutamate are $D_{2/3}$R dependent and not D_1R dependent.

Meshul et al. (1999) examined changes in the glutamatergic system following unilateral 6-OHDA lesions (8 μg/4 μl) of the medial forebrain bundle in Sprague-Dawley rats after 1 or 3 months. After 1 month they observed an increase in striatal extracellular glutamate release (146%). However, after 3 months a decrease in release was observed (31.25%). Increased extracellular glutamate release after 1 month was paralleled by a decrease in the density of glutamate immunoreactivity (44%) and a decrease in vesicular (42.65%) and mitochondrial (50%) nerve terminal pools of glutamate. After 3 months there was an increase in the density of glutamate immunoreactivity (51.7%), and in vesicular (50%) and mitochondrial (54%) pools of glutamate. This data collectively suggests that there are time-specific changes in the striatal glutamate system following dopamine depletion, likely reflecting compensatory mechanisms following chronic catecholamine loss. Specifically, 1 month or less of dopamine denervation may result in an increase in extracellular levels of glutamate in the striatum compared to controls, whereas >3 months of dopamine denervation may result in a decrease.

Jonkers et al. (2002) examined the effect of unilateral 6-OHDA lesions (4 μg/μl), in Wistar rats, for 18–21 days. In accordance with the findings of Meshul and colleagues, this 1-month period of dopamine denervation resulted in an increase in extracellular glutamate levels in the striatum(45%). However, Galeffi et al. (2003) did not replicate this finding in Wistar rats after 28 days of unilateral 6-OHDA lesions (5–7 μg of 3 mg/ml), observing no change. Similarly, Robelet et al. (2004) observed no change in striatal glutamate in Wistar rats after 14 days of unilateral 6-OHDA lesions (12 μg/6 μl).

Holmer et al. (2005) examined the effect of acute versus chronic dopamine denervation, via the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), on striatal glutamate in C57BL/6J mice. The acute dose of MPTP (20 mg/kg, 4 doses in 2 h) results in rapid and extensive dopamine denervation, while the chronic dose (30 mg/kg/day, 7 days) results is protracted dopamine denervation. The acute dose of MPTP resulted in an increase in extracellular glutamate (54%) in the dorsolateral striatum. Administration of L-DOPA (80

mg/kg) reversed this increase and further decreased extracellular glutamate levels below controls (36%). The chronic dose of MPTP, on the other hand, decreased extracellular levels of glutamate (65%), and concurrent L-DOPA administration increased these levels to −20% of controls. These data further suggest that there are strikingly different changes in the glutamatergic system depending on the extent and length of dopamine denervation, and L-DOPA may normalize these glutamatergic changes. Finally, Walker et al. (2009) demonstrated that bilateral 6-OHDA lesions (2 μg/μl) in Sprague-Dawley rats increased extracellular levels of glutamate (130%) in the striatum. In male vervet monkeys, striatal dopamine denervation via MPTP resulted in a substantial increase in striatal glutamate (~280%) and GABA (~280%) levels measured with microdialysis (Boulet et al., 2008). Specifically, these increases occurred in the sensorimotor striatum, but not the limbic striatum, and persisted after motor symptom recovery.

Data from a substantial portion of the aforementioned studies suggest that extracellular levels of glutamate in the striatum may increase after acute dopamine denervation. These findings are difficult to reconcile with the classical model of the basal ganglia, which predicts striatal levels of glutamate will decrease after dopamine denervation. However, some studies demonstrate that extracellular glutamate levels decrease after prolonged dopamine denervation. Furthermore, some studies found no effect of dopamine denervation on extracellular glutamate in the striatum. It is unclear why there is a discrepancy between these studies. It is also unknown whether the change in extracellular glutamate levels is of neuronal or glial origins. The finding that intracellular pools of glutamate were decreased concurrently with an increase in extracellular levels is suggestive of a glial contribution (Meshul et al., 1999). Hypoactivation of $D_{2/3}$ receptors and not D_1 seems to be necessary (though not sufficient) for the increases in extracellular glutamate after acute dopamine denervation, suggesting a neuronal contribution (Biggs and Starr, 1997). Unfortunately, none of the aforementioned studies examined changes in extracellular glutamate levels in the cortex.

4. Ex vivo ^{1}H-MRS in rodents

One study examined the effect of bilateral 6-hydroxydopamine (6-OHDA) lesions in Sprague-Dawley rats on striatal concentrations of glutamate, glutamine, and GABA measured with ^{1}H-MRS ex vivo (Gao et al., 2013). Compared to controls, 6-OHDA rats showed increased concentrations of glutamate (1.63 ± 0.24 vs. 1.91 ± 0.1, p = 0.010) and GABA (0.55 ± 0.12 vs. 0.69 ± 0.05, p = 0.009) in the right striatum, as well as a decrease in glutamine (1.37 ± 0.32 vs. 1.13 ± 0.06, p = 0.049). In the left striatum, they observed increased levels of glutamate (1.85 ± 0.33 vs. 2.15 ± 0.12, p = 0.037), decreased levels of GABA (0.63 ± 0.14 vs. 0.52 ± 0.05, p = 0.047), and no change in glutamine.

5. In vivo ^{1}H-MRS in rodents

One study has examined, using ^{13}C NMR spectroscopy (4.7-T), how the synthesis of glutamate/glutamine from[2-^{13}C] sodium acetate is affected by unilateral 6-OHDA injections in male Sprague-Dawley rats (Chassain et al., 2005). This study found that dopamine-depletion resulted in an increase in glutamate metabolism in the striatum, which

was restored by administration of levodopa. Using a high field MR scanner (9.4-T), it has been demonstrated that MPTP-lesioned C57B1/6J mice have increased concentrations of glutamate, glutamine, and GABA in the dorsal striatum, both in vivo and in vitro (Chassain et al., 2008). However, MPTP-lesioned C57B1/6 J mice showed no difference in cortical concentrations of these three amino acids in vivo, despite increased concentrations in the dorsal striatum (Chassain et al., 2010. In C57B1/6J mice given MPTP injections, the extent of dopamine denervation in the substantia nigra and ventral tegmental area was related to increased concentrations of glutamate, glutamine, and GABA in the dorsal and ventral striatum, respectively (Chassain et al., 2013). Contrary to the previous findings in rodents, MPTP administration in adult beagles did not affect the concentration of glutamate + glutamine/creatine ratio in the striatum assessed at 3-T (Choi et al., 2011). However, it is important to note that all of the aforementioned in vivo ^{1}H-MRS studies were performed while the animals were under anesthesia, and it is unknown how this affects glutamate, glutamine, and GABA levels in combination with chemically induced dopamine denervation (Pfeuffer et al., 2004). Furthermore, all the studies by Chassain and colleagues (Chassain et al., 2013; Chassain et al., 2008; Chassain et al., 2010) in C57B1/6J mice collected MRS spectra only from the right hemisphere of the striatum.

6. Summary of dopamine–glutamate interactions

The predictions made by the classical model of the basal ganglia, regarding how depleting dopamine levels should alter striatal and cortical glutamate levels, has largely been unsupported by the in vivo and ex vivo animal literature. Specifically, the animal literature suggests that *acute* hypoactivity of striatal D_2Rs (i.e., increasing activity through the indirect pathway), but not D_1Rs, may increase striatal glutamate levels while leaving cortical glutamate levels unchanged. Conversely, the model would predict a decrease in striatal and cortical glutamate via increased activity through the indirect pathway and decreased activity through the direct pathway (consequence of D_2R and D_1R hypofunction, respectively). Notably, it appears that manipulations of chronic dopamine depletion (>4months) produces decreases in striatal glutamate levels which are consistent with the classical model.

7. Future directions and limitations

This review highlights several avenues of future research. It is currently unknown how acute dopamine depletion in humans affects striatal and cortical glutamate concentrations measured with ^{1}H-MRS. Acute dopamine depletion is possible in humans via administration of the tyrosine hydroxylase inhibitor alpha-methyl-para-tyrosine (AMPT). Challenges with AMPT have been successfully employed in conjunction with PET to estimate endogenous dopamine levels at $D_{2/3}$R in living humans (Caravaggio et al., 2015; Caravaggio et al., 2014; Kegeles et al., 2010; Laruelle et al., 1997; Martinez et al., 2009; Verhoeff et al., 2001). Thus, measuring glutamate concentrations with ^{1}H-MRS before and after AMPT administration could help elucidate how dopamine depletion alters glutamatergic functioning in healthy persons and persons with neuropsychiatric diseases. The results from such a study could be contrasted with changes observed given acute doses of D_1R, D_2R, and D_3R selective antagonists. This would help clarify how hypofunctioning at particular dopamine receptors results in glutamatergic changes at a systems level. Moreover, the results from such studies

may either prove to be in line with the acute findings in animals, or vindicate the predictions of the classical model of the basal ganglia.

There are several limitations to the current investigation. Firstly, this review was not a systematic review, nor did we examine all of the neurochemical and physiological alterations observed given dopamine depletion in animals and humans. Rather, we focused on the consequence of dopamine depletion on measures of glutamate levels in two specific regions of interest: the striatum and cortex. We did this since these regions of interest are commonly employed in human ^{1}H-MRS studies to quantify in vivo glutamate concentrations. Second, we did not examine indirect or secondary measures of changes in glutamate levels given dopamine depletion – such as genetic expression changes or changes in glutamate precursor or metabolite levels. Third, evidence suggests that midbrain dopamine neurons (particularly in the VTA)may not only release dopamine, but also co-release glutamate (Descarries et al., 2008; Rayport, 2001; Sulzer et al., 1998). In fact, co-transmission of several neurotransmitters may occur for all monoaminergic neurons (El Mestikawy et al., 2011; Nusbaumet al., 2001; Trudeau, 2004). This co-transmission from dopamine neurons may be age-dependent (decreasing with age) (Berube-Carriere et al., 2009) and may be modified by 6-OHDA administration (Dal Bo et al., 2008). This is another layer of complexity not captured by the classical model of the basal ganglia. Future studies should investigate how acute and chronic dopamine depletion (via AMPT or specific 6-OHDA/MPTP lesions) affects glutamate release from these neurons into the striatum, and in turn striatal glutamate concentrations measured using in vivo ^{1}H-MRS. Finally, we did not review how gross physiological changes from glutamate-induced neurotoxicity may alter the relationship between dopamine and glutamate levels in the striatum and cortex (Plitman et al., 2014). These will be important aspects to investigate in future reviews.

It was our hope that by conducting this review, we could help inform and guide *a priori* hypotheses for ^{1}H-MRS studies in humans. Specifically, it may help guide those studies which i) cross-sectionally examine glutamate concentrations in persons with neuropsychiatric diseases where there are known abnormalities in the dopamine system, and, ii) examine how acutely or chronically altering dopamine functioning – either in healthy persons or persons with neuropsychiatric diseases – affects glutamate concentrations.

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