PSYCHIATRIA ET NEUROLOGIA JAPONICA

Special Feature Article

Treatment-resistant Schizophrenia, Clozapine, and Glutamate Hypothesis

Shinichiro NAKAJIMA
Department of Neuropsychiatry, School of Medicine, Keio University
Psychiatria et Neurologia Japonica 122: 441-448, 2020

Abstract

About 20-35% of schizophrenia patients do not respond to first-line antipsychotics (treatment-resistant schizophrenia: TRS). The glutamate hypothesis is an important hypothesis that explains the pathophysiology of schizophrenia. As a common biological property of TRS, increased levels of glutamatergic neurometabolites in the anterior cingulate have been consistently reported. However, few studies have examined the pathophysiology underlying TRS and clozapine resistance, and to date no robust neuroimaging correlates for these conditions have been found. Future studies need to elucidate the neuroimaging correlates of TRS and the mechanism of action of clozapine.

Keywords: schizophrenia, clozapine, glutamate, treatment resistance, ^{1}H-MRS

Introduction.

Schizophrenia is a chronic disease that affects approximately 1% of the world population. Schizophrenia is a disorder that presents with positive symptoms, such as delusions and hallucinations, negative symptoms, such as emotional lability, decreased spontaneity, and social withdrawal, and cognitive dysfunction. The mainstay of treatment for schizophrenia is pharmacotherapy using antipsychotic drugs that inhibit

the dopamine D2 receptors. Currently, the main treatment for schizophrenia is antipsychotic drugs with dopamine receptor antagonism. The clinical efficacy of antipsychotics is the basis of the dopamine hypothesis of schizophrenia, in which abnormal dopaminergic function is thought to be involved in the pathophysiology of schizophrenia. However, most antipsychotics are effective only for positive symptoms and have no clinically significant effect on negative symptoms or cognitive dysfunction. In addition, approximately 20-35% of patients with schizophrenia do not respond to first-line antipsychotics and are therefore considered to have treatment-resistant schizophrenia (TRS) 27)31).

Clozapine (CLZ) is the most effective antipsychotic agent for TRS. In contrast to other antipsychotics, CLZ has a low affinity for dopamine D2 receptors. The fact that CLZ is effective when other D2 receptor antagonists are ineffective also suggests that the clinical efficacy of CLZ in TRS may be related to other mechanisms. In addition, studies using [18F]-DOPA positron emission topography have shown a lower capacity for dopamine production in the striatum of TRS patients before and after treatment compared to treatment-responsive schizophrenic patients (non-TRS patients) 5)6)15). In summary, these findings suggest that the pathophysiology of TRS may not be related to elevated striatal dopamine levels.

I. The Glutamate Hypothesis of Schizophrenia

On the other hand, the glutamate (Glu) hypothesis has been proposed for several decades as an important hypothesis to explain the mechanism of schizophrenia 19)22). Dissociative anesthetics, such as phencyclidine (PCP) and ketamine, inhibit the NMDA receptors. When ketamine was administered to healthy control (HC) subjects, schizophrenia-like symptoms were observed, and these symptoms were also aggravated in chronic schizophrenic patients taking antipsychotics 27). The functional impairment induced by ketamine was improved by a glutamate negative modulator, but a D2 receptor inhibitor had no effect 20)21). In addition, postmortem brain autopsies revealed changes in the NMDA receptors, and genetic studies revealed a correlation between abnormalities in the NMDA receptor gene and the risk of schizophrenia 11). The results of these studies provide evidence for the Glu hypothesis.

II. Study of schizophrenia using proton nuclear magnetic resonance

spectroscopy (1H-MRS).

In recent years, magnetic resonance spectroscopy (MRS) has been utilized in many studies to elucidate the pathogenesis of brain diseases 35). MRS is a technique for non-invasively measuring chemical substances in living organisms using nuclear magnetic resonance. Nuclear magnetic resonance (NMR) is a phenomenon in which the application of electromagnetic waves to a substance in a strong static magnetic field causes the nuclei to enter an excited state. The signal emitted from the excited nucleus is received by the MR equipment, and when it is Fourier transformed, the frequency-signal intensity curve is obtained. Since the resonance frequency of the nucleus differs depending on the molecular structure and environment, MRS can identify the type of chemical substance that emitted the signal. Although there are several nuclear species used in MRS, this paper describes proton MRS (1H-MRS), which is currently in clinical use. The main findings of this meta-analysis are as follows. The primary objective of this meta-analysis was to perform a meta-analysis of all case-control studies in which brain Gluergic neurometabolites were measured by 1H-MRS in patients with high-risk schizophrenia, first-episode psychosis, and chronic schizophrenia. We selected single-voxel 1H-MRS studies in which the Glu-ergic neurometabolite concentrations were compared between patients or high-risk and HC groups, and 59 articles containing data from 1,686 patients and 1,451 HCs were extracted. Using a variational effect model and the inverse variance method, effect sizes were obtained separately for Gluergic neurometabolite concentrations in each brain region from at least three different studies. We found increased Glu and Glu+glutamine (Glx) concentrations in the basal ganglia and increased Glx concentrations in the medial temporal lobe in schizophrenic patients. Subgroup analyses reported increased Glx in the prefrontal region in high-risk individuals, increased Glx in the basal ganglia in patients with first-episode psychosis, and increased Glx in the frontal white matter and medial temporal lobe in patients with chronic schizophrenia. A decrease in Glu-ergic neurometabolites was not observed in any brain region. The Gluergic metabolite levels were not significantly related to patient age, antipsychotic medication, or disease severity. These results suggest that schizophrenia may be associated with elevated concentrations of Gluergic neurometabolites in several brain regions. However, it is noteworthy that these findings take into account the stage of illness, including high-risk

states, first-episode psychosis, and chronic schizophrenia. We also performed a meta-analysis of Gluergic neurometabolite concentrations in unmedicated schizophrenic patients and found no significant difference in the medial frontal cortex Glx concentrations between unmedicated patients and HC 13). In addition, a recent meta-analysis pointed out that there was no difference in Glx concentration in the medial frontal cortex between schizophrenic patients and HC 25). However, these studies did not consider the detailed location of voxels in the anterior cingulate cortex (ACC) [i.e., pregenual ACC (pgACC) or dorsal ACC (dACC)]. Most studies examining the concentrations of Gluergic neurometabolites in the ACC of schizophrenic patients have reported increased concentrations of pgACC and decreased concentrations of dACC 14). In addition, a recent study in 7T 1H-MRS also reported lower Glu concentrations in the dACC of patients with first episode psychosis 34). Therefore, there may be heterogeneity in the concentrations of Gluergic neurometabolites in different brain regions.

III. Proton nuclear magnetic resonance spectroscopy in treatment-resistant schizophrenia.

In a previous cross-sectional 1H-MRS study, increased Glu concentrations in ACC were found in patients with TRS compared with responders to HC and first-line antipsychotics (non-TRS patients) 6)26). These results suggest an association between increased concentrations of Glu-ergic neurometabolites and TRS. It is worth noting that the clinical severity of TRS in these 1H-MRS studies ranged from mild to moderate, which does not reflect the clinical picture of TRS patients often observed in daily clinical practice. Furthermore, these studies did not examine cognitive dysfunction, a core symptom of schizophrenia. Further studies are needed to better understand Gluergic dysfunction in severely symptomatic TRS patients.

It has also been reported that 40-70% of TRS patients do not respond to CLZ 16). This group is considered to have ultra-resistant schizophrenia (URS), and this difference in clinical response suggests that the pathophysiological mechanisms may be different between URS and CLZ-responsive schizophrenia (non-URS). A previous study compared Glu and Glx levels among URS patients, non-URS patients, first-line antipsychotic responders (non-TRS), and HCs. In this study, the Glx concentrations in the dorsolateral prefrontal cortex (DLPFC) were lower in URS patients than in non-TRS patients, but the Glx concentrations in

the corpus callosum were higher in URS patients than in non-URS and non-TRS patients. In this study, however, we distinguished URS from non-URS patients when the patients were taking antipsychotic medications other than CLZ. In addition, to minimize the state effect of symptom severity, patients with mild illness were included in both URS and non-URS. In addition, this study did not account for previous treatment failures prior to CLZ treatment, so patients may have started CLZ due to side effects or intolerance to previous medications. Therefore, it was unclear whether patients with mild URS responded to treatment with CLZ or additional antipsychotics.

To further elucidate the relationship between abnormal Gluergic neurometabolism and TRS, we conducted two studies, the first of which examined Glx concentrations in the dACC and dorsal caudate nucleus in severely symptomatic TRS patients, non-TRS patients, and HCs 32). We selected the dACC as our region of interest because most previous studies suggest abnormal Gluergic neurometabolite concentrations in the ACC of TRS patients. We chose the dACC based on previous studies suggesting a relationship between increased dopaminergic function in the dorsal caudate nucleus and psychotic symptoms 24). The caudate nucleus voxel was placed in the dorsal caudate nucleus to represent the functional segment of the association striatum, where the most significant increase in presynaptic dopaminergic function relative to HC has been reported in schizophrenic patients. We also included patients with TRS who exhibited levels of symptoms that exceeded those in previous studies, particularly by adopting more stringent criteria for TRS 12). In the second study, we included both symptomatic and non-symptomatic TRS patients receiving CLZ monotherapy 14). More specifically, we divided the patients into three groups: 1) URS, 2) non-URS, and 3) non-TRS. In addition, existing guidelines were used to establish treatment resistance to non-CLZ antipsychotics. The main objective of this study was to compare the concentrations of Gluergic neurometabolites in the caudate nucleus, dACC, and DLPFC between the patient and HC groups.

All participants underwent imaging on a 3T GE Discovery MR750 scanner with an 8-channel head coil. Participants also underwent 3D IR-enhanced T1-weighted magnetic resonance imaging (MRI). 1H-MRS was performed using point-resolved spectroscopy [PRESS, TE=35 ms, TR=2000 ms, spectral width=5,000 Hz, 4,096 data points, 128 water suppression, 16 water depressions, 8 excitations (NEX)].

Shimming was performed with full width at half maximum (FWHM) ≤ 12 Hz as measured by the unsuppressed water signal from the voxel. 1H-MRS voxels were placed in the left dorsal caudate (association striatum) (voxel size = 7.5 mL), bilateral dACC (voxel size = 9.0 mL), and left DLPFC (voxel size = 13.5 mL). Water suppression spectra were analyzed using the LCModel. Metabolite concentrations were estimated with an appropriate basis set of fields matching the TE (=35 ms) provided by the LCModel. Metabolite concentrations were then expressed in facility units by normalizing the peak area of each metabolite to the peak area of the uninhibited water signal. T1-weighted MRI was performed using FSL's FIRST tool on gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF). T1-weighted MRI was divided into gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF) using FSL's FIRST tool. "Gannet" (http://www.gabamrs.com) was used to create a mask of voxel size and position on the segmented T1-weighted images. The spatial coordinates in the scanner were used to correct the concentration of neurometabolites for a portion of the CSF in the region of interest (ROI).

The main statistical analysis was the difference in Glx concentration between the groups. First, the Glx concentrations were compared between the groups using analysis of variance (ANOVA). Next, analysis of covariance was performed, controlling for age, GM ratio in the voxel brain tissue [GM/(GM+WM)], and spectral quality values that differed significantly between the groups. Further analysis of the patient groups was performed using ANOVA, controlling for smoking status and chlorpromazine equivalent daily dose separately.

A total of 95 patients (29 TRS patients, 33 non-TRS patients, and 33 HC patients) participated in the first study. The Glx concentration of dACC was higher in the TRS patients than in the HC group, and there was no significant difference between the patient groups or between the non-TRS and HC groups. In both the dACC and the caudate nucleus, the Glx concentrations were significantly higher in TRS and non-TRS patients than in the HC group, and did not differ significantly between patient groups or between non-TRS and HC groups, the Neuropsychological Status (RBANS) total score, subscale score 29), or Executive Interview score 30).

The second study included 100 patients: 26 URS patients, 27 non-URS patients, 21 non-TRS patients, and 26 HC patients 14). There was a tendency for significant differences in Glx concentrations in the dACC between

groups, which became significant after controlling for the GM ratio. In the caudate nucleus and DLPFC, there were no differences in Glx concentrations between groups. When the relationship between psychotic symptoms and concentrations of Gluergic neurometabolites was examined, the Glx concentrations were not associated with the total or subscale scores on the Positive and Negative Symptom Rating Scale in the entire patient sample. This is the first 1H-MRS study to compare Glx concentrations in the caudate nucleus, dACC, and DLPFC in symptomatic URS, non-URS, and non-TRS patients, as well as in the HC group.

To our knowledge, six prospective studies have examined the effects of antipsychotics on Gluergic neurometabolite concentrations in ACC in schizophrenia, with inconsistent results: three studies reported a decrease in Gluergic neurometabolite concentrations 4)8)10), one reported an increase 1), and two studies found no change 2)18). However, only two of these studies prospectively examined the effect of antipsychotics on dACC Glx concentrations in untreated patients with schizophrenia, and no change in Glx concentrations was observed after 6 weeks of treatment with risperidone or aripiprazole 2)18). These studies suggest that antipsychotic medication does not directly affect dACC Glx concentrations in schizophrenic patients.

Egerton et al. reported that the higher the pre-treatment pgACC Glu concentration, the lower the likelihood of remission at 4 weeks, and that lower pgACC Glu concentrations after antipsychotic treatment were not associated with treatment response 8). Similarly, a previous cross-sectional 1H-MRS study reported higher concentrations of Gluergic neurometabolites in pgACC in patients with TRS compared with those who responded to HC or treatment 6)26). These findings are consistent with our findings that dACC Glx levels were higher in URS patients than in HC. In summary, the results of our study suggest that higher concentrations of Gluergic neurometabolites are one of the common biological characteristics of resistance to treatment with antipsychotics, including CLZ.

Goldstein et al. compared Glx concentrations in the capsular and DLPFC in a group similar to our second study 9), and our study examined the caudate nucleus, ACC, and DLPFC 14). Goldstein et al. reported that Glx concentrations in the DLPFC were lower in URS patients than in non-TRS patients. Consistent with this finding, our data showed numerically lower Glu concentrations in the DLPFC of URS

patients than in non-TRS patients. On the other hand, we did not observe a difference in Glx concentrations in the caudate nucleus between groups, but Goldstein et al. showed that URS and non-TRS patients had lower Glx concentrations in the putamen than non-URS patients. This discrepancy may be due to (1) the fact that we placed voxels in the dorsal caudate nucleus and Goldstein et al. placed them in the putamen, and (2) the fact that we included symptomatic URS patients and Goldstein et al. included patients with mild URS. Despite significant differences in symptom severity, there were no significant differences in Glx concentrations at any site between the URS, non-URS, and non-TRS groups. This was also true for the comparison between the symptomatic and non-symptomatic patient groups. Furthermore, there was no association between symptom severity and Glx concentration. Therefore, Glx concentrations measured by 1H-MRS in the caudate nucleus, dACC, and DLPFC did not appear to be associated with symptom severity. Consistent with these findings, a recent meta-analysis found no significant correlation between Glu-ergic markers and symptom severity in patients with schizophrenia 4)25). However, it should be noted that no patients in this study had moderate symptom severity as a result of the inclusion criteria. A wider range of symptom severity and more sensitive clinical measures may be needed to clarify the association between Glx concentrations and symptom severity in the patient population.

In addition, there are several limitations to both of our studies. First, 1H-MRS cannot distinguish between neurotransmitters or vesicles and metabolic pools of Glu-ergic neurometabolites. Second, although we were able to include 100 subjects as planned, the sample size within each group may still be small. Third, the neurochemical concentrations were corrected for the CSF ratio, but this study did not take into account the relaxation effect. Fourth, response and resistance to treatment were determined based on symptom severity at the time of assessment in a cross-sectional design, and the effect of antipsychotic medication on symptom severity was not examined forward. Finally, due to the cross-sectional nature of this study, we were unable to determine a causal relationship between Glx concentrations and antipsychotic medication intake. To address this issue, prospective studies are needed that allow the measurement of Glx concentrations in TRS patients before and after antipsychotic treatment.

Conclusion.

High ACC Glx levels in schizophrenia suggest a common biological characteristic of resistance to treatment with antipsychotics, including CLZ. Few studies have examined the pathophysiology underlying TRS and URS, and to date, robust neuroimaging correlates of these disorders have not been found. Future studies are needed to elucidate the neuroimaging correlates of TRS/URS and the mechanism of action of CLZ.

There are no conflicts of interest to be disclosed in relation to this paper.

References

1) Aoyama, N., Théberge, J., Drost, D. J., et al.: Grey matter and social functioning correlates of glutamatergic metabolite loss in schizophrenia. Br J Psychiatry, 198 (6); 448-456, 2011

2) Bojesen, K. B., Ebdrup, B. H., Jessen, K., et al.: Treatment response after 6 and 26 weeks is related to baseline glutamate and GABA levels in antipsychotic-naïve patients with psychosis. Psychol Med, 1-12, 2019 (Epub ahead of print)

3) Bush, G., Shin, L. M., Holmes, J., et al.: The Multi-Source Interference Task: validation study with fMRI in individual subjects. Mol Psychiatry, 8 (1); 60-70, 2003

4) de la Fuente-Sandoval, C., Reyes-Madrigal, F., Mao, X., et al.: Prefrontal and striatal gamma-aminobutyric acid levels and the effect of antipsychotic treatment in first-episode psychosis patients. Biol Psychiatry, 83 (6); 475-483, 2018

5) Demjaha, A., Murray, R. M., McGuire, P. K., et al.: Dopamine synthesis capacity in patients with treatment-resistant schizophrenia. Am J Psychiatry, 169 (11); 1203-1210, 2012

6) Demjaha, A., Egerton, A., Murray, R. M., et al.: Antipsychotic treatment resistance in schizophrenia associated with elevated glutamate levels but normal dopamine function. Biol Psychiatry, 75 (5); e11-13, 2014

7) Drevets, W. C., Raichle, M. E.: Suppression of regional cerebral blood during emotional versus higher cognitive implications for interactions between emotion and cognition. Cognition and Emotion, 12 (3); 353-385, 1998

8) Egerton, A., Broberg, B. V., Van Haren, N., et al.: Response to initial antipsychotic treatment in first episode psychosis is related to anterior cingulate glutamate levels: a multicentre ^{1}H-MRS study (OPTiMiSE). Mol Psychiatry, 23 (11); 2145-2155, 2018

9) Goldstein, M. E., Anderson, V. M., Pillai, A., et al.: Glutamatergic neurometabolites in clozapine-responsive and -resistant schizophrenia. Int J Neuropsychopharmacol, 18 (6); pyu 117, 2015

10) Goto, N., Yoshimura, R., Kakeda, S., et al.: Six-month treatment with atypical antipsychotic drugs decreased frontal-lobe levels of glutamate plus glutamine in early-stage first-episode schizophrenia. Neuropsychiatr Dis Treat, 8; 119-122, 2012

11) Howes, O., McCutcheon, R., Stone, J.: Glutamate and dopamine in schizophrenia: an update for the 21st century. J Psychopharmacol, 29 (2); 97-115, 2015

12) Howes, O. D., McCutcheon, R., Agid, O., et al.: Treatment-Resistant Schizophrenia: Treatment Response and Resistance in Psychosis (TRRIP) Working Group Consensus Guidelines on Diagnosis and Terminology. Am J Psychiatry, 174 (3); 216-229, 2017

13) Iwata, Y., Nakajima, S., Plitman, E., et al.: Neurometabolite levels in antipsychotic-naïve/free patients with schizophrenia: a systematic review and meta-analysis of ^{1}H-MRS studies. Prog Neuropsychopharmacol Biol Psychiatry, 86; 340-352, 2018

14) Iwata, Y., Nakajima, S., Plitman, E., et al.: Glutamatergic neurometabolite levels in patients with ultra-treatment-resistant schizophrenia: a cross-sectional 3T proton magnetic resonance spectroscopy study. Biol Psychiatry, 85 (7); 596-605, 2019

15) Jauhar, S., Veronese, M., Nour, M. M., et al.: The effects of antipsychotic treatment on presynaptic dopamine synthesis capacity in first—episode psychosis: a positron emission tomography study. Biol Psychiatry, 85 (1); 79-87, 2019

16) Kane, J. M., Honigfeld, G., Singer, J., et al.: Clozapine for the treatment-resistant schizophrenic: results of a US multicenter trial.

Psychopharmacology, 99; S60-63, 1989

17) Kay, S. R., Fiszbein, A., Opler, L. A.: The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. Schizophr Bull, 13 (2); 261-276, 1987

18) Kraguljac, N. V., Morgan, C. J., Reid, M. A., et al.: A longitudinal magnetic resonance spectroscopy study investigating effects of risperidone in the anterior cingulate cortex and hippocampus in schizophrenia. Schizophr Res, 210; 239-244, 2019

19) Krystal, J. H., Karper, L. P., Seibyl, J. P., et al.: Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. Arch Gen Psychiatry, 51 (3); 199-214, 1994

20) Krystal, J. H., D'Souza, D. C., Karper, L. P., et al.: Interactive effects of subanesthetic ketamine and haloperidol in healthy humans. Psychopharmacology (Berl), 145 (2); 193-204, 1999

21) Krystal, J. H., Abi-Saab, W., Perry, E., et al.: Preliminary evidence of attenuation of the disruptive effects of the NMDA glutamate receptor antagonist, ketamine, on working memory by pretreatment with the group II metabotropic glutamate receptor agonist, LY354740, in healthy human subjects. Psychopharmacology (Berl), 179 (1); 303-309, 2005

22) Lahti, A. C., Koffel, B., LaPorte, D., et al.: Subanesthetic doses of ketamine stimulate psychosis in schizophrenia. Neuropsychopharmacology, 13 (1); 9-19, 1995

23) Mayberg, H. S., Liotti, M., Brannan, S. K., et al.: Reciprocal limbic-cortical function and negative mood: converging PET findings in depression and normal sadness. Am J Psychiatry, 156 (5); 675-682, 1999

24) McCutcheon, R., Beck, K., Jauhar, S., et al.: Defining the locus of dopaminergic dysfunction in schizophrenia: a meta—analysis and test of the mesolimbic hypothesis. Schizophr Bull, 44 (6); 1301-1311, 2018

25) Merritt, K., Egerton, A., Kempton, M. J., et al.: Nature of glutamate alterations in schizophrenia: a meta-analysis of proton magnetic

resonance spectroscopy studies. JAMA Psychiatry, 73 (7); 665-674, 2016

26) Mouchlianitis, E., Bloomfield, M. A., Law, V., et al.: Treatment-resistant schizophrenia patients show elevated anterior cingulate cortex glutamate compared to treatment-responsive. Schizophr Bull, 42 (3); 744-752, 2016

27) Poels, E. M., Kegeles, L. S., Kantrowitz, J. T., et al.: Imaging glutamate in schizophrenia: review of findings and implications for drug discovery. Mol Psychiatry, 19 (1); 20-29, 2014

28) Raichle, M. E., Fiez, J. A., Videen, T. O., et al.: Practice-related changes in human brain functional anatomy during nonmotor learning. Cereb Cortex, 4 (1); 8-26, 1994

29) Randolph, C., Tierney, M. C., Mohr, E., et al.: The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): preliminary clinical validity. J Clin Exp Neuropsychol, 20 (3); 310-319, 1998

30) Royall, D. R., Mahurin, R. K., Gray, K. F.: Bedside assessment of executive cognitive impairment: the executive interview. J Am Geriatr Soc, 40 (12); 1221-1226, 1992

31) Suzuki, T., Remington, G., Mulsant, B. H., et al.: Treatment resistant schizophrenia and response to antipsychotics: a review. Schizophr Res, 133 (1-3); 54-62, 2011

32) Tarumi, R., Tsugawa, S., Noda, Y., et al.: Levels of glutamatergic neurometabolites in patients with severe treatment-resistant schizophrenia: a proton magnetic resonance spectroscopy study. Neuropsychopharmacology, 45 (4); 632-640, 2020

33) Vogt, B. A.: Midcingulate cortex: structure, connections, homologies, functions and diseases. J Chem Neuroanat, 74; 28-46, 2016

34) Wang, A. M., Pradhan, S., Coughlin, J. M., et al.: Assessing brain metabolism with 7-T proton magnetic resonance spectroscopy in patients with first-episode psychosis. JAMA Psychiatry, 76 (3); 314-323, 2019

35) Wijtenburg, S. A., Yang, S., Fischer, B. A., et al.: In vivo assessment of neurotransmitters and modulators with magnetic resonance spectroscopy: application to

schizophrenia. Neurosci Biobehav Rev, 51; 276-295, 2015