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GABA abnormalities in schizophrenia: A methodological review of in vivo studies

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Abstract

Abnormalities of GABAergic interneurons are some of the most consistent findings from post-mortem studies of schizophrenia. However, linking these molecular deficits with in vivo observations in patients – a critical goal in order to evaluate interventions that would target GABAergic deficits – presents a challenge. Explanatory models have been developed based on animal work and the emerging experimental literature in schizophrenia patients. This literature includes: neuroimaging ligands to GABA receptors, magnetic resonance spectroscopy (MRS) of GABA concentration, transcranial magnetic stimulation of cortical inhibitory circuits and pharmacologic probes of GABA receptors to dynamically challenge the GABA system, usually in combination with neuroimaging studies. Pharmacologic challenges have elicited behavioral changes, and preliminary studies of therapeutic GABAergic interventions have been conducted. This article critically reviews the evidence for GABAergic dysfunction from each of these areas. These methods remain indirect measures of GABAergic function, and a broad array of dysfunction is linked with the putative GABAergic measures, including positive symptoms, cognition, emotion, motor processing and sensory processing, covering diverse brain areas. Measures of receptor binding have not shown replicable group differences in binding, and MRS assays of GABA concentration have yielded equivocal evidence of large-scale alteration in GABA concentration. Overall, the experimental base remains sparse, and much remains to be learned about the role of GABAergic interneurons in healthy brains. Challenges with pharmacologic and functional probes show promise, and may yet enable a better characterization of GABAergic deficits in schizophrenia.

Keywords

fMRI; MRS; TMS; PET; psychosis; benzodiazepine

1.0 Introduction

Post-mortem studies of schizophrenia have yielded definitive evidence of GABAergic abnormalities (Akbarian and Huang, 2006; Benes, 2010; Lewis et al., 2012; Nakazawa et al., 2012), but what is not clear is how these GABAergic abnormalities cause symptoms of the illness. While animal models provide helpful test beds for modeling schizophrenia and

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designing pharmacologic interventions, functional targets in patients linking behavior with the underlying molecular mechanisms are needed. In this article, we will critically review methodologies used for assaying in vivo function of GABA in schizophrenia, focusing on neuroimaging studies, transcranial magnetic stimulation (TMS) probes and pharmacologic challenges.

2.0 Post-mortem GABA findings in schizophrenia

GABAergic interneurons are the predominant machinery of inhibition in the brain. In schizophrenia, the most replicated findings are reductions in the 67-kDa isoform of the synthetic enzyme for GABA, glutamic acid decarboxylase (GAD67; Curley et al., 2011; Guidotti et al., 2000). This reduction has been localized to parvalbumin (PV) positive interneurons (Hashimoto et al., 2003) and has been observed in the dorsolateral prefrontal cortex (dLPFC; Akbarian et al., 1995), anterior cingulate cortex (ACC; Woo et al., 2004), motor cortex (Hashimoto et al., 2008b), visual cortex (Hashimoto et al., 2008b) and hippocampus (Benes et al., 2007; Knable et al., 2004). Levels of PV mRNA are also reduced in schizophrenia, and some findings show that the density of these interneurons does not differ from comparison groups (Beasley et al., 2002; Hashimoto et al., 2003; Woo et al., 1997), suggesting no loss of PV-positive inhibitory interneurons in schizophrenia. However, using different techniques for counting PV-positive neurons, as well as cresyl violet stains useful for counting the entire population of interneurons, other groups have found reduced cell counts of PV-positive and other interneurons in hippocampus (Benes et al., 1998; Konradi et al., 2011) and layers II/III of the anterior cingulate gyrus (Benes et al., 1991). Reductions in other GABAergic-related markers have also been noted, such as mRNA levels of neuropeptide Y, somatostatin and cholecystokinin (Hashimoto et al., 2008a). Evidence suggests that the changes are not due to extraneous factors such as age, sex or medication effects. In sum, a variety of techniques have been applied to examine GABAergic systems, which have not always yielded consistent findings, but it is clear that GABA-related dysfunction is an important feature of schizophrenia.

Focusing on the PV-positive interneurons, at least two varieties are relevant for schizophrenia: Fast-spiking PV-positive basket cells (PVBC) synapse on the pyramidal cell body and dendrites in layer III, whereas chandelier cells (PVChC) synapse on the axon initial segment (AIS) of the pyramidal cells (for review, see (Markram et al., 2004)). Perisomatic GABA receptors (GABAR) of the PVBC neurons, predominantly containing the α -1 subunit, show mRNA reductions, while the GABAR on the AIS, predominantly containing the α -2 subunit, appear to be upregulated (Beneyto et al., 2011; Volk et al., 2002), along with down regulation of PVChC GAT1 (GABA membrane transporter; Pierri et al., 1999). Importantly, PVChCs appear to *depolarize and excite* pyramidal cells when releasing GABA at the AIS (Szabadics et al., 2006; Woodruff et al., 2009), whereas the PVBCs inhibit pyramidal cells (Markram et al., 2004). In schizophrenia, these changes could be compensations, possibly for reduced excitatory drive to the layer III pyramidal cells, implied by reduced dendritic spine density (Lewis et al., 2012). In this conceptualization, the findings may reflect alterations in the excitatory/inhibitory balance of the cellular micro-circuits.

Interestingly, PVBCs are associated with cortical gamma oscillations (Bartos et al., 2007; Fuchs et al., 2007; Sohal et al., 2009). These cortical rhythms are associated with integrative cortical function (Buzsaki and Draguhn, 2004), including attention (Fries et al., 2001), working memory (Tallon-Baudry et al., 1998) and perception (Gray et al., 1989). Abnormal gamma oscillations have also been implicated in schizophrenia – a potential link between the PV abnormalities and cognitive dysfunction observed in the illness (Gonzalez-Burgos et al., 2011; Uhlhaas and Singer, 2010). However, since abnormal gamma oscillations can arise from a variety of pathological mechanisms – not necessarily GABAergic -- in the sections that follow, we will consider other methodologies that more specifically target GABA function in schizophrenia.

Given that many of these studies combine samples of schizophrenia and schizoaffective disorder, we will use ‘schizophrenia’ to refer to both diagnostic groups.

3.0 In vivo measurement of GABA and GABARs

3.1 Radioligand studies

Several radioligands exist to measure the availability of GABARs in the brain. Positron emission tomographic (PET) studies have used [^{11}C]flumazenil, or a fluoridated derivative [^{18}F]fluoroflumazenil, which bind to α -1,2,3,6 subunits (See Figure 1 for an overview of the GABAR subunit pharmacology). Single photon emission computed tomography (SPECT) studies have employed [^{123}I]iomazenil, with similar pharmacology except for inverse agonist properties. PET studies have more recently used [^{11}C]Ro15-4513, an inverse agonist binding to α -1,5. Although these neuroimaging ligand studies permit reliable quantification of receptor densities, the diversity of GABAR and differential distribution in the brain presents an interpretative challenge when assaying for pathological changes.

Overall, the density of GABAR in schizophrenia does not appear abnormal in radioligand studies (see Table 1). SPECT studies with [^{123}I]iomazenil reported no group differences in comparison with control subjects (Abi-Dargham et al., 1999; Ball et al., 1998; Busatto et al., 1997; Verhoeff et al., 1999), as did a PET study with [^{11}C]Ro15-4513 (Asai et al., 2008). One group found that medial frontal cortex binding was positively associated with total symptoms, but negatively associated with outcome measures across the brain after displacement of the ligand following a diazepam infusion (Schroder et al., 1997). While other groups also found symptom correlations with binding (Ball et al., 1998; Busatto et al., 1997), another group failed to replicate these symptom correlations using a quantitative measurement of binding not sensitive to cerebral blood flow (Abi-Dargham et al., 1999). Considering what is now known from the post-mortem findings, these essentially negative findings should not be too surprising. If the α -1 subunit GABAR's are downregulated at the pyramidal cell body and the α -2 subunit GABAR's are upregulated at the AIS of the pyramidal cells, a relatively non-selective ligand is not likely to show aggregate differences. Furthermore, 45% of the GABAergic cells in dLPFC are calretinin containing (not PV), which are not compromised in schizophrenia (Lewis et al., 2012). Using more selective agents, such as [^{11}C]Ro15-4513, in combination with a pharmacologic challenge may provide a more promising approach. Recently, tiagabine, which increases GABA levels by blocking GAT1, has been shown to demonstrate shifts in α -1 binding due to endogenous

GABA in healthy individuals (Stokes et al., 2014). Such a strategy may be effective at evaluating the α -1 subunit changes reported in schizophrenia (Beneyto et al., 2011; Volk et al., 2002).

3.2 Magnetic resonance spectroscopy studies

Magnetic resonance spectroscopy (MRS) is another imaging technique, which, in distinction to PET/SPECT studies, can assay GABA concentrations in vivo. However, measurement is limited by low signal-to-noise ratio, large voxel sizes, typically around 18 cm³, and sparse sampling, usually no more than 3 voxels sampled with a 3-tesla magnet. In contrast to radioligand studies of GABAR, a prediction of reduced GABA concentration from MRS is more straightforward, although MRS cannot separate intra-cellular from extra-cellular GABA, somewhat complicating interpretation. However, results to date are mixed, as Table 2 demonstrates. Of 17 voxels studied, 4 show reduced GABA, 3 reported increased GABA and 10 showed no difference. Reduced GABA in occipital cortex has been associated with impaired performance on visual orientation surround suppression, a GABAergic-dependent early visual process deficient in schizophrenia (Yoon et al., 2010). Linking MRS-measured GABA with disrupted visual processing in schizophrenia represents an important step, although another group failed to find a relationship between another visual processing measure (contrast sensitivity) and GABA levels (Kelemen et al., 2013).

Reliable measurement of GABA is relatively new, with the first report in schizophrenia appearing in 2009 (Goto et al., 2009b). Medication status may be a confounding factor, as suggested by one study finding increased GABA only in unmedicated subjects in a medial prefrontal cortex (MPFC) voxel (Kegeles et al., 2012), although another report found reduced GABA in occipital cortex in unmedicated patients (Kelemen et al., 2013). Sampling of voxels across the brain has also been sparse due to long acquisition times for single voxels, and it is too early to tell whether or not there is regional variation in GABA abnormalities based on MRS findings. One promising development is linking GABA levels to risk genes for schizophrenia that are involved in GABA synthesis, such as the gene for GAD1 (Marenco et al., 2010) or Erbb4, associated with risk and interneuron development (Marenco et al., 2011). Another interesting approach found a positive correlation between GABA levels and gamma activity over the dLPFC (Chen et al., 2014). In summary, while studies to date have not provided confirmation of reduced GABA levels in schizophrenia, the power of this technology has yet to be fully exploited.

4.0 GABA pharmacologic challenge and cognition

Cognitive impairment is a prominent feature of schizophrenia, and several investigators have proposed theories linking cognitive dysfunction to GABAergic abnormalities in schizophrenia (Gonzalez-Burgos et al., 2011; Lewis et al., 2012; Lisman et al., 2008). A critical constituent of some of these theories has been hypofunction of the excitatory N-methyl-D-aspartic acid glutamate receptors (NMDAR; Coyle, 2004; Javitt and Zukin, 1991; Olney and Farber, 1995). NMDAR antagonists, such as ketamine and PCP, cause schizophrenia-like symptoms when administered to healthy volunteers, including interpersonal withdrawal and cognitive impairment not seen with dopaminergic agonists (Krystal et al., 1994; Lahti et al., 1995b). In animal models, NMDA antagonists inhibit

GABAergic interneurons, leading to excitation of the disinhibited pyramidal cells (Homayoun and Moghaddam, 2007), accounting for observations from neuroimaging studies in humans of increased cerebral blood flow and metabolism after ketamine challenge (Holcomb et al., 2005; Lahti et al., 1995a; Vollenweider, 1998). Animal work has shown that down-regulation of the GAD67 enzyme occurs as a response of the interneuron to NMDA antagonism, which has been attributed to reduced Ca^{++} flux from the hypofunctioning NMDAR (Kinney et al., 2006; Zhang et al., 2008), and reduction of the NR2A subunit of the NMDAR has been associated with PV neurons in schizophrenia (Woo et al., 2004). Putting this work together, Lisman has suggested that GABAergic interneurons might falsely sense reduced pyramidal cell activity, and reduced GAD67 production may reflect the attempt to rebalance excitation/inhibition (Lisman, 2012). As mentioned above, Lewis and colleagues have also suggested that a re-setting of the excitatory/inhibitory balance occurs in conjunction with reduced layer III excitation, inferred from reduced dendritic spine density (Lewis et al., 2012). In both interpretations, the implication is that overall cortical capacity is reduced, potentially linked to a reduction in the gamma-oscillations mediated by PVBCs and PVChCs.

To address GABAergic mechanisms more specifically, Menzies and colleagues conducted a pharmacologic fMRI study, in which schizophrenia patients performed a working memory task ('n-back') after taking lorazepam (a benzodiazepine [BDZ], which allosterically modulates the GABAR and potentiates inhibitory function), flumazenil (an antagonist at the BDZ receptor on the GABAR with partial inverse agonist properties) and saline (Menzies et al., 2007). Working memory performance was worsened by lorazepam and improved by flumazenil in the schizophrenia patients, changes not seen in the controls. Overall, lorazepam and flumazenil both decreased activation and deactivation in the controls, whereas lorazepam did not reduce deactivation and flumazenil tended to enhance deactivation in the schizophrenia patients. Regional drug-by-group interactions were also noted in several brain areas. Their results confirm differential potency of GABAergic inhibitory systems in the schizophrenia brain and also highlight the difficulty of straightforward predictions in this paradigm. The use of the challenging n-back task may have confounded their experiment, since performance in the schizophrenia patients was at chance level for many of the experimental conditions. Together, these findings illustrate the importance of considering the balance between inhibitory and excitatory systems, as reflected by the fact that both potentiating and reducing overall GABA tone, in the healthy subjects, resulted in a similar change in overall activation and deactivation.

The Menzies study illustrates – albeit in a very small sample -- the possibility of targeting the BDZ site on the GABAR to improve cognition in schizophrenia. Benzodiazepines bind relatively non-selectively to the α -1,2,3,5 subunits, and it has been suggested that drugs with subtype selectivity, e. g. for the α -2,3 subunits (Guidotti et al., 2005; Korpi and Sinkkonen, 2006; Rudolph and Mohler, 2014) or the α -5 subunit (Lodge and Grace, 2011) may be more efficacious in treating schizophrenia. A recent trial with an α -2,3 selective agent, MK-0777 (also known as TPA-023) showed promise in a small, proof-of-concept trial, improving performance on several cognitive tasks and increasing gamma band power (Lewis et al., 2008). Unfortunately, the drug failed to improve cognition or symptoms in a larger trial (Buchanan et al., 2011), but relatively poor affinity for the α -2 subunit make MK-0777

(Rudolph and Knoflach, 2011) an imperfect test of the hypothesis that these subunit selective compounds can play a role in schizophrenia therapeutics.

5.0 TMS studies of GABA and motor activity

TMS has been employed as another tool to study GABA-related inhibition in schizophrenia. TMS delivers a pulsed magnetic field that stimulates electrical current in nervous tissue. The most common paradigms use TMS to stimulate over the motor cortex, leading to contraction of a peripheral muscle, typically of the thumb or finger (motor evoked potential, MEP). One paradigm, called short-interval intra-cortical inhibition (SICI), involves the delivery of a sub-threshold conditioning stimulus (CS), which does not elicit a motor response by itself, approximately 1-4 msec prior to a suprathreshold test stimulus (TS), which does elicit a motor response (Kujirai et al., 1993). The pairing of CS with TS reduces the amplitude of the MEP compared to the TS alone, referred to as inhibition. Of relevance for schizophrenia, pharmacologic evidence indicates the SICI is mediated by GABA_A interneurons (Di Lazzaro et al., 2000; Ziemann, 2003), probably with the α -2,3 subunit (Di Lazzaro et al., 2006). A recent meta-analysis of 12 published studies found a significant reduction in SICI in schizophrenia patients (Hedge's $g = 0.476$, $p < 0.0005$), and no effect of age or medication status (Radhu et al., 2013). As Table 3 shows, reduced SICI has been reported across all phases of the illness. Some groups have found symptom correlations (less inhibition with greater symptom severity) (Daskalakis et al., 2002; Daskalakis et al., 2008; Liu et al., 2009), but this has not been found in other centers (see Table 3). Interestingly, one recent report found a correlation between greater SICI inhibition and working memory performance (Takahashi et al., 2013). Although these studies cannot rule out non-GABAergic causes of reduced SICI, this literature provides some of the most direct evidence for reduced inhibitory function predicted by the post-mortem GABA findings.

Expanding the reach of TMS probes outside the motor cortex and dependency upon measuring the MEP is desirable if one wishes to study more complex cortical functions. Recent innovations have combined TMS with other modalities, such as EEG, MEG and fMRI. For instance, using interleaved TMS and EEG, Ferrarelli and colleagues demonstrated decreased evoked gamma oscillations in fronto-central cortex after TMS stimulation of pre-motor cortex in schizophrenia (Ferrarelli et al., 2008). While gamma oscillations have been linked with GABAergic abnormalities (Gonzalez-Burgos et al., 2011; Uhlhaas and Singer, 2010), it is not entirely clear that this TMS-EEG paradigm implicates GABA deficits. However, with additional study and pharmacologic manipulation, it may yet be possible to use such a paradigm to link with the underlying molecular deficits.

6.0 GABA and emotion processing

It is well established that drugs acting on GABARs, such as valproate and BDZ, affect emotion regulation and have been used to treat schizophrenia, e. g. (Wassef et al., 1999). These drugs treat anxiety associated with psychosis, but GABAergic systems are also more directly implicated in psychotic symptoms. Benzodiazepines can prevent a psychotic episode in the early stages of relapse (Carpenter et al., 1999), and blocking GABAR activity with iomazenil, an antagonist and partial inverse agonist of the BDZ receptor, can induce

psychotic symptoms in clinically stable schizophrenia patients (Ahn et al., 2011). Furthermore, considering that GAD67 deficits have been identified in patients with bipolar disorder (Guidotti et al., 2000; Torrey et al., 2005; Woo et al., 2008), affect may be an appropriate behavioral target for a schizophrenia drug aimed at one of the α -subunits of GABARs.

Benzodiazepine challenges during fMRI have been used to address GABAergic mechanisms of emotion processing in schizophrenia. Using a lorazepam challenge while subjects viewed salient visual stimuli, Taylor and colleagues (Taylor et al., 2014) found that schizophrenia patients exhibited a predicted group by drug interactions in the dorsal MPFC (dMPFC), as well as right superior frontal gyrus and left and right occipital regions. Instead of lorazepam causing a decreased BOLD signal as it did in the healthy subjects, it caused either less signal drop or, in the case of the dMPFC, increased BOLD signal in schizophrenia patients. These findings are consistent with the GABAR changes from the post-mortem data, because decreased α -1 GABAR would lead to less effect of lorazepam inhibiting neuronal activity, whereas increased α -2 GABAR on the AIS would lead to increased excitation (Lewis et al., 2012). Interestingly, the magnitude of BOLD change with lorazepam correlated with several measures of negative affect, in both the schizophrenia patients and the comparison subjects, suggesting that GABAergic function is associated with negative affect in schizophrenia, on a continuum with normal behavior.

Using an alprazolam challenge while identifying emotional faces, Wolf and colleagues found that the first degree relatives of schizophrenia patients exhibited a stronger reduction in the amygdala and hippocampus than control subjects, who showed no BOLD signal change in these regions (Wolf et al., 2011), findings which may be consistent with at least one study showing decreases in high affinity GABA uptake sites in the amygdala (Simpson et al., 1989). Differences between these two BDZ challenge studies with emotional stimuli, as well as the BDZ challenge during a cognitive task described in section 4.0, may reflect the differential effects of task to uncover different aspects of abnormal GABA function. While these preliminary pharmacofMRI studies implicate GABAR abnormalities in schizophrenia, the fMRI signal is a composite of many physiological factors, and alternative interpretations are difficult to rule out.

7.0 Conclusions

GABAergic abnormalities in post-mortem studies of schizophrenia provide a rich database and fertile ground for theoretical models, although as this review demonstrates, functional implications of this post-mortem work have not been definitively established. The in vivo studies face a number of challenges, such as: 1) considerable variability exists at the subject level in all studies of post-mortem and in vivo GABA markers; 2) uncertainty exists as to whether or not a single or multiple etio-pathological processes characterizes patient samples gathered under the label of 'schizophrenia;' 3) not all findings have been replicated by all groups in all samples; 4) even if one assumes a single etio-pathological process and 100% replication, it remains difficult to predict implications of molecular level abnormalities on large-scale, aggregate measures of behavior; 5) regional variation across brain structures is poorly characterized; and 6) limited understanding of the molecular mechanisms and

microcircuitry of the brain hinders our ability to interpret and predict effects on behavior. Most of the specific studies cited here have small sample sizes, usually less than 20 subjects, meaning that heterogeneity may lead to null results. Lastly, the experimental base for studies aimed at functional implications provides very sparse coverage of different functions and brain regions.

In spite of these limitations, several conclusions may be offered. The indirect measures available with current methodologies implicate a wide range of functions and brain regions associated with GABAergic abnormalities. In other words, it may be premature to limit attention to the dLPFC, hippocampus and cognitive function, when motor cortex and visual cortex may be involved, along with simple motor activity, perception, emotion processing and positive symptoms. As mentioned above, the post-mortem findings have been observed across all cortical regions examined, and it is easy to imagine that a pan-cortical defect in the microarchitecture might characterize some individuals with schizophrenia. Obviously, much work remains, but combinations of existing methodologies, such as pharmacologic challenges with neuroimaging studies, have the potential to yield new information that may refine our understanding of treatment targets and, ultimately, benefit those patients suffering from this devastating disorder.

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none

References

- Abi-Dargham A, Laruelle M, Krystal J, D'Souza C, Zoghbi S, Baldwin RM, Seibyl J, Mawlawi O, de Erasmquin G, Charney D, Innis RB. No evidence of altered in vivo benzodiazepine receptor binding in schizophrenia. *Neuropsychopharmacology*. 1999; 20(6):650–661. [PubMed: 10327433]
- Ahn K, Gil R, Seibyl J, Sewell RA, D'Souza DC. Probing GABA receptor function in schizophrenia with iomazenil. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology*. 2011; 36(3):677–683. [PubMed: 21068719]
- Akbarian S, Huang HS. Molecular and cellular mechanisms of altered GAD1/GAD67 expression in schizophrenia and related disorders. *Brain research reviews*. 2006; 52(2):293–304. [PubMed: 16759710]
- Akbarian S, Kim JJ, Potkin SG, Hagman JO, Tafazzoli A, Bunney WE Jr, Jones EG. Gene Expression for Glutamic Acid Decarboxylase is Reduced Without Loss of Neurons in Prefrontal Cortex of Schizophrenics. *Arch Gen Psychiatry*. 1995; 52:258–266. [PubMed: 7702443]
- Asai Y, Takano A, Ito H, Okubo Y, Matsuura M, Otsuka A, Takahashi H, Ando T, Ito S, Arakawa R, Asai K, Suhara T. GABAA/Benzodiazepine receptor binding in patients with schizophrenia using [¹¹C]Ro15-4513, a radioligand with relatively high affinity for alpha5 subunit. *Schizophrenia research*. 2008; 99(1-3):333–340. [PubMed: 18042347]
- Ball S, Busatto GF, David AS, Jones SH, Hemsley DR, Pilowsky LS, Costa DC, Ell PJ, Kerwin RW. Cognitive functioning and GABAA/benzodiazepine receptor binding in schizophrenia: a 123I-iomazenil SPET study. *Biol Psychiatry*. 1998; 43(2):107–117. [PubMed: 9474443]
- Bartos M, Vida I, Jonas P. Synaptic mechanisms of synchronized gamma oscillations in inhibitory interneuron networks. *Nature reviews Neuroscience*. 2007; 8(1):45–56. [PubMed: 17180162]
- Beasley CL, Zhang ZJ, Patten I, Reynolds GP. Selective deficits in prefrontal cortical GABAergic neurons in schizophrenia defined by the presence of calcium-binding proteins. *Biological psychiatry*. 2002; 52(7):708–715. [PubMed: 12372661]

- Benes FM. Amygdalocortical circuitry in schizophrenia: from circuits to molecules. *Neuropsychopharmacology* : official publication of the American College of Neuropsychopharmacology. 2010; 35(1):239–257. [PubMed: 19727065]
- Benes FM, Kwok EW, Vincent SL, Todtenkopf MS. A reduction of nonpyramidal cells in sector CA2 of schizophrenics and manic depressives. *Biol Psychiatry*. 1998; 44(2):88–97. [PubMed: 9646890]
- Benes FM, Lim B, Matzilevich D, Walsh JP, Subburaju S, Minns M. Regulation of the GABA cell phenotype in hippocampus of schizophrenics and bipolars. *Proceedings of the National Academy of Sciences of the United States of America*. 2007; 104(24):10164–10169. [PubMed: 17553960]
- Benes FM, McSparren J, Bird ED, SanGiovanni JP, Vincent SL. Deficits in small interneurons in prefrontal and cingulate cortices of schizophrenic and schizoaffective patients. *Arch Gen Psychiatry*. 1991; 48(11):996–1001. [PubMed: 1747023]
- Beneyto M, Abbott A, Hashimoto T, Lewis DA. Lamina-specific alterations in cortical GABA(A) receptor subunit expression in schizophrenia. *Cereb Cortex*. 2011; 21(5):999–1011. [PubMed: 20843900]
- Brickley SG, Mody I. Extrasynaptic GABA(A) receptors: their function in the CNS and implications for disease. *Neuron*. 2012; 73(1):23–34. [PubMed: 22243744]
- Buchanan RW, Keefe RS, Lieberman JA, Barch DM, Csernansky JG, Goff DC, Gold JM, Green MF, Jarskog LF, Javitt DC, Kimhy D, Kraus MS, McEvoy JP, Mesholam-Gately RI, Seidman LJ, Ball MP, McMahon RP, Kern RS, Robinson J, Marder SR. A randomized clinical trial of MK-0777 for the treatment of cognitive impairments in people with schizophrenia. *Biological psychiatry*. 2011; 69(5):442–449. [PubMed: 21145041]
- Busatto GF, Pilowsky LS, Costa DC, Ell PJ, David AS, Lucey JV, Kerwin RW. Correlation between reduced in vivo benzodiazepine receptor binding and severity of psychotic symptoms in schizophrenia. *Am J Psychiatry*. 1997; 154(1):56–63. [PubMed: 8988959]
- Buzsaki G, Draguhn A. Neuronal oscillations in cortical networks. *Science*. 2004; 304(5679):1926–1929. [PubMed: 15218136]
- Carpenter WT Jr, Buchanan RW, Kirkpatrick B, Breier AF. Diazepam treatment of early signs of exacerbation in schizophrenia. *Am J Psychiatry*. 1999; 156(2):299–303. [PubMed: 9989567]
- Chen CM, Stanford AD, Mao X, Abi-Dargham A, Shungu DC, Lisanby SH, Schroeder CE, Kegeles LS. GABA level, gamma oscillation, and working memory performance in schizophrenia. *Neuroimage Clin*. 2014; 4:531–539. [PubMed: 24749063]
- Coyle JT. The GABA-glutamate connection in schizophrenia: which is the proximate cause? *Biochem Pharmacol*. 2004; 68(8):1507–1514. [PubMed: 15451393]
- Curley AA, Arion D, Volk DW, Asafu-Adjei JK, Sampson AR, Fish KN, Lewis DA. Cortical deficits of glutamic acid decarboxylase 67 expression in schizophrenia: clinical, protein, and cell type-specific features. *The American journal of psychiatry*. 2011; 168(9):921–929. [PubMed: 21632647]
- Daskalakis ZJ, Christensen BK, Chen R, Fitzgerald PB, Zipursky RB, Kapur S. Evidence for impaired cortical inhibition in schizophrenia using transcranial magnetic stimulation. *Arch Gen Psychiatry*. 2002; 59(4):347–354. [PubMed: 11926935]
- Daskalakis ZJ, Christensen BK, Fitzgerald PB, Moller B, Fountain SI, Chen R. Increased cortical inhibition in persons with schizophrenia treated with clozapine. *Journal of psychopharmacology*. 2008; 22(2):203–209. [PubMed: 18308816]
- Di Lazzaro V, Oliviero A, Meglio M, Cioni B, Tamburrini G, Tonali P, Rothwell JC. Direct demonstration of the effect of lorazepam on the excitability of the human motor cortex. *Clinical neurophysiology* : official journal of the International Federation of Clinical Neurophysiology. 2000; 111(5):794–799. [PubMed: 10802448]
- Di Lazzaro V, Pilato F, Dileone M, Ranieri F, Ricci V, Profice P, Bria P, Tonali PA, Ziemann U. GABAA receptor subtype specific enhancement of inhibition in human motor cortex. *The Journal of physiology*. 2006; 575(Pt 3):721–726. [PubMed: 16809358]
- Eichhammer P, Wiegand R, Kharraz A, Langguth B, Binder H, Hajak G. Cortical excitability in neuroleptic-naïve first-episode schizophrenic patients. *Schizophrenia research*. 2004; 67(2-3):253–259. [PubMed: 14984885]

- Ferrarelli F, Massimini M, Peterson MJ, Riedner BA, Lazar M, Murphy MJ, Huber R, Rosanova M, Alexander AL, Kalin N, Tononi G. Reduced evoked gamma oscillations in the frontal cortex in schizophrenia patients: a TMS/EEG study. *The American journal of psychiatry*. 2008; 165(8):996–1005. [PubMed: 18483133]
- Fitzgerald PB, Brown TL, Daskalakis ZJ, Kulkarni J. A transcranial magnetic stimulation study of inhibitory deficits in the motor cortex in patients with schizophrenia. *Psychiatry research*. 2002a; 114(1):11–22. [PubMed: 11864806]
- Fitzgerald PB, Brown TL, Daskalakis ZJ, Kulkarni J. A transcranial magnetic stimulation study of the effects of olanzapine and risperidone on motor cortical excitability in patients with schizophrenia. *Psychopharmacology*. 2002b; 162(1):74–81. [PubMed: 12107621]
- Fitzgerald PB, Brown TL, Marston NA, Oxley T, De Castella A, Daskalakis ZJ, Kulkarni J. Reduced plastic brain responses in schizophrenia: a transcranial magnetic stimulation study. *Schizophrenia research*. 2004; 71(1):17–26. [PubMed: 15374568]
- Fries P, Reynolds JH, Rorie AE, Desimone R. Modulation of oscillatory neuronal synchronization by selective visual attention. *Science*. 2001; 291(5508):1560–1563. [PubMed: 11222864]
- Fuchs EC, Zivkovic AR, Cunningham MO, Middleton S, Lebeau FE, Bannerman DM, Rozov A, Whittington MA, Traub RD, Rawlins JN, Monyer H. Recruitment of parvalbumin-positive interneurons determines hippocampal function and associated behavior. *Neuron*. 2007; 53(4):591–604. [PubMed: 17296559]
- Gonzalez-Burgos G, Fish KN, Lewis DA. GABA neuron alterations, cortical circuit dysfunction and cognitive deficits in schizophrenia. *Neural Plast*. 2011; 2011:723184. [PubMed: 21904685]
- Goto N, Yoshimura R, Kakeda S, Moriya J, Hayashi K, Ikenouchi-Sugita A, Umene-Nakano W, Hori H, Ueda N, Korogi Y, Nakamura J. Associations between plasma levels of 3-methoxy-4-hydroxyphenylglycol (MHPG) and negative symptoms or cognitive impairments in early-stage schizophrenia. *Hum Psychopharmacol*. 2009a; 24(8):639–645. [PubMed: 19946939]
- Goto N, Yoshimura R, Moriya J, Kakeda S, Ueda N, Ikenouchi-Sugita A, Umene-Nakano W, Hayashi K, Oonari N, Korogi Y, Nakamura J. Reduction of brain gamma-aminobutyric acid (GABA) concentrations in early-stage schizophrenia patients: 3T Proton MRS study. *Schizophrenia research*. 2009b; 112(1-3):192–193. [PubMed: 19464152]
- Gray CM, König P, Engel AK, Singer W. Oscillatory responses in cat visual cortex exhibit inter-columnar synchronization which reflects global stimulus properties. *Nature*. 1989; 338(6213):334–337. [PubMed: 2922061]
- Guidotti A, Auta J, Davis JM, Di-Giorgi-Gerevini V, Dwivedi Y, Grayson DR, Impagnatiello F, Pandey G, Pesold C, Sharma R, Uzunov D, Costa E. Decrease in reelin and glutamic acid decarboxylase67 (GAD67) expression in schizophrenia and bipolar disorder: a postmortem brain study. *Archives of general psychiatry*. 2000; 57(11):1061–1069. [PubMed: 11074872]
- Guidotti A, Auta J, Davis JM, Dong E, Grayson DR, Veldic M, Zhang X, Costa E. GABAergic dysfunction in schizophrenia: new treatment strategies on the horizon. *Psychopharmacology (Berl)*. 2005; 180(2):191–205. [PubMed: 15864560]
- Hasan A, Nitsche MA, Rein B, Schneider-Axmann T, Guse B, Gruber O, Falkai P, Wobrock T. Dysfunctional long-term potentiation-like plasticity in schizophrenia revealed by transcranial direct current stimulation. *Behavioural brain research*. 2011; 224(1):15–22. [PubMed: 21645555]
- Hasan A, Wobrock T, Grefkes C, Labusga M, Levold K, Schneider-Axmann T, Falkai P, Müller H, Klosterkötter J, Bechdolf A. Deficient inhibitory cortical networks in antipsychotic-naïve subjects at risk of developing first-episode psychosis and first-episode schizophrenia patients: a cross-sectional study. *Biological psychiatry*. 2012; 72(9):744–751. [PubMed: 22502988]
- Hashimoto T, Arion D, Unger T, Maldonado-Aviles JG, Morris HM, Volk DW, Mirmics K, Lewis DA. Alterations in GABA-related transcriptome in the dorsolateral prefrontal cortex of subjects with schizophrenia. *Mol Psychiatry*. 2008a; 13(2):147–161. [PubMed: 17471287]
- Hashimoto T, Bazmi HH, Mirmics K, Wu Q, Sampson AR, Lewis DA. Conserved regional patterns of GABA-related transcript expression in the neocortex of subjects with schizophrenia. *Am J Psychiatry*. 2008b; 165(4):479–489. [PubMed: 18281411]

- Hashimoto T, Volk DW, Eggan SM, Mirnics K, Pierri JN, Sun Z, Sampson AR, Lewis DA. Gene expression deficits in a subclass of GABA neurons in the prefrontal cortex of subjects with schizophrenia. *J Neurosci*. 2003; 23(15):6315–6326. [PubMed: 12867516]
- Holcomb HH, Lahti AC, Medoff DR, Cullen T, Tamminga CA. Effects of noncompetitive NMDA receptor blockade on anterior cingulate cerebral blood flow in volunteers with schizophrenia. *Neuropsychopharmacology*. 2005; 30(12):2275–2282. [PubMed: 16034443]
- Homayoun H, Moghaddam B. NMDA receptor hypofunction produces opposite effects on prefrontal cortex interneurons and pyramidal neurons. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2007; 27(43):11496–11500. [PubMed: 17959792]
- Javitt DC, Zukin SR. Recent advances in the phencyclidine model of schizophrenia. *The American journal of psychiatry*. 1991; 148(10):1301–1308. [PubMed: 1654746]
- Kegeles LS, Mao X, Stanford AD, Girgis R, Ojeil N, Xu X, Gil R, Slifstein M, Abi-Dargham A, Lisanby SH, Shungu DC. Elevated prefrontal cortex gamma-aminobutyric acid and glutamate-glutamine levels in schizophrenia measured in vivo with proton magnetic resonance spectroscopy. *Archives of general psychiatry*. 2012; 69(5):449–459. [PubMed: 22213769]
- Kelemen O, Kiss I, Benedek G, Keri S. Perceptual and cognitive effects of antipsychotics in first-episode schizophrenia: the potential impact of GABA concentration in the visual cortex. *Progress in neuro-psychopharmacology & biological psychiatry*. 2013; 47:13–19. [PubMed: 23954737]
- Kinney JW, Davis CN, Tabarean I, Conti B, Bartfai T, Behrens MM. A specific role for NR2A-containing NMDA receptors in the maintenance of parvalbumin and GAD67 immunoreactivity in cultured interneurons. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2006; 26(5):1604–1615. [PubMed: 16452684]
- Knable MB, Barci BM, Webster MJ, Meador-Woodruff J, Torrey EF. Molecular abnormalities of the hippocampus in severe psychiatric illness: postmortem findings from the Stanley Neuropathology Consortium. *Mol Psychiatry*. 2004; 9(6):609–620. 544. [PubMed: 14708030]
- Konradi C, Yang CK, Zimmerman EI, Lohmann KM, Gresch P, Pantazopoulos H, Berretta S, Heckers S. Hippocampal interneurons are abnormal in schizophrenia. *Schizophr Res*. 2011; 131(1-3):165–173. [PubMed: 21745723]
- Korpi ER, Sinkkonen ST. GABA(A) receptor subtypes as targets for neuropsychiatric drug development. *Pharmacol Ther*. 2006; 109(1-2):12–32. [PubMed: 15996746]
- Krystal JH, Karper LP, Seibyl JP, Freeman GK, Delaney R, Bremner JD, Heninger GR, Bowers MB Jr, Charney DS. Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. *Arch Gen Psychiatry*. 1994; 51(3):199–214. [PubMed: 8122957]
- Kujirai T, Caramia MD, Rothwell JC, Day BL, Thompson PD, Ferbert A, Wroe S, Asselman P, Marsden CD. Corticocortical inhibition in human motor cortex. *The Journal of physiology*. 1993; 471:501–519. [PubMed: 8120818]
- Lahti AC, Holcomb HH, Medoff DR, Tamminga CA. Ketamine activates psychosis and alters limbic blood flow in schizophrenia. *Neuroreport*. 1995a; 6(6):869–872. [PubMed: 7612873]
- Lahti AC, Koffel B, LaPorte D, Tamminga CA. Subanesthetic doses of ketamine stimulate psychosis in schizophrenia. *Neuropsychopharmacology*. 1995b; 13(1):9–19. [PubMed: 8526975]
- Lee JS, Lee JD, Park HJ, Oh MK, Chun JW, Kim SJ, Kim E, Kim JJ. Is the GABA System Related to the Social Competence Improvement Effect of Aripiprazole? An (18)F-Fluorofluminazenil PET Study. *Psychiatry Investig*. 2013; 10(1):75–80.
- Lewis DA, Cho RY, Carter CS, Eklund K, Forster S, Kelly MA, Montrose D. Subunit-selective modulation of GABA type A receptor neurotransmission and cognition in schizophrenia. *Am J Psychiatry*. 2008; 165(12):1585–1593. [PubMed: 18923067]
- Lewis DA, Curley AA, Glausier JR, Volk DW. Cortical parvalbumin interneurons and cognitive dysfunction in schizophrenia. *Trends in neurosciences*. 2012; 35(1):57–67. [PubMed: 22154068]
- Lisman J. Excitation, inhibition, local oscillations, or large-scale loops: what causes the symptoms of schizophrenia? *Current opinion in neurobiology*. 2012; 22(3):537–544. [PubMed: 22079494]
- Lisman JE, Coyle JT, Green RW, Javitt DC, Benes FM, Heckers S, Grace AA. Circuit-based framework for understanding neurotransmitter and risk gene interactions in schizophrenia. *Trends Neurosci*. 2008; 31(5):234–242. [PubMed: 18395805]

- Liu SK, Fitzgerald PB, Daigle M, Chen R, Daskalakis ZJ. The relationship between cortical inhibition, antipsychotic treatment, and the symptoms of schizophrenia. *Biological psychiatry*. 2009; 65(6): 503–509. [PubMed: 18950746]
- Lodge DJ, Grace AA. Hippocampal dysregulation of dopamine system function and the pathophysiology of schizophrenia. *Trends in pharmacological sciences*. 2011; 32(9):507–513. [PubMed: 21700346]
- Marenco S, Geramita M, van der Veen JW, Barnett AS, Kolachana B, Shen J, Weinberger DR, Law AJ. Genetic association of ErbB4 and human cortical GABA levels in vivo. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2011; 31(32):11628–11632. [PubMed: 21832192]
- Marenco S, Savostyanova AA, van der Veen JW, Geramita M, Stern A, Barnett AS, Kolachana B, Radulescu E, Zhang F, Callicott JH, Straub RE, Shen J, Weinberger DR. Genetic modulation of GABA levels in the anterior cingulate cortex by GAD1 and COMT. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology*. 2010; 35(8):1708–1717. [PubMed: 20357758]
- Markram H, Toledo-Rodriguez M, Wang Y, Gupta A, Silberberg G, Wu C. Interneurons of the neocortical inhibitory system. *Nature reviews Neuroscience*. 2004; 5(10):793–807. [PubMed: 15378039]
- Menzies L, Ooi C, Kamath S, Suckling J, McKenna P, Fletcher P, Bullmore E, Stephenson C. Effects of gamma-aminobutyric acid-modulating drugs on working memory and brain function in patients with schizophrenia. *Arch Gen Psychiatry*. 2007; 64(2):156–167. [PubMed: 17283283]
- Nakazawa K, Zsiros V, Jiang Z, Nakao K, Kolata S, Zhang S, Belforte JE. GABAergic interneuron origin of schizophrenia pathophysiology. *Neuropharmacology*. 2012; 62(3):1574–1583. [PubMed: 21277876]
- Olney JW, Farber NB. Glutamate receptor dysfunction and schizophrenia. *Arch Gen Psychiatry*. 1995; 52(12):998–1007. [PubMed: 7492260]
- Ongur D, Prescott AP, McCarthy J, Cohen BM, Renshaw PF. Elevated gamma-aminobutyric acid levels in chronic schizophrenia. *Biological psychiatry*. 2010; 68(7):667–670. [PubMed: 20598290]
- Oxley T, Fitzgerald PB, Brown TL, de Castella A, Daskalakis ZJ, Kulkarni J. Repetitive transcranial magnetic stimulation reveals abnormal plastic response to premotor cortex stimulation in schizophrenia. *Biological psychiatry*. 2004; 56(9):628–633. [PubMed: 15522245]
- Pascual-Leone A, Manocha DS, Birnbaum R, Goff DC. Motor cortical excitability in schizophrenia. *Biological psychiatry*. 2002; 52(1):24–31. [PubMed: 12079727]
- Pierri JN, Chaudry AS, Woo TU, Lewis DA. Alterations in chandelier neuron axon terminals in the prefrontal cortex of schizophrenic subjects. *Am J Psychiatry*. 1999; 156(11):1709–1719. [PubMed: 10553733]
- Radhu N, de Jesus DR, Ravindran LN, Zanjani A, Fitzgerald PB, Daskalakis ZJ. A meta-analysis of cortical inhibition and excitability using transcranial magnetic stimulation in psychiatric disorders. *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology*. 2013; 124(7):1309–1320. [PubMed: 23485366]
- Rowland LM, Edden RA, Kontson K, Zhu H, Barker PB, Hong LE. GABA predicts inhibition of frequency-specific oscillations in schizophrenia. *The Journal of neuropsychiatry and clinical neurosciences*. 2013a; 25(1):83–87. [PubMed: 23487198]
- Rowland LM, Kontson K, West J, Edden RA, Zhu H, Wijtenburg SA, Holcomb HH, Barker PB. In vivo measurements of glutamate, GABA, and NAAG in schizophrenia. *Schizophrenia bulletin*. 2013b; 39(5):1096–1104. [PubMed: 23081992]
- Rudolph U, Knoflach F. Beyond classical benzodiazepines: novel therapeutic potential of GABAA receptor subtypes. *Nat Rev Drug Discov*. 2011; 10(9):685–697. [PubMed: 21799515]
- Rudolph U, Mohler H. GABAA receptor subtypes: Therapeutic potential in Down syndrome, affective disorders, schizophrenia, and autism. *Annu Rev Pharmacol Toxicol*. 2014; 54:483–507. [PubMed: 24160694]
- Schroder J, Bubeck B, Demisch S, Sauer H. Benzodiazepine receptor distribution and diazepam binding in schizophrenia: an exploratory study. *Psychiatry research*. 1997; 68(2-3):125–131. [PubMed: 9104759]

- Simpson MD, Slater P, Deakin JF, Royston MC, Skan WJ. Reduced GABA uptake sites in the temporal lobe in schizophrenia. *Neuroscience letters*. 1989; 107(1-3):211–215. [PubMed: 2616032]
- Sohal VS, Zhang F, Yizhar O, Deisseroth K. Parvalbumin neurons and gamma rhythms enhance cortical circuit performance. *Nature*. 2009; 459(7247):698–702. [PubMed: 19396159]
- Stokes PR, Myers JF, Kalk NJ, Watson BJ, Erritzoe D, Wilson SJ, Cunningham VJ, Barros DR, Hammers A, Turkheimer FE, Nutt DJ, Lingford-Hughes AR. Acute increases in synaptic GABA detectable in the living human brain: A [C]Ro15-4513 PET study. *NeuroImage*. 2014
- Strube W, Wobrock T, Bunse T, Palm U, Padberg F, Malchow B, Falkai P, Hasan A. Impairments in motor-cortical inhibitory networks across recent-onset and chronic schizophrenia: a cross-sectional TMS Study. *Behavioural brain research*. 2014; 264:17–25. [PubMed: 24509248]
- Szabadics J, Varga C, Molnar G, Olah S, Barzo P, Tamas G. Excitatory effect of GABAergic axo-axonic cells in cortical microcircuits. *Science*. 2006; 311(5758):233–235. [PubMed: 16410524]
- Takahashi S, Ukai S, Kose A, Hashimoto T, Iwatani J, Okumura M, Tsuji T, Shinosaki K. Reduction of cortical GABAergic inhibition correlates with working memory impairment in recent onset schizophrenia. *Schizophrenia research*. 2013; 146(1-3):238–243. [PubMed: 23523695]
- Tallon-Baudry C, Bertrand O, Peronnet F, Pernier J. Induced gamma-band activity during the delay of a visual short-term memory task in humans. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 1998; 18(11):4244–4254. [PubMed: 9592102]
- Tan KR, Rudolph U, Luscher C. Hooked on benzodiazepines: GABAA receptor subtypes and addiction. *Trends in neurosciences*. 2011; 34(4):188–197. [PubMed: 21353710]
- Taylor SF, Demeter E, Phan KL, Tso IF, Welsh RC. Abnormal GABAergic function and negative affect in schizophrenia. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology*. 2014; 39(4):1000–1008. [PubMed: 24154667]
- Tayoshi S, Nakataki M, Sumitani S, Taniguchi K, Shibuya-Tayoshi S, Numata S, Iga J, Ueno S, Harada M, Ohmori T. GABA concentration in schizophrenia patients and the effects of antipsychotic medication: a proton magnetic resonance spectroscopy study. *Schizophrenia research*. 2010; 117(1):83–91. [PubMed: 20022731]
- Torrey EF, Barci BM, Webster MJ, Bartko JJ, Meador-Woodruff JH, Knable MB. Neurochemical markers for schizophrenia, bipolar disorder, and major depression in postmortem brains. *Biological psychiatry*. 2005; 57(3):252–260. [PubMed: 15691526]
- Uhlhaas PJ, Singer W. Abnormal neural oscillations and synchrony in schizophrenia. *Nature reviews Neuroscience*. 2010; 11(2):100–113. [PubMed: 20087360]
- Verhoeff NP, Soares JC, D'Souza CD, Gil R, Degen K, Abi-Dargham A, Zoghbi SS, Fujita M, Rajeevan N, Seibyl JP, Krystal JH, van Dyck CH, Charney DS, Innis RB. [123I]Iomazenil SPECT benzodiazepine receptor imaging in schizophrenia. *Psychiatry Res*. 1999; 91(3):163–173. [PubMed: 10641580]
- Volk DW, Pierri JN, Fritschy JM, Auh S, Sampson AR, Lewis DA. Reciprocal alterations in pre- and postsynaptic inhibitory markers at chandelier cell inputs to pyramidal neurons in schizophrenia. *Cereb Cortex*. 2002; 12(10):1063–1070. [PubMed: 12217970]
- Vollenweider FX. Advances and pathophysiological models of hallucinogenic drug actions in humans: a preamble to schizophrenia research. *Pharmacopsychiatry*. 1998; 31(Suppl 2):92–103. [PubMed: 9754840]
- Wassef AA, Dott SG, Harris A, Brown A, O'Boyle M, Meyer WJ 3rd, Rose RM. Critical review of GABA-ergic drugs in the treatment of schizophrenia. *J Clin Psychopharmacol*. 1999; 19(3):222–232. [PubMed: 10350028]
- Wobrock T, Hasan A, Malchow B, Wolff-Menzler C, Guse B, Lang N, Schneider-Axmann T, Ecker UK, Falkai P. Increased cortical inhibition deficits in first-episode schizophrenia with comorbid cannabis abuse. *Psychopharmacology*. 2010; 208(3):353–363. [PubMed: 19997844]
- Wobrock T, Schneider M, Kadovic D, Schneider-Axmann T, Ecker UK, Retz W, Rosler M, Falkai P. Reduced cortical inhibition in first-episode schizophrenia. *Schizophrenia research*. 2008; 105(1-3):252–261. [PubMed: 18625547]
- Wolf DH, Satterthwaite TD, Loughhead J, Pinkham A, Overton E, Elliott MA, Dent GW, Smith MA, Gur RC, Gur RE. Amygdala abnormalities in first-degree relatives of individuals with

- schizophrenia unmasked by benzodiazepine challenge. *Psychopharmacology*. 2011; 218(3):503–512. [PubMed: 21603892]
- Woo TU, Kim AM, Viscidi E. Disease-specific alterations in glutamatergic neurotransmission on inhibitory interneurons in the prefrontal cortex in schizophrenia. *Brain Res*. 2008; 1218:267–277. [PubMed: 18534564]
- Woo TU, Miller JL, Lewis DA. Schizophrenia and the parvalbumin-containing class of cortical local circuit neurons. *The American journal of psychiatry*. 1997; 154(7):1013–1015. [PubMed: 9210755]
- Woo TU, Walsh JP, Benes FM. Density of glutamic acid decarboxylase 67 messenger RNA-containing neurons that express the N-methyl-D-aspartate receptor subunit NR2A in the anterior cingulate cortex in schizophrenia and bipolar disorder. *Archives of general psychiatry*. 2004; 61(7):649–657. [PubMed: 15237077]
- Woodruff A, Xu Q, Anderson SA, Yuste R. Depolarizing effect of neocortical chandelier neurons. *Front Neural Circuits*. 2009; 3:15. [PubMed: 19876404]
- Yoon JH, Maddock RJ, Rokem A, Silver MA, Minzenberg MJ, Ragland JD, Carter CS. GABA concentration is reduced in visual cortex in schizophrenia and correlates with orientation-specific surround suppression. *J Neurosci*. 2010; 30(10):3777–3781. [PubMed: 20220012]
- Zhang Y, Behrens MM, Lisman JE. Prolonged exposure to NMDAR antagonist suppresses inhibitory synaptic transmission in prefrontal cortex. *Journal of neurophysiology*. 2008; 100(2):959–965. [PubMed: 18525022]
- Ziemann U. Pharmacology of TMS. *Suppl Clin Neurophysiol*. 2003; 56:226–231. [PubMed: 14677399]

GABAR Subunit	Sedation	Anxiolysis	Muscle relaxation	Anti-convulsant	Amnesia	Addiction	Extra-synaptic	Intra-synaptic
α -1	✓			✓	✓	✓	✓	✓
α -2		✓	✓					✓
α -3			✓					✓
α -5			✓		✓		✓	

Figure 1. Pharmacology of GABA receptor subunits

The GABAR is a heteropentameric glycoprotein, composed of combinations of at least 19 different subunits in 7 families, affecting function as well as ligand affinity, of which the α -subunit family is most relevant for BDZ pharmacology. The figure shows the functions and distributions of the subunits most relevant for schizophrenia. Information in the figure derived from (Brickley and Mody, 2012; Tan et al., 2011)

Table 1
Radioligand studies of GABAR binding in schizophrenia and schizoaffective disorder

Study	# SZ M/F	SZ Age	#HC M/F	HC Age	Subject type ¹	Med status	Ligand	Analysis	Results
Busatto et al, 1997; Ball et al, 1998	14/1	29	11/1	28 yr	Mixed	Mixed	IMZ	ROI	Group comparison n.s.; L med temp neg corr w/pos Sx; MFC neg corr w/neg Sx; OC pos corr w/GAF; 10 ROIs have many pos corr w/cognitive measures and a few neg corr w/in SZ but not HC ²
Schroder et al, 1997	20	30 yr	--	--	Chronic	Med	IMZ	ROI	MFC pos corr w/BPRS total before DZP; after DZP: MFC, TPC, OC neg corr w/outcome ²
Verhoeff et al, 1999	25/0	41 yr	24	37 yr	Chronic	Mixed	IMZ	WB	Relative binding SZ<HC in L BA6, (l) in R BA9/44; n.s.
Abi-Dargham et al, 1999	16/0	44 yr	16/0	45 yr	Chronic	Med	IMZ	ROI/WB	Group comparison n.s.; n.s. w/BPRS total or subscales
Asai et al, 2008	6/5	33 yr	12/0	29 yr	Mixed	Mixed	Ro15	ROI	Group comparison n.s; PFC neg corr w/PANSS negative, general, total; HIPP neg corr w/PANSS neg ²
Lee et al, 2013	8/9	29 yr	9/9	26 yr	Chronic	Med	FMZ	WB	SZ<HC in BA25, L BA38; HC<SZ in BA19 ²

¹ Acute = average duration of illness < 3 years; Chronic = average duration of illness ≥ 3 years

² Corrections for multiple comparisons not done

Abbreviations: SZ, Schizophrenia/schizoaffective subjects; HC, healthy control subjects; M, male; F, female; Med, medicated; Unmed, unmedicated; IMZ, [¹²³I]iomazenil; Ro15, [¹¹C]Ro15-4513; FMZ, [¹⁸F]fluorofluoromazenil; ROI, region of interest; WB, whole brain voxel-wise; n.s., no significant differences/correlations; neg corr w/, negative correlation with; pos corr w/, positive correlation with; (l), trend; pos Sx, positive symptoms; neg Sx, negative symptoms; L med temp, left medial temporal; MFC, medial frontal cortex; BPRS, Brief Psychiatric Rating Scale; DZP, diazepam; TPC, temporo-parietal cortex; OC, occipital cortex; GAF, Global Assessment of Functioning; BA, Brodman Area; PANSS, positive and negative syndrome scale; PFC, prefrontal cortex; HIPP, hippocampus;

Table 2
MRS studies of GABA in schizophrenia and schizoaffective disorder

Study	# SZ M/F	SZ Age	#HC M/F	HC Age	Subject Type ¹	Med status	Measure	Voxel	Result
Goto et al, 2009a, b	9/9	29 yr	9/9	30 yr	?	Med	3T GABA/Cr	Frontal	n.s.; trend neg corr w/perseverative errors on WCST
								L BG	HC>Sz
								POC	n.s.
Tayoshi et al, 2010	20/18	34 yr	17/12	34 yr	Chronic	Med	3T GABA	ACC	n.s.; neg corr w/APD
								L BG	n.s.; pos corr w/APD
Ongur et al, 2010	14/7	39 yr	12/7	36 yr	Chronic	Med	4T GABA/Cr	ACC	SZ>HC ²
								POC	SZ>HC ²
Yoon et al, 2010	11/2	27 yr	11/2	28 yr	Mixture		3T GABA/Cr	Occ	HC>SZ; pos corr w/visual OSSS
Kegeles et al, 2012	11/5	32 yr	14/8	33 yr	Chronic	Unmed	3T GABA/w	MPFC ³	SZ>HC, unmed(t) >med
								L dLPFC	n.s.
	11/5	32 yr	“	“	Chronic	Med		MPFC ³	n.s.
								dLPFC	n.s.
Rowland et al, 2013	9/2	30 yr	5/5	33 yr	Chronic	Med	3T GABA/w	ACC	n.s.
								CSO	n.s.
	7/3	51 yr	7/3	49 yr	Chronic	Med		ACC	HC>SZ
								CSO	n.s.
Rowland et al, 2013	8/2	43 yr			Chronic	Med	3T GABA/w	ACC	Neg corr w/theta-alpha and beta ratio in auditory paired click
Kelemen et al, 2013	18/10	25 yr	14/6	24 yr	Acute	Unmed/med ⁴	3T GABA/Cr	Occ	HC>SZ pre and post medication; n.s. corr w/visual contrast sensitivity
Chen et al, 2014 ⁵	9/3	31 yr	6/6	33 yr	Chronic	Mixture	3T GABA/w	L dLPFC	Pos corr w/surface gamma amplitude at rest and during working memory (both groups combined)

¹ Acute = average duration of illness < 3 years; Chronic = average duration of illness ≥ 3 years

² Effect of diagnosis not significant when patients on anti-convulsants excluded

³ Voxel overlaps with rostral ACC voxels

⁴ Patients studied medication-free and 8 weeks after various pharmacotherapy regimens begun

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5 Partial overlap with sample of Kegeles et al, 2012

Abbreviations: SZ, Schizophrenia/schizoaffective subjects; HC, healthy control subjects; M, male; F, female; Med, medicated; Unmed, unmedicated; GABA/Cr, GABA/creatine ratio; GABA/w, GABA/water ratio; n.s., no significant differences; neg corr w/, negative correlation with; pos corr w/, positive correlation with; APD, anti-psychotic dose; L BG, left basal ganglia; WCST, Wisconsin Card Sort; POC, midline parieto-occipital cortex; ACC, anterior cingulate cortex; L dLPFC, left dorsolateral prefrontal cortex; OSSS, orientation-specific surround suppression; (t), trend; MPFC, medial prefrontal cortex; CSO, centrum semiovale white matter;

Table 3
TMS studies of short interval cortical inhibition (SICI) in schizophrenia

Study	# SZ M/F	SZ Age	#HC M/F	HC Age	Subject type ¹	Med status	SICI ²	Correlations ³
Pascual-Leone et al, 2002	7/1	41 yr	6/1	41 yr	Chronic	Unmed	n.s.	
	6/1	46 yr	--	--	Chronic	Med	Med < Unmed, HC	
Daskalakis et al, 2002	8/7	33 yr	10/5	28 yr	Chronic	Unmed	Unmed < HC; Unmed (t) < Med	All SZ: pos corr w/PANSS positive, global, (t) negative
	10/5	32 yr	--	--	Chronic	Med	Med (t) < HC	
Fitzgerald et al, 2002a	17/5	29 yr	14/7	32 yr	Chronic	Med	n.s.	n.s. with PANSS
Fitzgerald et al, 2002b	32/8	28 yr	15/7	32 yr	Chronic	Med	n.s.	
Fitzgerald et al, 2004	8/2	33 yr	15/3	31 yr	Chronic	Unmed	n.s.	n.s. with PANSS
	10/6	32 yr	--	--	Chronic	Med	Med < HC	
Oxley et al, 2004	8/4	34 yr	8/4	28 yr	Chronic	Mixed	SZ < HC	
Eichhammer et al, 2004	10/11	29 yr	10/11	31 yr	Acute	Unmed	SZ (t) < HC	
Wobrock et al, 2008, 2009	21/8	30 yr	23/21	34 yr	Acute	Med	SZ < HC	n.s. with PANSS, CGI, GAF
Daskalakis et al, 2008	4/2	32 yr	7/3	33 yr	Chronic	Unmed	n.s.	All SZ: pos corr w/PANSS positive & total
	7/3	30 yr	--	--	Chronic	Med	n.s.	
Liu et al, 2009	78	36 yr	38	34 yr	Chronic	Mixed	SZ (t) < HC; SZ clozapine < other med SZ, HC	Pos corr w/PANSS positive
Hasan et al, 2011	6/3	29 yr	13/9	30 yr	Acute	Mixed	All SZ < HC	
	9/4	36 yr	--	--	Chronic	Mixed		
Hasan et al, 2012	14/4	25 yr	14/4	24 yr	Acute	Med	n.s.	n.s. with PANSS
Takahashi et al, 2013	9/11	27 yr	10/10	28 yr	Acute	Mixed	SZ < HC	n.s with PANSS, neg corr w/digit span
Strube et al, 2014 ⁴	29/12	30 yr	37/22	32 yr	Acute	Mixed	3 groups ANOVA (t); 2 groups: SZ < HC	All SZ: n.s. with PANSS
	33/9	38 yr	--	--	Chronic	Mixed		

¹ Acute = average duration of illness < 3 years; Chronic = average duration of illness ≥ 3 years

² Results coded positively for greater inhibition, either smaller % of control MEP or smaller ratio in comparison with control MEP

³ Correlations reported as positive for less inhibition associating with more symptoms or worse performance

⁴ Includes subjects from Wobrock et al 2008 and Hasan et al 2011

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Abbreviations: SZ, Schizophrenia/schizoaffective subjects; HC, healthy control subjects; M, male; F, female; Med, medicated; Unmed, unmedicated; SICI, short interval cortical inhibition; n.s., no significant differences/correlations; neg corr w/, negative correlation with; pos corr w/, positive correlation with; PANSS, positive and negative syndrome scale; (l), trend; L, left; R, Right;