Published in final edited form as:

Schizophr Res. 2015 September ; 167(1-3): 42–56. doi:10.1016/j.schres.2014.10.010.

GABA receptor subunit distribution and FMRP-mGluR5 signaling abnormalities in the cerebellum of subjects with schizophrenia, mood disorders, and autism

S. Hossein Fatemi^{a,b,*} and Timothy D. Folsom^a

^aDepartment of Psychiatry, Division of Neuroscience Research, University of Minnesota Medical School, 420 Delaware St SE, MMC 392, Minneapolis, MN 55455, USA

^bDepartment of Neuroscience, University of Minnesota Medical School, 321 Church St. SE, Minneapolis, MN 55455, USA

Abstract

Gamma-aminobutyric acid (GABA) is the main inhibitory neurotransmitter in the brain. GABAergic receptor abnormalities have been documented in several major psychiatric disorders including schizophrenia, mood disorders, and autism. Abnormal expression of mRNA and protein for multiple GABA receptors has also been observed in multiple brain regions leading to alterations in the balance between excitatory/inhibitory signaling in the brain with potential profound consequences for normal cognition and maintenance of mood and perception. Altered expression of GABA_A receptor subunits has been documented in Fragile X mental retardation 1 (FMR1) knockout mice, suggesting that loss of its protein product, fragile X mental retardation protein (FMRP), impacts GABA_A subunit expression. Recent postmortem studies from our laboratory have shown reduced expression of FMRP in brains of subjects with schizophrenia, bipolar disorder, major depression, and autism. FMRP acts as a translational repressor and, under normal conditions, inhibits metabotropic glutamate receptor 5 (mGluR5)-mediated signaling. In fragile X syndrome (FXS), absence of FMRP is hypothesized to lead to unregulated mGluR5 signaling, ultimately resulting in the behavioral and intellectual impairments associated with this disorder. Our laboratory has identified changes in mGluR5 expression in autism, schizophrenia, and mood disorders. In the current review article, we discuss our postmortem data on GABA receptors, FMRP, and mGluR5 levels and compare our results with other laboratories. Finally, we discuss the interactions between these molecules and the potential for new therapeutic interventions that target these interconnected signaling systems.

* Corresponding author: S. Hossein Fatemi, Department of Psychiatry, University of Minnesota, 420 Delaware St SE, MMC 392, Minneapolis, MN 55455, Phone: 612-626-3633, Fax: 612-624-8935, fatem002@umn.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Contributions

Both SHF and TDF wrote and edited this manuscript and approve of the final version of the manuscript.

Conflict of Interest

The authors declare that they have no conflict of interest.

Keywords

GABA; schizophrenia; bipolar disorder; cerebellum; FMRP; mGluR5

1. Introduction

This article reviews the current postmortem evidence for dysfunction of the gamma-aminobutyric acid (GABA) and the fragile X mental retardation protein (FMRP)-metabotropic glutamate receptor 5 (mGluR5) signaling pathways in four major psychiatric disorders: schizophrenia, bipolar disorder, major depression, and autism. GABAergic dysfunction has long been implicated in deficits associated with schizophrenia, mood disorders, and autism (Gonzales-Burgos et al., 2011; Luscher et al., 2011; Coghlan et al., 2012). Disruption of inhibitory GABAergic signaling and the resulting imbalance between excitatory and inhibitory circuitry in the brain may be associated with behavioral and cognitive deficits in each disorder. Postmortem findings from our laboratory (Fatemi et al., 2009a,b, 2010a, 2014) and others (Akbarian et al., 1995; Beneyto et al., 2011; Duncan et al., 2010; Glausier and Lewis, 2011; Hashimoto et al., 2008; Maldonado-Aviles et al., 2009) have identified changes in mRNA and protein for a number of individual GABA receptor subunits in brains of subjects with schizophrenia, mood disorders, and autism.

Data from animal models of fragile X syndrome (FXS), which lack FMRP (an RNA binding master protein that targets 5% of all brain genes including some of the GABA receptors) show altered expression of GABA receptor subunits in brain (Adusei et al., 2010; El Idrissi et al., 2005; D'Hulst et al., 2006; Gantois et al., 2006; Hong et al., 2012). Novel data from our laboratory has recently shown reduced expression of FMRP in schizophrenia, bipolar disorder, major depression, and autism (Fatemi and Folsom, 2011; Fatemi et al., 2010b, 2011a, 2013a), and represents the first data to show altered expression of FMRP in subjects who do not have a diagnosis of fragile X syndrome (FXS). These results have now been replicated in schizophrenia by other laboratories (Kelemen et al., 2013; Kóvacs et al., 2013).

FMRP negatively regulates mGluR5 activity. The mGluR5 theory of FXS proposes that in the absence of FMRP, mGluR5 activity is greatly increased ultimately resulting in the deficits associated with FXS (Bear et al., 2004; Dölen and Bear, 2008). Our laboratory has identified the upregulation of mGluR5 expression in autistic children (Fatemi and Folsom, 2011; Fatemi et al. 2011a) and this finding has been replicated by another group in patients with FXS (Lohith et al., 2013). In schizophrenia and mood disorders, we have determined reduced mGluR5 protein expression (Fatemi et al., 2013a), while other groups have found either no change (Corti et al., 2011; Gupta et al., 2005; Matosin et al., 2013, 2014) or only a reduction of this receptor in major depression (Deschwanden et al., 2011); details of which will be further discussed in section 4.

Taken together, changes in GABA-FMRP-mGluR5 signaling may have profound effects and contribute significantly to the etiology of major psychiatric disorders. These changes also offer the potential for therapeutic intervention. In particular, modulators of GABA receptor and mGluR5 activity are discussed in section 7 as potential means of ameliorating symptoms of schizophrenia, mood disorders, and autism.

2. GABA

2.1. GABA Receptors

GABA is the main inhibitory neurotransmitter in the brain. In the central nervous system approximately 20% of all neurons are GABAergic (Charych et al., 2009). There are two classes of GABA receptors: GABA_A and GABA_B, which differ in terms of composition, pharmacology, and action. There are 19 different GABA_A receptor subunits: alpha 1–6 (α 1–6), beta 1–3 (β 1–3), gamma 1–3 (γ 1–3), delta (δ), epsilon (ϵ), pi (π), theta (θ), and rho 1–3 (ρ 1–3) that combine to form the various GABA_A receptors (Brandon et al., 2000; Ma et al., 2005). These receptors are either mostly synaptic/postsynaptic (α 1–4, β 1–3, γ 1–3, δ , ϵ , θ , π , ρ 1–3), predominantly extrasynaptic (α 4, α 5, α 6, and δ), or both (α 5, ρ 1) (Errington, 2014; Wafford, 2014). GABA_A receptors are binding sites for benzodiazepines, steroids, and anesthetics, thus mediating their effects. While synaptic receptors, because of the presence of γ subunits, are sensitive to the action of benzodiazepines; extrasynaptic receptors the presence of the δ subunit are insensitive to benzodiazepines but are sensitive to the agonist 4,5,6,7-tetrahydroisoxazolo[5,4-c]pyridin-3-ol (THiP or Gaboxadol; Wafford and Ebert, 2006) as well as neurosteroids (Stell et al., 2003; Belelli and Lambert, 2005). Interestingly, extrasynaptic GABA_A receptors can be modulated both directly and indirectly by GABA_B, serotonin, dopamine, noradrenalin, and metabotropic glutamate receptors (Errington, 2014). Additionally, synaptic GABA_A receptors are composed of α 1, α 2, and α 3 subunits along with β 1–3, and γ 2 subunits, while extrasynaptic receptors are composed of α 1, α 4, α 5, β , γ 2 and δ subunits (Farrar et al., 1999; Wafford, 2014). GABA_B receptors are heterodimeric receptors consisting of one GABA_B receptor 1 subunit (GABBR1) and one GABA_B receptor 2 subunit (GABBR2). GABA_B receptors are coupled via G-proteins to potassium and calcium channels as well as adenylate cyclase (Bowery, 2000). Additionally, the action of GABA_B receptors is slower than GABA_A receptors. Presynaptically, GABA_B receptors facilitate neurotransmitter release including glutamate and GABA, while postsynaptically, they generate inhibitory potentials (Bowery, 2000; Kuriyama et al., 2000). GABA_A receptors, upon binding GABA, lead to increased membrane permeability to both chloride and bicarbonate ions (Errington, 2014; Chebib and Johnston, 2000). There are essentially two types of GABAergic inhibition: 1) phasic inhibition which results from a transient rise in GABA in synapse and activation of postsynaptic GABA receptors and production of inhibitory postsynaptic potentials (IPSP); and 2) tonic inhibition which results from very low nanomolar (nM) concentrations of GABA and activation of extrasynaptic GABA receptors located in several brain sites such as cerebellar granule cells, layer II/III and V cortical pyramidal cells, medium spiny neurons of striatum, CA1 and CA3 pyramidal neurons, dentate granule cells, and thalamocortical neurons (Errington, 2014).

Altered GABAergic synaptic transmission has been associated with panic, anxiety, impaired learning and memory, and sleep abnormalities (Heulens et al., 2010; Pinna et al., 2006, 2009), and thus contributes to deficits associated with schizophrenia, bipolar disorder, major depression, and autism (Gonzalez-Burgos et al., 2011; Luscher et al., 2011; Möhler et al., 2012).

2.2. Changes in GABA Binding Site Density in Major Psychiatric Disorders

Initial pioneering studies by Benes and colleagues have demonstrated increased GABA_A receptor binding in brains of subjects with schizophrenia (Benes et al., 1992, 1996a,b, 1997). An initial study identified an increase in ³H-muscimol-labeled GABA_A receptor binding sites in layers II and III, but not IV or V of the anterior cingulate cortex of subjects with schizophrenia (Benes et al., 1992). Further experiments revealed increased GABA_A receptor binding sites in layers II, III, V, and VI in prefrontal cortex (PFC) of subjects with schizophrenia (Benes et al., 1996a) and in the area dentata (granule cell layer), CA4, CA3, subiculum, and presubiculum in the hippocampus of subjects with schizophrenia (Benes et al., 1996b). ³H-flunitrazepam-labeled benzodiazepine binding sites were also increased in the striatum oriens of CA3, subiculum, and presubiculum in the hippocampus of subjects with schizophrenia (Benes et al., 1997).

Quantitation of GABA receptor binding sites has also been performed in brains of subjects with autism (Blatt et al. 2001; Oblak et al. 2010, 2011). Reduced ³H-muscimol-labeled GABA_A receptor binding sites and ³H-flunitrazepam-labeled benzodiazepine binding sites have been found in hippocampus of subjects with autism (Blatt et al., 2001). Finally reduced ³H-muscimol-labeled GABA_A receptor binding sites have been observed in the posterior cingulate cortex and fusiform gyrus of subjects with autism (Oblak et al., 2011). Additionally, reduced GABA_B receptor binding sites, as measured using ³H-CGP54626-labeling, have also been identified in the posterior cingulate cortex and fusiform gyrus of subjects with autism (Oblak et al., 2010).

Taken together, these studies have demonstrated widespread changes in GABA binding sites in brains of subjects with schizophrenia and autism. Additional biochemical studies have identified changes in expression of mRNA and protein for individual GABA_A and GABA_B receptor subunits, primarily by Fatemi and collaborators in four psychiatric disorders spanning 17 GABA_A and B receptors in cerebellum, BA9, and parietal cortices of subjects with autism and primarily in cerebellum of subjects with schizophrenia, bipolar disorder, and major depression which are described below. Results from these studies will be contrasted with those reported by other investigators in the ensuing sections (vide infra).

2.3. Expression of Individual GABA Receptor Subunits in Brains of Subjects with Major Psychiatric Disorders

The gene that codes for GABRα1 (GABRA1) is located at 5q34-q35 (Buckle et al., 1989). In rat brain, mRNA for GABRα1 is distributed throughout the brain including the neocortex, hippocampus, globus pallidus, medial septum, thalamus, and cerebellum (Wisden et al., 1992). The GABRα1 subunit is expressed in most GABA_A receptors. Our laboratory has found that GABRα1 protein level was significantly increased in lateral cerebellum of subjects with major depression while there were no changes in subjects with schizophrenia or bipolar disorder (Fatemi et al., 2013b) (Table 1). Moreover, we found that mRNA for GABRα1 is significantly reduced in lateral cerebella of subjects with schizophrenia and major depression (Fatemi et al., 2013b; Table 1). Three studies have identified reduced expression of GABRα1 mRNA in prefrontal cortex (PFC) and dorsolateral prefrontal cortex (DLPC) of subjects with schizophrenia (Beneyto et al., 2011; Glausier and Lewis, 2011;

Hashimoto et al., 2008), while two other studies found no change in GABRA1 mRNA in the same regions (Akbarian et al., 1995; Duncan et al., 2010) (Table 1). In subjects with autism, we determined that GABRA1 protein is also significantly reduced in superior frontal cortex [Brodmann Area 9 (BA9)], parietal cortex (BA40), and cerebellum without any change in mRNA levels (Fatemi et al., 2009a) (Table 1).

The GABRA2 gene (GABRA2), is localized to 4q13-p12 (Buckle et al., 1989). In situ hybridization experiments have identified GABRA2 mRNA in multiple regions of rat brain including the neocortex, hippocampus, hypothalamus, and cerebellum (Laurie et al., 1992; Wisden et al., 1992). We observed that GABRA2 protein level was increased in lateral cerebella of subjects with schizophrenia, bipolar disorder, and major depression (Fatemi et al., 2013b) (Table 1). Our laboratory further identified reduced GABRA2 mRNA expression in lateral cerebella of subjects with schizophrenia. Beneyto et al (2011) also found increased mRNA expression for GABRA2 in DLPFC in subjects with schizophrenia (Table 1). Two other studies found no change in GABRA2 mRNA expression in PFC and DLPFC (Akbarian et al., 1995; Duncan et al., 2010) (Table 1). In subjects with autism, we found that GABRA2 protein was significantly reduced in BA40 (Fatemi et al., 2009a) while its mRNA expression was significantly reduced in BA9 and significantly increased in cerebellum (Fatemi et al., 2014) (Table 1). The GABRA2 subunit has been implicated in depression as GABRA2 KO mice display depressive behavior (i.e., increased immobility) in response to the forced swim test (FST) and the tail suspension test (TST) (Vollenweider et al., 2011).

GABRA3, the gene that codes for GABRA3 is located at Xq28 (Buckle et al., 1989). In rat brain, mRNA for GABRA3 has been found in multiple regions including septum, thalamus, cerebellum, and neocortex (Laurie et al., 1992; Wisden et al., 1992). We observed that GABRA3 protein and mRNA were not altered in lateral cerebellum of subjects with schizophrenia and mood disorders (Table 1). Similarly, other groups found no difference in mRNA for GABRA3 in DLPFC of subjects with schizophrenia vs. controls (Beneyto et al., 2011; Duncan et al., 2010) (Table 1). In BA40 of subjects with autism, we determined that both mRNA and protein levels for GABRA3 were significantly reduced (Fatemi et al., 2009a, 2014) (Table 1). We also observed that mRNA for GABRA3 was also significantly reduced in BA9 and increased in cerebellum of subjects with autism (Fatemi et al., 2014). Interestingly, GABRA3 KO mice display sensorimotor gating deficits as measured by prepulse inhibition (PPI) of the acoustic startle response (Yee et al., 2005), a deficit that is common to subjects with autism and schizophrenia.

The gene that codes for GABRA4 (GABRA4) is located at 4p14-q12 (McLean et al., 1995), and is a member of the novel group of extrasynaptic GABA_A receptors (Errington, 2014). mRNA for GABRA4 shows particularly strong expression in the hippocampus and thalamus of rat brain as well as caudate, putamen and neocortex (Laurie et al., 1992; Wisden et al., 1992). We have not yet determined if there are any changes in GABRA4 mRNA or protein in subjects with schizophrenia and mood disorders. Duncan et al. (2010) found no change in mRNA expression for GABRA4 in DLPFC of subjects with schizophrenia (Table 1). Hashimoto et al., (2008) determined a significant decrease in gene transcript for this receptor subunit in DLPFC of subjects with schizophrenia. However, this change was not verified at the level of mRNA by either qRT-PCR or another technique (Hashimoto et al., 2008).

Maldonado-Avilés et al (2009) found reduced mRNA expression in BA9 of subjects with schizophrenia who were taking benzodiazepines, mood stabilizers, or antidepressants at the time of death, suggesting a medication-specific effect on GABR α 4 expression (Table 1). Our laboratory observed that both mRNA and protein levels for GABR α 4 were reduced in BA9 of subjects with autism (Fatemi et al., 2010a) (Table 1). In contrast, we have observed significantly increased mRNA for GABR α 4 in cerebellum of subjects with autism (Fatemi et al., 2010a).

The GABR α 5 gene (GABRA5) is localized to 15q11.2-q13 (Knoll et al., 1992) and is considered one of the extrasynaptic GABA_A receptors involved in tonic inhibitory neurotransmission (Wafford, 2014). mRNA for GABR α 5 is expressed in the hippocampus, olfactory bulb, and hypothalamus in rat brain (Laurie et al., 1992; Wisden et al., 1992) as well as amygdala (Martin and Huntsman, 2014). We did not observe changes in GABR α 5 mRNA or protein expression in lateral cerebellum of subjects with schizophrenia, bipolar disorder, or major depression (Table 1). However, previous reports have identified reduced GABR α 5 mRNA in DLPFC of subjects with schizophrenia (Beneyto et al., 2011; Duncan et al., 2010), while Akbarian et al (1995) found no change in PFC (Table 1). In BA9 of subjects with autism, we observed that GABR α 5 mRNA and protein were significantly reduced (Fatemi et al., 2010a) (Table 1). In contrast, GABR α 5 mRNA was significantly increased in cerebellum of subjects with autism (Fatemi et al., 2010a). Improvements in cognitive behavior in a mouse model of Down Syndrome following the use of inverse agonists of GABR α 5 (i.e., α 5IA or RO4938581) suggest that this receptor subunit could be targeted to improve cognitive deficits associated with intellectual impairment (Braudeau et al., 2011; Martinez-Cue et al., 2013). Mice that display reduced GABR α 5 in the hippocampus also show deficits in latent inhibition (Gerdjikov et al., 2008), further implicating this subunit in cognition. Additionally, because of the importance of this receptor in cognition, it has also been a focus of therapeutic intervention for both Alzheimer's disease and schizophrenia (Wafford, 2014).

GABRA6, the gene that codes for GABR α 6 subunit, is located at 5q31.1-q35 (Hicks et al., 1994) and is another member of the extrasynaptic GABA_A receptors (Wafford, 2014). GABR α 6 mRNA has been found to localize exclusively to cerebellar granule neurons in rat brain (Laurie et al., 1992; Wisden et al., 1992). We observed a significant increase in GABR α 6 protein in lateral cerebella of subjects with major depression while there were no changes observed in the lateral cerebella of subjects with schizophrenia and bipolar disorder (Fatemi et al., 2013b) (Table 1). GABR α 6 mRNA has been shown to be increased in lateral cerebella of subjects with schizophrenia (Bullock et al., 2008). In BA9 of subjects with autism, we observed that GABR α 6 protein level was significantly reduced while mRNA was significantly increased (Fatemi et al., 2014) (Table 1). In cerebellum of subjects with autism, we determined that GABR α 6 mRNA level was significantly reduced (Fatemi et al., 2014) (Table 1).

The cytogenetic location of the gene which codes for GABR β 1 (GABRB1) is 4p12 (Kirkness et al., 1991). GABR β 1 mRNA localizes to numerous regions of rat brain with particularly strong expression in hippocampus, amygdala, and cerebellum (Wisden et al., 1992). Findings from our laboratory identified reduced protein expression of GABR β 1 in

lateral cerebellum of subjects with schizophrenia, bipolar disorder, and major depression (Fatemi et al., 2013b) (Table 1) with no change in level of mRNA in cerebellum of subjects with schizophrenia and mood disorders (Table 1). Other laboratories have found no change in mRNA for GABR β 1 expression in PFC and DLPFC of subjects with schizophrenia, confirming our data in cerebellum (Akbarian et al., 1995; Beneyto et al., 2011) (Table 1). We observed that GABR β 1 mRNA and protein levels were significantly reduced in BA9 of subjects with autism (Fatemi et al., 2010a) (Table 1), while mRNA for GABR β 1 was significantly increased in cerebellum of subjects with autism (Fatemi et al., 2010a) (Table 1).

The gene that codes for GABR β 2 (GABRB2) is localized to 5q34-q35 (Russek and Farb, 1994). GABR β 2 mRNA has been found in olfactory bulb, neocortex, globus pallidus, thalamus and cerebellum of rat brain (Laurie et al., 1992; Wisden et al., 1992). In lateral cerebella of subjects with bipolar disorder, our laboratory observed a significant reduction in protein expression for GABR β 2 with no change in mRNA or protein for subjects with schizophrenia or major depression (Fatemi et al., 2013b) (Table 1). Similarly, mRNA for GABR β 2 has been found to be reduced in DLPFC of subjects with schizophrenia (Beneyto et al., 2011) while a separate study found no reduction in GABR β 2 mRNA in PFC of subjects with schizophrenia (Akbarian et al., 1995) similar to our observations (Table 1). We also observed that GABR β 2 protein was significantly reduced in BA9 of subjects with autism while in cerebellum, GABR β 2 mRNA level was significantly increased (Fatemi et al., 2014) (Table 1).

The GABR β 3 gene (GABRB3), is located at 15q11.2-q13. In rat brain, GABR β 3 mRNA has been localized to olfactory bulb, neocortex, hippocampus, hypothalamus, and cerebellum (Laurie et al., 1992; Wisden et al., 1992). While we determined that GABR β 3 protein level was unchanged in lateral cerebella of subjects with schizophrenia and mood disorders, its mRNA expression was significantly increased in subjects with schizophrenia (Fatemi et al., 2013b) (Table 1). There have been contradictory findings regarding mRNA for GABR β 3 in DLPFC of subjects with schizophrenia with one study reporting reduced expression in the transcript for β 3 (Hashimoto et al., 2008) and a separate study finding no change in its mRNA (Beneyto et al., 2011). Bullock et al. (2008) found no change in GABR β 3 mRNA expression in lateral cerebella of subjects with schizophrenia (Bullock et al., 2008). We identified significant reductions in GABR β 3 protein in cerebellum and BA40 of subjects with autism (Fatemi et al., 2009a) (Table 1). Similarly, reduced GABR β 3 protein expression has also been reported in PFC of subjects with autism (Samaco et al., 2005). Our laboratory determined that mRNA for GABR β 3 was significantly reduced in BA9 of subjects with autism while significantly increased in cerebella of subjects with autism (Fatemi et al., 2014). GABR β 3 KO mice display deficits in learning and memory while exhibiting presence of epilepsy (DeLorey et al., 1998, 2008), suggesting that reduced expression of this subunit is relevant to the pathology of autism. Indeed, gene abnormalities in the 15q11-q13 locus, which includes GABR α 5, GABR β 3, and GABR γ 3 are found in 1–4% of subjects with autism (McCauley et al., 2004; Schroer et al., 1998). Epigenetic mechanisms and monoallelic expression of GABR β 3 may explain reduced expression of this subunit in autism (Hogart et al., 2007; Samaco et al., 2005).

GABRD, the gene that codes for the GABR δ subunit is located at 1p36.3 (Emberger et al. 2000), and exclusively localized extrasynaptically, exhibits higher sensitivity to GABA agonism, is activated at less than one micromolar (1 μ M) GABA concentration, and shows lower degree of receptor desensitization (Wafford, 2014). In rat brain, GABR δ mRNA has been localized to the cerebellum, olfactory bulb, dorso-lateral geniculate nucleus, thalamus, striatum and the nucleus accumbens (Pirker et al. 2000; Schwarzer et al. 2001; Wisden et al. 1992). We did not observe any changes in GABR δ mRNA or protein expression in subjects with schizophrenia or mood disorders (Fatemi et al., 2013b). Other groups have demonstrated reduced expression of GABR δ mRNA in BA9 (Maldonado-Avilés et al., 2009) and DLPFC (Hashimoto et al., 2008) of subjects with schizophrenia (Table 1). Additionally, Bullock et al. (2008) found increased expression of GABR δ mRNA in lateral cerebella of subjects with schizophrenia. In BA9 of subjects with autism, we observed significantly reduced expression of the GABR δ subunit expression (Fatemi et al., 2014) (Table 1).

GABRE, the gene that codes for the GABR ϵ subunit, clusters at Xq28 with the genes that code for GABR α 3 and GABR θ (Korpi et al., 2002). GABR ϵ mRNA has been localized to the septum, thalamus, hypothalamus, and amygdala in rat brain and is often coexpressed with mRNA for GABR θ (Moragues et al., 2002). We discovered that GABR ϵ protein expression was significantly increased in lateral cerebella of subjects with schizophrenia, bipolar disorder, or major depression without any change in the level of its mRNA, indicating that protein changes observed were due to posttranslational processes (Fatemi et al., 2013b) (Table 1). Protein for GABR ϵ however, was observed to be significantly reduced in BA9 of subjects with autism (Fatemi et al., 2014) (Table 1). Presence of the GABR ϵ subunit (or its increased expression) is known to reduce GABA $_A$ receptor sensitivity to benzodiazepines and anesthetics (Belujon et al., 2009; Kasparov et al., 2001; Thompson et al., 2002) and altered expression may impair responses to these pharmacologic agents.

GABR γ 2 is coded by the GABRG2 gene, which is located at 15q31.1-q33.1 (Wilcox et al. 1992). There is widespread expression of GABR γ 2 mRNA in both the developing and adult rat brain including the olfactory bulb, amygdala, septum, hypothalamus, and cerebellum (Laurie et al. 1992; Pirker et al. 2000; Schwarzer et al. 2001; Wisden et al. 1992). We observed no changes in protein or mRNA expression for GABR γ 2 in lateral cerebellum of subjects with schizophrenia or mood disorders (Fatemi et al., 2013b) (Table 1). Akbarian et al (1995) similarly observed no change in GABR γ 2 mRNA in PFC of subjects with schizophrenia, while Hashimoto et al (2008) found reduced expression of GABR γ 2 transcript in DLPFC as measured by DNA microarray (Table 1). However, this finding was not verified by qRT-PCR (Hashimoto et al., 2008). We found that GABR γ 2 protein was significantly reduced in BA9 of subjects with autism while its mRNA was significantly increased in cerebellum of subjects with autism (Fatemi et al., 2014) (Table 1). Similar to the α 2 subunit, the γ 2 subunit has been implicated in depression. Mice with selective heterozygous deletion of GABR γ 2, display increased immobility following the forced swim test or the novelty-suppressed feeding test (Earnheart et al., 2007) and exhibit increased anxiety (Crestani et al., 1999).

The gene that codes for GABR γ 3 (GABRG3) localizes to 15q11.2-q13 where it clusters with the genes for GABR α 5 and GABR β 3 (Greger et al., 1995). mRNA for GABR γ 3 has been identified in multiple areas of the rat brain including neocortex, caudate, putamen, nucleus accumbens, and cerebellum (Laurie et al., 1992; Wisden et al., 1992). We determined that GABR γ 3 protein was significantly and specifically increased in lateral cerebella of subjects with major depression with no change observed in either schizophrenia or bipolar disorder (Fatemi et al., 2013b). mRNA for GABR γ 3 was also observed to be significantly increased in cerebellum and BA40 of subjects with autism, while it was significantly reduced in BA9 of subjects with autism (Fatemi et al., 2014).

GABR π is coded by the GABRP gene, which is located at 5q32-q33 (Whiting et al., 1999). GABR π mRNA has been shown to be expressed in human hippocampus and temporal cortex (Hedblom and Kirkness, 1997). We did not identify significant alterations in GABR π mRNA or protein levels in subjects with schizophrenia, bipolar disorder, major depression, or autism (Fatemi et al., 2013b, 2014) (Table 1).

GABRQ, the gene that codes for GABR θ , clusters with the gene for GABR ϵ at Xq28 (Korpi et al. 2002). In human brain, GABR θ is expressed in multiple regions including the cerebral cortex (cingulate and piriform areas), hypothalamus, amygdala, hippocampus, substantia nigra, locus coeruleus, and hindbrain (Bonnert et al. 1999). A recent study by our laboratory discovered significant reductions in GABR θ protein in lateral cerebella of subjects with schizophrenia, bipolar disorder, and major depression and in BA9 of subjects with schizophrenia and bipolar disorder (Fatemi et al., 2013a) (Table 1). We also determined that GABR θ mRNA expression was reduced in lateral cerebella of subjects with schizophrenia and increased in BA9 of subjects with schizophrenia (Fatemi et al., 2013a). Our laboratory has observed that GABR θ mRNA was significantly reduced in BA9 and significantly increased in cerebellum of subjects with autism (Fatemi et al., 2014).

GABRR2, the gene that codes for GABR ρ 2, is located at 6q15 (Ma et al., 2005). In rat brain, mRNA for GABR ρ 2 has been identified in multiple regions including prefrontal cortex, hippocampus, and cerebellum (Alakuijala et al., 2005; Boue-Grabot et al., 1998). We observed significantly increased expression of GABR ρ 2 in lateral cerebella of subjects with bipolar disorder and major depression while there was no change in BA9 of subjects with schizophrenia and bipolar disorder (Fatemi et al., 2013a) (Table 1). mRNA expression for GABR ρ 2 was significantly increased in both lateral cerebella and BA9 of subjects with bipolar disorder (Fatemi et al., 2013a). GABA $_A$ receptors that include GABR ρ 2 are known to be involved in mediating phasic inhibitory GABAergic transmission at interneuron-Purkinje cell synapses in cerebellum (Harvey et al., 2006). Altered expression of GABR ρ 2 is likely to change inhibitory neurotransmission. A recent report shows reduced expression of GABR ρ 2 mRNA in blood of subjects with schizophrenia who were taking risperidone (Ota et al., 2014). Moreover, Ota et al (2014) found that higher GABR ρ 2 mRNA levels were associated with more severe Positive and Negative Syndrome Scale (PANSS) negative, psychopathology and total score ratings, however, these comparisons did not remain significant following Bonferroni's correction. The authors hypothesized that reduction in GABR ρ 2 mRNA levels resulted in a better response to antipsychotic treatment (Ota et al., 2014). Taken together, the GABR ρ 2 subunit may be a highly important biomarker in the

pathology and treatment of schizophrenia, bipolar disorder, and major depression. We have also observed significantly reduced GABRP2 protein level in BA9 of subjects with autism (Fatemi et al., 2014).

The cytogenetic location of GABBR1 is 6p21.3 (Goei et al., 1998) while the GABBR2 gene is located at 9q22.1 (Martin et al., 1999). Both GABBR1 and GABBR2 show strong expression in piriform cortex, hippocampus, olfactory bulb, and medial habenula with moderate expression in thalamic nuclei and cortex (Li et al., 2003). We have found that both GABBR1 and GABBR2 proteins were significantly reduced in lateral cerebella of subjects with schizophrenia, bipolar disorder, and major depression (Fatemi et al., 2011b) (Table 1). More recently, we have identified significant reductions in GABBR1 protein in BA9 of subjects with schizophrenia and bipolar disorder (Fatemi, unpublished observations). In subjects with autism, we observed that GABBR1 protein was significantly reduced in cerebellum, BA40, and BA9 while its mRNA expression was reduced in cerebellum, but increased in BA40 (Fatemi et al., 2009b, 2010a). We also determined that GABBR2 protein was significantly reduced in cerebellum of subjects with autism (Fatemi et al., 2009b) (Table 1). Altered expression of GABBR1 and GABBR2 have been associated with seizure disorder in animal models (Han et al., 2006; Princivalle et al., 2003; Straessle et al., 2003), which is relevant to subjects with autism where the presence of comorbid seizure disorder ranges from 4–44% (Tuchman and Rapin, 2002).

Collectively, postmortem studies by our laboratory have demonstrated detailed biochemical analysis of GABA_A and GABA_B receptor subunit distribution in cerebellum of subjects with schizophrenia, bipolar disorder, and major depression, showing significant alterations in several subunits as follows: 1) significant downregulation in protein levels for β 1, θ , R1, and R2 and significant upregulation in protein for α 2 and ϵ in subjects with schizophrenia (Table 2); 2) significant downregulation in protein levels for β 1, β 2, θ , R1, and R2 and significant upregulation in protein for α 2, ϵ , and ρ 2 in subjects with bipolar disorder (Table 3); 3) significant downregulation in protein levels for β 1, θ , R1, and R2 and significant upregulation in protein for α 1, α 2, α 6, ϵ , ρ 2, and γ 3 in subjects with major depression (Table 4); 4) significant downregulation in mRNA levels for α 1, α 2, and θ and significant upregulation in mRNA for β 3 in subjects with schizophrenia (Table 2); 5) significant upregulation in mRNA for ρ 2 in subjects with bipolar disorder (Table 3); and 6) significant downregulation in mRNA levels for α 1 in subjects with major depression (Table 4) (Fatemi et al., 2013a,b). There are currently no other published studies correlating protein and mRNA levels for 17 GABA receptor subunits in cerebella of subjects with schizophrenia, bipolar disorder, or major depression with the exception of a study by Bullock et al (2008) who measured mRNA levels for three GABA receptor subunits. However, several groups have investigated receptor levels using different techniques, (i.e. in situ hybridization, microarray, qRT-PCR), and different brain areas (i.e., DLPFC, PFC) and demonstrated increases or decreases in mRNA levels for various GABA receptors limited to schizophrenic samples (Akbarian et al., 1995; Beneyto et al., 2011; Bullock et al., 2008; Duncan et al., 2010; Glausier and Lewis, 2011; Hashimoto et al., 2008; Maldonado-Aviles et al., 2009) (Tables 2–4). However, it is difficult to compare and contrast our data vs. others due to different brain sites and different techniques used. Experiments are currently underway in

our laboratory to expand our studies using tissue from the prefrontal cortex in subjects with schizophrenia and bipolar disorder vs. healthy controls.

To summarize our findings in autism with regard to GABA_A and GABA_B receptor protein expression, we identified: 1) significant downregulation for protein levels of $\alpha 1$, $\beta 3$, R1, and R2 in cerebellum; 2) significant downregulation of $\alpha 1$, $\alpha 2$, $\alpha 3$, $\alpha 5$, $\beta 3$, and R1 proteins in BA40; and 3) significant downregulation of $\alpha 1$, $\alpha 4$, $\alpha 5$, $\alpha 6$, $\beta 1$, $\beta 2$, δ , ϵ , $\gamma 2$, $\rho 2$, and R1 proteins in BA9 (Table 5). With regard to mRNA expression we discovered: 1) significant upregulation of $\alpha 2$, $\alpha 3$, $\alpha 4$, $\alpha 5$, $\beta 1$, $\beta 3$, $\gamma 2$, $\gamma 3$, and θ mRNA and significant downregulation of $\alpha 6$ and R1 mRNA in cerebellum; 2) significant upregulation of $\gamma 3$ and R1 mRNAs and significant downregulation of $\alpha 3$ mRNA in BA40; and 3) significant upregulation of $\alpha 6$ mRNA and significant downregulation of $\alpha 2$, $\alpha 3$, $\alpha 4$, $\alpha 5$, $\beta 1$, $\beta 3$, $\gamma 3$, and θ mRNAs in BA9 (Table 5). Ultimately, it is the protein expression that has functional consequences and our findings of consistent, global reductions in the expression of GABA receptor subunits in brains of subjects with autism has the potential to alter the excitatory/inhibitory balance in the brain and help to explain learning deficits and presence of seizure disorder in this devastating neurodevelopmental disorder (Blatt and Fatemi, 2011).

3. FMRP

FMRP is an RNA binding protein that primarily functions as a regulator of translation. FMRP targets 842 mRNAs - approximately 5% of all mRNAs - expressed in brain (Darnell and Klann, 2013). FMRP is highly expressed in neurons (Devys et al., 1993) where it is involved in mediating neurotransmitter release, synaptic transmission, and plasticity (Deng et al., 2011, 2013). In individuals with fragile X syndrome (FXS), the gene that codes for FMRP, fragile X mental retardation 1 (FMR1) is transcriptionally silenced due to hypermethylation of multiple (>200) CGG repeats in the 5' untranslated portion of the gene including the CpG islands of the FMR1's promoter region (Pieretti et al., 1991). Absence of FMRP results in loss of inhibition of protein synthesis mediated by mGluR5. As a result there is increased synthesis of synaptic proteins (Weiler and Greenough, 1999) which results in increased epileptiform discharges (Chuang et al., 2005), altered long-term depression (Hou et al., 2006), and an increase in long, immature dendritic spines (Irwin et al., 2002). The mGluR5 theory of FXS posits that these changes underlie the multiple pathologies of FXS including intellectual impairment and presence of seizure disorder (Bear et al., 2004; Dölen and Bear, 2008). However, as discussed below, underproduction of FMRP may also be associated with additional abnormalities seen in several psychiatric disorders which do not exhibit evidence for mutations in the FMR1 gene (Fatemi and Folsom, 2011; Fatemi et al., 2010b, 2011a, 2013a; Kelemen et al., 2013; Kovács et al., 2013; Lohith et al., 2013).

3.1. Reduction of FMRP Expression in Schizophrenia, Mood Disorders, and Autism

Significant reductions in FMRP were first identified in lateral cerebella of subjects with schizophrenia, bipolar disorder, and major depression (Fatemi et al., 2010b, 2013a) (Table 6). A follow-up study also identified reductions in FMRP in BA9 of subjects with schizophrenia and bipolar disorder (Fatemi et al., 2013a) (Table 6). In contrast, we found no change in FMRP mRNA in schizophrenia, bipolar disorder, or major depression, indicating

that the observed changes were most likely secondary to posttranscriptional mechanisms. Subsequently, FMRP expression has been found to be reduced in peripheral blood lymphocytes of subjects with schizophrenia, confirming our initial observations (Kelemen et al., 2013; Kóvacs et al., 2013) (Table 6). This reduction was associated with lower IQ and earlier onset of illness (Kóvacs et al., 2013) as well as with deficits in visual perception (Kelemen et al., 2013) in subjects with schizophrenia. Thus, the observed reductions in FMRP protein levels result in functional consequences that could contribute to schizophrenic deficits. We similarly discovered reduced expression of FMRP in cerebellar vermis and BA9 of adults with autism (Fatemi and Folsom, 2011; Fatemi et al., 2011a) (Table 6). Moreover, we observed reduced expression of FMRP phosphorylated on serine 499 in cerebellar vermis of children and adults with autism and in BA9 of adults with autism (Rustan et al., 2013). Dephosphorylation of FMRP is known to lead to its ubiquitination and degradation (Nalavadi et al., 2012). In contrast, we discovered that there was no change in FMRP protein expression in children with autism and no change in mRNA levels in either age group (Fatemi and Folsom, 2011; Fatemi et al., 2011a) (Table 6). These findings are highly relevant as none of the individuals in these studies displayed the FMR1 mutation (Fatemi and Folsom, 2011; Fatemi et al., 2010b, 2011a, 2013a; Kóvacs et al., 2013). The phosphorylation status of FMRP in schizophrenia and mood disorders is currently unknown.

Recent work has identified *de novo* mutations are overrepresented among FMRP target proteins in subjects with schizophrenia including protein UNC-13 homolog A (UNC13A), kinesin-like protein KIF1A (KIF1A), glutamate receptor, ionotropic, N-methyl-D-aspartate subunit 2A (GRIN2A), discs large, *Drosophila* homolog 2 (DLG2), G-protein coupled receptor kinase-interacting protein 1 (GIT1), protein tyrosine phosphatase, and receptor type gamma (PTPRG) (Fromer et al., 2014). Fromer et al. (2014) suggested that these findings may indicate pathogenic disruption of synaptic plasticity in subjects with schizophrenia. An analysis of the exome sequences of 2,536 subjects with schizophrenia and 2,543 controls found that FMRP targets including calcium/calmodulin-dependent protein kinase II alpha and beta (CAMK2A and CAMK2B), aconitase, mitochondrial (ACO2), and calcium channel, voltage-dependent, N-type, alpha 1B subunit (CACNA1B) were identified as particularly enriched for mutations (Purcell et al., 2014). The overall conclusions of these two studies were that overlap existed between genes that were targets of FMRP and mutations affecting these genes impacted cognition both in schizophrenia and autism, further confirming our initial observations. While Fromer et al (2014) identified direct evidence for specific FMRP target genes, Purcell et al.'s (2014) study supported a broad and indirect evidence for FMRP target gene involvement in schizophrenia.

4. mGluR5 Expression in Major Psychiatric Disorders

mGluR5 exists in monomeric and dimeric forms with dimerized mGluR5 assumed to be the active form of the receptor (Goudet et al., 2005; Romano et al., 2001; Schwendt and McGinty, 2007). mGluR5 has multiple functions including involvement in activity-dependent synaptic plasticity both developmentally and during adulthood as well as regulation of proliferation, differentiation, and survival of neurons (reviewed by Catania et al., 2007). As mentioned previously, in the absence of FMRP, unregulated mGluR5 signaling is believed to lead to the intellectual impairment associated with FXS (Bear et al., 2004;

Dölen and Bear, 2008). Because of its normal physiological roles as well as its pathological role in FXS, mGluR5 has emerged as a target of therapeutic intervention in FXS, autism, and schizophrenia (Gürkan and Hagerman 2012; Hashimoto et al., 2013).

In subjects with schizophrenia, major depression, and bipolar disorder, our laboratory has identified reduced expression of the monomeric form of mGluR5 in lateral cerebellum (Fatemi et al., 2013a) (Table 6). qRT-PCR experiments also found that there was reduced mRNA expression for mGluR5 in the same brain region in schizophrenia and major depression (Fatemi et al., 2013a) (Table 6). We have also identified reduced expression of monomeric mGluR5 in BA9 of subjects with schizophrenia and bipolar disorder with mRNA values similarly reduced in BA9 of subjects with bipolar disorder (Fatemi et al., 2013a) (Table 6).

There are currently no other postmortem studies of mGluR5 in cerebellum of subjects with schizophrenia or mood disorders. However, results by other groups (Corti et al., 2011; Gupta et al. 2005; Matosin et al., 2013, 2014) found no change in levels of mGluR5 protein in other regions (anterior cingulate cortex, BA10, DLPFC, PFC, or striatum) in subjects with schizophrenia. A study by Deschwanden et al (2011), however, has identified a reduction in mGluR5 by western blotting in PFC in subjects with major depression, supporting our results. The above contradicting results can be due to several factors: 1) brain site differences; 2) different techniques used; and more importantly 3) lack of measurement of both monomeric and dimeric forms of mGluR5 by SDS-PAGE and western blotting. For example, as shown in Table 6, none of the above mentioned studies in schizophrenia discussed whether a monomer or dimer of mGluR5 was measured. The studies by Corti et al (2011) and Deschwanden et al (2011) showed a single band at 150 kDa, Gupta et al (2005) a band at 130 kDa, and Matosin et al (2013) a band at 130 kDa. Furthermore, Matosin et al. (2014) measured mGluR5 using receptor autoradiography which would not be able to identify either forms of mGluR5. Similarly, a recent study by Pretto et al. (2014) used immunocytochemistry to measure levels of mGluR5 whereby molecular species of mGluR5 could not be identified or quantified and reported a reduction in mGluR5 in FXS-ataxia syndrome. Similarly, three groups measured mRNA levels of mGluR5 in schizophrenia and did not report any changes in hippocampus, thalamus, BA9, or BA42 (Ohnuma et al., 2000; Richardson-Burns et al., 2000; Volk et al., 2010). Thus as recently discussed (Fatemi and Folsom, 2014), measurements of both monomer and dimer forms of mGluR5 by western blotting is a requirement for accurate measurement of any change in postmortem studies. In contrast, a positron emission tomography (PET) study found reduced expression in mGluR5 in the PFC, cingulate cortex (CC), insula, thalamus, and hippocampus of subjects with depression while western blotting found reduction in PFC (Deschwanden et al., 2011) (Table 6). Moreover, Volk et al (2010) found that subjects with schizoaffective disorder displayed significantly reduced mGluR5 mRNA than subjects with schizophrenia, further confirming our results in both schizophrenia and bipolar subjects who exhibit symptoms similar to subjects with a diagnosis of schizoaffective disorder.

In children with autism, we observed increased expression of the dimeric form of mGluR5 in BA9 and cerebellar vermis when compared to controls (Fatemi and Folsom, 2011; Fatemi et al., 2011a) (Table 6). The observed increased expression of mGluR5 in brains of children

with autism appeared to be both age and disease specific (Fatemi and Folsom, 2014). Upregulation in the dimer form of mGluR5 in autistic children may be due to increased dimerization as a result of oxidative stress, ischemia, or via auto-induction (Copani et al., 2000). Altered expression of mGluR5 has also been observed in a number of disorders including Alzheimer's disease (Tsamis et al., 2013), Huntington's disease (Gulyás et al., 2014) and Down's syndrome (Oka and Takashima, 1999), as well as in animal models of Parkinson's disease (Sanchez-Pernaute et al., 2008). These changes may reflect greater excitotoxicity which contributes to the pathology of these disorders.

5. Expression of FMRP-mGluR5 Molecular Targets in Schizophrenia, Mood Disorders and Autism

In addition to some of the GABA receptors, a number of important molecules are targets of FMRP-mGluR5 signaling and synaptic transmission (Darnell et al., 2011; Darnell and Klann, 2013). We identified changes in four such targets – homer 1, amyloid beta A4 precursor protein (APP), ras-related C3 botulinum toxin substrate 1 (RAC1), and striatal-enriched protein tyrosine phosphatase (STEP) - in cerebellar vermis and BA9 of adults and children with autism when compared to controls (Fatemi et al., 2013c) (Table 6). APP is involved in synapse formation and neural plasticity (Priller et al., 2006; Turner et al., 2003). STEP is present in the postsynaptic density (PSD), where it is an important regulator of N-methyl-D-aspartate (NMDA) receptor function (Goebel-Goody et al., 2012). Homer proteins are components of the PSD and have multiple roles in synaptogenesis, receptor trafficking, and dopaminergic and glutamatergic signaling (Szumlinski et al., 2006). RAC1 is involved in functions that are relevant to neurotransmission, specifically the modulation of dendritic spine morphology and density (Luo et al., 1996; Nakayama et al., 2000; Threadgill et al., 1997).

More recently, we have investigated the protein expression of the same molecules in subjects with schizophrenia and mood disorders. In BA9 of subjects with schizophrenia, we determined reduced protein expression for APP and STEP (Folsom and Fatemi, unpublished observations). In BA9 of subjects with bipolar disorder, we determined significant reductions in APP and homer 1 (Folsom and Fatemi, unpublished observations). In lateral cerebella, we identified increased expression of RAC1 in subjects with schizophrenia, bipolar disorder, and major depression (Folsom and Fatemi, unpublished observations). When combined with previous observations of reduced expression of FMRP and mGluR5 in the same areas (Fatemi et al., 2010b, 2013a), our results provide further evidence that this signaling pathway is altered in schizophrenia and mood disorders.

6. FMRP Regulon Impacts Expression of GABA Receptor Subunits and mGluR5

A number of studies involving animal models of FXS have established that there is altered expression of GABA_A receptor subunits in brain as a result of reduced or absent FMRP expression (Adusei et al., 2010; El Idrissi et al., 2005; D'Hulst et al., 2006; Gantois et al., 2006; Hong et al., 2012). An initial study found that there was reduced protein expression of

the GABR β subunit in the cortex, hippocampus, diencephalon, and brainstem of adult FMR1 knockout (KO) mice (El Idrissi et al., 2005). A follow up study by the same group found reduced mRNA for GABR β 1 in cerebellum, reduced mRNA for GABR β 2 in hippocampus and cerebellum, and reduced mRNA for GABR β 3 in cortex of male FMR1 KO mice (Hong et al., 2012). However, mRNA for GABR β 3 was significantly upregulated in hippocampus of male FMR1 KO mice (Hong et al., 2012). A separate study found that mRNA for GABR δ was reduced in multiple brain regions of FMRP KO mice including hippocampus, neocortex, cerebellum, caudate, putamen, thalamus and olfactory bulb (Gantois et al., 2006). A comprehensive study of 17 GABA $_A$ subunits found reduced expression of mRNA for GABR α 1, GABR α 3, GABR α 4, GABR β 1, GABR β 2, GABR γ 1, and GABR γ 2 in cortex of FMR1 KO mice (D'Hulst et al., 2006).

Complex developmental patterns of GABA $_A$ receptor subunits have also been identified in forebrain of FMR1 KO mice - i.e., downregulation of GABR α 1 protein during early postnatal development while displaying similar expression as wild type during adulthood vs. GABR β 2 which displayed similar expression as wild type at postnatal day five (PN5), but showed significantly reduced expression at PN12 and adulthood (Adusei et al., 2010). Importantly, treatment with allosteric modulators of GABA $_A$ receptors (ganaxolone) or GABA $_B$ receptors (arbaclofen) rescued many FXS-related deficits in FMR1 KO mice including reducing audiogenic seizures, spine density, protein synthesis, and internalization of AMPA receptors (Henderson et al., 2012; Heulens et al., 2012).

It is well known that FMRP is involved in the normal maturation and function of GABAergic interneurons (Olmos-Serrano et al., 2010; Martin and Huntsman, 2014) with its loss or reduction leading to abnormal GABA release presynaptically, abnormal production of GAD65/67 enzymes, decreases in GABA transporter 1 expression and excitatory drive of parvalbumin positive GABAergic interneurons (Martin and Huntsman, 2014). As FMRP binds to the GABA $_A$ delta subunit; reduction in δ subunit mRNA, protein, or both (D'Hulst et al., 2006; Curia et al., 2009) can result in defective tonic GABAergic conductance (Martin and Huntsman, 2014). Quite interestingly, reports by two groups indicate that absence of FMRP in amygdala of Fmr1 KO mice results in decreased tonic inhibitory tone, most likely due to several reasons: 1) limited GABA production and release, leading to reduced availability of GABA ligand for tonic receptors; 2) decreased capacity for tonically active currents; 3) lack of co-expression of α 3 subunits with postsynaptic protein gephyrin; 4) small α 5 subunit-mediated tonic currents; 5) reduced inhibitory synaptic efficacy; and 6) ineffective glutamate-related plasticity (Martin and Huntsman, 2014; Martin et al., 2014; Olmos-Serrano et al., 2010). Analogously, observation of significant decreases in protein expression for α 3 (both mRNA and protein), α 5, and δ subunits in brains of subjects with autism (Fatemi et al., 2009a, 2010a, 2014; Tables 1 and 5) demonstrate that similar mechanisms may be operational in idiopathic autism, probably due to reduction in levels of FMRP protein. A further mechanism whereby reduction in FMRP may lead to alterations in several GABA receptor subunits is potentially through failure of translation of one subunit, i.e., δ subunit causing decreased translation of other coassembled subunits (i.e., α 4 and α 5) (Sur et al., 2001; Martin and Huntsman, 2014).

Taken together, these studies show that FMRP impacts multiple GABA receptor subunit mRNAs, resulting in altered expression and, consequently leading to abnormalities associated with FXS. The exact mechanism by which FMRP alters GABA receptor subunit expression is currently unknown although FMRP effects may be at the transcriptional or translational levels. The reduction of mRNA for GABA receptors in FMR1 KO mice suggests some level of transcriptional control (D'Hulst et al., 2006; Gantois et al., 2006; Hong et al., 2012). Reduced protein expression in FMR1 KO mice also suggests that translational control may be abnormal (Adusei et al., 2010; El Idrissi et al., 2005). FMRP has been shown to directly bind GABBR1, GABBR2, and GABR δ mRNAs (Darnell et al., 2011; Miyashiro et al., 2003) while no direct binding of FMRP to mRNAs for GABR α 1- α 6, GABR β 1- β 3, or GABR γ 1- γ 3 has been demonstrated (Brown et al., 2001; Chen et al., 2003; Darnell et al., 2011). Further experiments are needed to elucidate the exact molecular mechanism by which GABA receptor subunit expression is altered by FMRP regulon.

The recent findings of reduced expression of FMRP in multiple brain regions of subjects with schizophrenia, bipolar disorder, major depression, and autism (Fatemi and Folsom, 2011; Fatemi et al., 2010b, 2011a, 2013a) and in peripheral blood lymphocytes of subjects with schizophrenia (Kelemen et al., 2013; Kóvacs et al., 2013) are novel. They represent the first findings of altered FMRP expression outside of subjects with FXS, in individuals who do not carry the FMR1 mutation. The cause of reduced FMRP expression in major psychiatric disorders is currently unknown. In FXS, it is well-established that hypermethylation of the CGG-trinucleotide expansion at the FMR1 promoter inhibits production of FMRP (Colak et al., 2014; Pieretti et al., 1991). Hypomethylation of the FMR1 promoter has also been observed in an individual with the FMR1 mutation who did not display intellectual impairment (Burman et al., 1999). It is unclear whether similar epigenetic mechanisms are at work in schizophrenia, mood disorders, and autism, especially as none of the individuals studied thus far carried the FMR1 mutation (Fatemi and Folsom, 2011; Fatemi et al., 2010b, 2011a, 2013a; Keleman et al., 2013; Kóvacs et al., 2013). Moreover, none of these studies indicate any abnormalities in mRNA levels for FMRP, clearly pointing to translational abnormalities in these studies. Lastly, recent positive associations between FMRP target mutations in schizophrenia and autism (Fromer et al., 2014; Iossifov et al., 2012; Purcell et al., 2014) clearly expand the pathological role of FMRP in these diseases.

Our laboratory's findings of reduced FMRP, increased mGluR5, and reduced expression of GABA receptors in autism are consistent with the mGluR5 theory of FXS. Due to the extensive phenotypic overlap between autism and FXS, these findings are not unexpected. As mentioned above, this pattern is similar to what has been observed in FMR1 KO mice (D'Hulst et al., 2006; Dölen and Bear et al., 2008; El Idrissi et al., 2005; Gantois et al., 2006). The theory is further strengthened by the findings of Lohith et al (2013) who found increased expression of mGluR5 protein in BA9 of subjects with FXS. Our results suggest increased mGluR5 activity in children with autism. Even in adults with autism, where mGluR5 levels were not significantly different than controls, ratios of mGluR5 to neuronal specific enolase (NSE) for both dimeric and total mGluR5 were increased by 96% in BA9 (Fatemi and Folsom, 2011; Fatemi et al., 2011a). In contrast, a recent article by Pretto et al. (2014) demonstrated reduced expression of both FMRP and mGluR5 in cerebella of subjects

with the FMR1 premutation who had been diagnosed with fragile X tremor/ataxia syndrome (FXTAS). The discrepancy between these findings and ours may be due to brain regional differences as we found non-significant reductions in mGluR5 in cerebellar vermis of adults with autism (Fatemi et al., 2011a). Additionally, while Lohith et al (2013) found marginally increased mGluR5 expression in carriers and subjects with FXS based on receptor binding assays ($p<0.056$) and western blotting ($p<0.048$), when carriers were removed from analysis, both mGluR5 expression and density were higher although significance was not attained (Lohith et al., 2013), possibly due to reduced sample size. Thus, the status of the individuals tested (carrier vs. FXS/autism diagnosis) or presence/absence of FXTAS or brain regional differences may impact mGluR5 levels.

In schizophrenia and mood disorders, which have no obvious phenotypic overlap with FXS, our findings of reduced levels of both FMRP and monomeric mGluR5, suggest that an as yet unknown mechanism might be at work (Fatemi et al., 2013a). The discrepancy between our results and those of other laboratories (Corti et al., 2011; Gupta et al., 2005; Matosin et al., 2013, 2014; Ohnuma et al., 2000; Pretto et al., 2014; Richardson-Burns et al., 2000; Volk et al., 2010) may reflect region-specific differences in mGluR5 expression (BA9 vs. BA10 vs. DLPFC vs. ACC vs. cerebellum); the different analytic techniques that were used (western blotting vs. receptor binding assays vs. qRT-PCR vs. immunocytochemistry); more importantly, the lack of measurement of monomer and dimer forms of mGluR5 in three studies (Corti et al., 2011; Gupta et al., 2005; Matosin et al., 2013) and the non-quantitative technique of measuring mGluR5 by immunocytochemistry in one study (Pretto et al., 2014); and lastly, differences between levels of mRNA and protein for mGluR5. The hypothesis that brain regional expression of mGluR5 may also account for differences between studies has recently been advocated by other laboratories (Matosin et al., 2014).

7. Potential for Treatment

Altered expression of GABAergic and FMRP-mGluR5 signaling system components provide opportunities for targeted therapeutic intervention. Several review articles have been published regarding targeting the FMRP-mGluR5 signaling system, including the use of allosteric modulators of mGluR5, for the treatment of autism and FXS (Gürkan and Hagerman, 2012; Hagerman et al., 2014; Wang et al., 2010). Minocycline is a semisynthetic second-generation tetracycline that prevents glutamate-induced excitotoxicity (Maier et al., 2007; Pi et al., 2004). Treatment with minocycline has been shown to improve behavior in subjects with FXS (Paribello et al., 2010). Preliminary trials of minocycline in subjects with schizophrenia have demonstrated a beneficial effect on the negative symptoms, and cognitive functioning (Levkovitz et al., 2010; Miyaoka et al., 2008). mGluR5 negative allosteric modulator 2-Methyl-6-(phenylethynyl)pyridine (MPEP) has shown promise in animal studies (de Vrij et al., 2008) and may prove effective in humans. Fenobam, an antagonist of mGluR5 was shown to improve PPI deficits in six out of 12 subjects with FXS in a pilot study (Berry-Kravis et al., 2009). Norbin is a positive endogenous mediator of mGluR5 which increases cell surface expression of mGluR5 (Wang et al., 2009), and may be useful where there are deficits in mGluR5 expression. Less is known about mGluR5 modulators in schizophrenia although preclinical studies of glutamate receptor modulators, including mGluR5 modulators are currently underway (Hashimoto et al., 2013; Herman et

al., 2012). In contrast, there have been multiple clinical trials of drugs that target GABA_A and GABA_B receptors in subjects with schizophrenia and mood disorders.

Drugs that modulate GABA function may prove to be beneficial for the treatment of schizophrenia. Pregnenolone and its metabolite allopregnanolone are positive allosteric modulators of GABA_A receptors. Pregnenolone has recently shown promise in ameliorating positive, negative, and cognitive deficits in schizophrenia (Kreinin et al., 2014; Marx et al., 2009; Ritsner et al., 2010, 2014). A proof-of-concept trial demonstrated that subjects with schizophrenia receiving pregnenolone showed improvement in negative symptoms as measured by the Scale for the Assessment of Negative Symptoms (SANS) and increased serum pregnenolone predicted scores on the Brief Assessment of Cognition in schizophrenia (BACS) (Marx et al., 2009). More recently, in a double-blind, randomized add-on trial, pregnenolone showed efficacy in improving negative symptoms, especially with respect to blunted affect, anhedonia, and avolition (Ritsner et al., 2014). Pregnenolone has also been shown to reduce deficits in visual attention, sustained attention, and executive function when compared against placebo (Kreinin et al., 2014). Additionally, pregnenolone has been shown to improve positive symptoms of schizophrenia as well as neuroleptic-induced extrapyramidal side-effects (Ritsner et al., 2010). In an animal model of schizophrenia, pregnenolone has been shown to correct deficits in PPI as well as hyperlocomotion (Wong et al., 2012). Antipsychotic drugs clozapine and olanzapine are known to increase levels of pregnenolone as well as allopregnanolone, in a dose dependent manner (Marx et al., 2003, 2006a,b), while haloperidol, risperidone, aripiprazole, quetiapine, and ziprasidone have no such effect (Marx et al., 2003, 2006b). Importantly, pregnenolone was increased in rat hippocampus and cerebral cortex by clozapine and olanzapine (Marx et al., 2006a,b), two brain areas implicated in the pathology of schizophrenia. The superior efficacy of clozapine in the treatment of refractory schizophrenia may be partly accounted for by its ability to increase pregnenolone and subsequent allosteric modulation of GABA_A receptors (Marx et al., 2006b).

Treatment with pregnenolone or allopregnanolone may be beneficial for mood disorders. Reduced levels of allopregnanolone in blood and cerebrospinal fluid have been associated with depression and anxiety disorders (reviewed by Schüle et al., 2014). Rats treated with fluoxetine display increased expression of pregnenolone and allopregnanolone in hippocampus (Marx et al., 2006a), suggesting that this may be part of its efficacy as an antidepressant. A recent double-blind, placebo-controlled trial of pregnenolone in subjects with bipolar disorder found that it was effective in treating depressive symptoms in this population (Brown et al., 2014).

Modulators of GABA_B receptors have also shown promise in reversing deficits in animal models of schizophrenia. *rac*-BHFF [(*R,S*)-5,7-di-*tert*-butyl-3-hydroxy-3-trifluoromethyl-3*H*-benzofuran-2-one], which acts as a positive allosteric modulator of GABA_B receptors has been shown to correct for sensorimotor gating deficits, as measured by PPI, in a dose-dependent manner (Frau et al., 2014). Baclofen, another GABA_B receptor agonist, has been shown to reverse deficits in social interaction and spatial working memory (Gandal et al., 2012). Baclofen can also reverse deficits in PPI and object recognition memory (Mizoguchi and Yamada, 2011). A small number of studies have investigated

baclofen for the treatment of schizophrenia with mixed results. There have been some reports of clinical improvement when baclofen is used on its own (Gulmann et al., 1976) or as an adjunctive treatment (Frederiksen, 1975), while another study found no improvement (Bigelow et al., 1977). However, in light of recent animal experiments and the availability of additional GABA_B modulators, use of these drugs may prove beneficial in the treatment of schizophrenia.

8. Conclusions

The GABAergic signaling system has been hypothesized to contribute to the pathology of major psychiatric disorders including schizophrenia, bipolar disorder, major depression, and autism. Our laboratory has demonstrated comprehensive changes in GABA receptor expression in cerebellum in all four disorders. A potential mechanism to explain altered GABA receptor expression is through reduced expression of FMRP and altered FMRP-mGluR5 signaling as shown by changes in expression for mGluR5 and downstream targets including RAC1, APP, STEP, and homer 1. Alternatively, other mechanisms such as epigenetics or monoallelic expression, as seen in the case of GABR β 3, may also play important roles in GABA receptor expression. Drugs that affect: 1) the GABAergic signaling system such as pregnenolone, allopregnanolone, *rac*-BHFF, or baclofen; 2) allosteric modulators of mGluR5 activity such as MPEP, fenobam, or norbin; or 3) minocycline's action preventing glutamate-induced excitotoxicity, are emerging as potential treatments for schizophrenia and mood disorders that may succeed where traditional treatments that target dopaminergic or serotonergic systems have not been as efficacious. Future studies should focus on these signaling systems as potential novel treatments for major psychiatric disorders.

Acknowledgments

Role of the Funding Source

Funding for this study was provided by the National Institute of Child Health and Human Development (NICHD), Grant #5R01HD052074-01A2 and 3R01HD052074-03S1, the National Institute of Mental Health (NIMH), Grant #5R01MH086000-01A2, the Winston and Maxine Wallin Neuroscience Discovery Fund, and the Ewald Bipolar Disease Research Fund (SHF). NICHD, NIMH, and the Ewald Bipolar Disease Research Fund had no further role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

References

- Adusei DC, Pacey LK, Chen D, Hampson DR. Early developmental alterations in GABAergic protein expression in fragile X knockout mice. *Neuropharmacology*. 2010; 59(3):167–171. [PubMed: 20470805]
- Akbadian S, Huntsman MM, Kim JJ, Tafazzoli A, Potkin SG, Bunney WE Jr, Jones EG. GABAA receptor subunit gene in human prefrontal cortex: comparison of schizophrenics and controls. *Cereb. Cortex*. 1995; 5(6):550–560. [PubMed: 8590827]
- Alakuijala A, Palgi M, Wegelius K, Schmidt M, Enz R, Paulin L, Saarna M, Pasternack M. GABA receptor rho subunit expression in the developing rat brain. *Brain Res. Dev. Brain Res*. 2005; 154(1):15–23. [PubMed: 15617751]
- Bear MF, Huber KM, Warren ST. The mGluR theory of fragile X mental retardation. *Trends. Neurosci*. 2004; 27(7):370–377. [PubMed: 15219735]

- Belelli D, Lambert JJ. Neurosteroids: endogenous regulators of the GABA(A) receptor. *Nat. Rev. Neurosci.* 2005; 6(7):565–575. [PubMed: 15959466]
- Belujon P, Baufreton J, Grandoso L, Boué-Grabot E, Batten TF, Ugedo L, et al. Inhibitory transmission in locus coeruleus neurons expressing GABAA receptor epsilon subunit has a number of unique properties. *J. Neurophysiol.* 2009; 102(4):2312–2325. [PubMed: 19625540]
- Benes FM, Vincent SL, Alterberg G, Bird ED, SanGiovanni JP. Increased GABAA receptor binding in superficial layers of cingulate cortex in schizophrenics. *J. Neurosci.* 1992; 12(3):924–929. [PubMed: 1372045]
- Benes FM, Vincent SL, Marie A, Khan Y. Up-regulation of GABA_A receptor binding on neurons of the prefrontal cortex in schizophrenic subjects. *Neuroscience.* 1996a; 75(4):1021–1031. [PubMed: 8938738]
- Benes FM, Khan Y, Vincent SL, Wickramasinghe R. Differences in the subregional and cellular distribution of GABAA receptor binding in the hippocampal formation of schizophrenic brain. *Synapse.* 1996b; 22(4):338–349. [PubMed: 8867028]
- Benes FM, Wickramasinghe R, Vincent SL, Khan Y, Todtenkopf M. Uncoupling of GABA(A) and benzodiazepine receptor binding activity in the hippocampal formation of schizophrenic brain. *Brain Res.* 1997; 755(1):121–129. [PubMed: 9163547]
- 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]
- Berry-Kravis E, Hessel D, Coffey S, Hervey C, Schneider A, Yuhas J, Hutchison J, Snape M, Tranfaglia M, Nguyen DV, Hagerman R. A pilot open label, single dose of fenobam in adults with Fragile X syndrome. *J. Med. Genet.* 2009; 46(4):266–271. [PubMed: 19126569]
- Bigelow LB, Nasrallah H, Carman J, Gillin JC, Wyatt RJ. Baclofen treatment in chronic schizophrenia: a clinical trial. *Am. J. Psychiatry.* 1977; 133(3):318–320.
- Blatt GJ, Fatemi SH. Alterations in GABAergic biomarkers in the autism brain: research findings and clinical implications. *Anat. Rec. (Hoboken).* 2011; 294(10):1642–1652.
- Blatt GJ, Fitzgerald CM, Guptill JT, Booker AB, Kemper TL, Bauman ML. Density and distribution of hippocampal neurotransmitter receptors in autism: an autoradiographic study. *J. Autism Dev. Disord.* 2001; 31(6):537–544. [PubMed: 11814263]
- Bonnert TP, McKernan RM, Farrar S, le Bourdellès B, Heavens RP, Smith DW, Hewson L, Rigby MR, Sirinathsinghji DJ, Brown N, Wafford KA, Whiting PJ. Theta, a novel gamma-aminobutyric acid type A receptor subunit. *Proc. Natl. Acad. Sci. USA.* 1999; 96(17):9891–9896. [PubMed: 10449790]
- Boué-Grabot E, Roudbaraki M, Bascles L, Tramu G, Bloch B, Garret M. Expression of GABA receptor rho subunits in rat brain. *J. Neurochem.* 1998; 70(3):899–907. [PubMed: 9489708]
- Bowery, NG. GABA_B receptors structure and function. In: Martin, DL., Olsen, RW., editors. *GABA in the nervous system: the view at fifty years.* Philadelphia, PA: Lippincott, Williams and Wilkins; 2000. p. 233–244.
- Brandon, NJ., Smart, TG., Moss, SJ. Regulation of GABAA Receptors by protein phosphorylation. In: Martin, DL., Olsen, RW., editors. *GABA in the nervous system: the view at fifty years.* Philadelphia, PA: Lippincott, Williams and Wilkins; 2000. p. 191–206.
- Braudeau J, Delatour B, Duchon A, Pereira PL, Dauphinot L, de Chaumont F, Olivo-Marin JC, Dodd RH, Héroult Y, Potier MC. Specific targeting of the GABA-A receptor $\alpha 5$ subtype by a selective inverse agonist restores cognitive deficits in Down syndrome mice. *J. Psychopharmacol.* 2011; 25(8):1030–1042. [PubMed: 21693554]
- Brown V, Jin P, Ceman S, Darnell JC, O'Donnell WT, Tenenbaum SA, Jin X, Feng Y, Wilkinson KD, Keene JD, Darnell RB, Warren ST. Microarray identification of FMRP-associated brain mRNAs and altered mRNA translational profiles in fragile X syndrome. *Cell.* 2001; 107(4):477–487. [PubMed: 11719188]
- Brown ES, Park J, Marx CE, Hynan LS, Gardner C, Davila D, Nakamura A, Sunderajan P, Lo A, Holmes T. A randomized, double-blind, placebo-controlled trial of pregnenolone for bipolar disorder. *Neuropsychopharmacology.* 2014; 39(12):2867–2873. [PubMed: 24917198]

- Buckle VJ, Fujita N, Bateson AN, Darlison MG, Barnard EA. Localization of human GABA-A receptor subunit genes to chromosomes 4 and 5. *Cytogenet. Cell Genet.* 1989; 51:972.
- Bullock WM, Cardon K, Bustillo J, Roberts RC, Perrone-Bizzozero NI. Altered expression of genes involved in GABAergic transmission and neuromodulation of granule cell activity in the cerebellum of schizophrenia patients. *Am. J. Psychiatry.* 2008; 165(12):1594–1603. [PubMed: 18923069]
- Burman RW, Yates PA, Green LD, Jacky PB, Turker MS, Popovich BW. Hypomethylation of an expanded FMR1 allele is not associated with a global DNA methylation. *Am. J. Hum. Genet.* 1999; 65(5):1375–1386. [PubMed: 10521303]
- Carty NC, Xu J, Kurup P, Brouillette J, Goebel-Goody SM, Austin DR, Yuan P, Chen G, Correa PR, Haroutunian V, Pittenger C, Lombroso PJ. The tyrosine phosphatase STEP: implications in schizophrenia and the molecular mechanism underlying antipsychotic medications. *Transl. Psychiatry.* 2012; 2:e137.
- Catania MV, D'Antoni S, Bonaccorso CM, Aronica E, Bear MF, Nicoletti F. Group I metabotropic glutamate receptors: a role in neurodevelopmental disorders? *Mol. Neurobiol.* 2007; 35(3):298–307. [PubMed: 17917118]
- Charych EI, Liu F, Moss SJ, Brandon NJ. GABAA receptors and their associated proteins: Implications in the etiology of schizophrenia and related disorders. *Neuropharmacology.* 2009; 57(5–6):481–495. [PubMed: 19631671]
- Chebib M, Johnston GA. GABA-activated ligand gated ion channels: medicinal chemistry and molecular biology. *J. Med. Chem.* 2000; 43(8):1427–1474. [PubMed: 10780899]
- Chen L, Yun SW, Seto J, Liu W, Toth M. The fragile X mental retardation protein binds and regulates a novel class of mRNAs containing U rich target sequences. *Neuroscience.* 2003; 120(4):1005–1017. [PubMed: 12927206]
- Chuang SC, Zhao W, Bauchwitz R, Yan Q, Bianchi R, Wong RK. Prolonged epileptiform discharges induced by altered group I metabotropic glutamate receptor-mediated synaptic responses in hippocampal slices of a fragile X mouse model. *J. Neurosci.* 2005; 25(35):8048–8055. [PubMed: 16135762]
- Coghlan S, Horder J, Inkster B, Mendez MA, Murphy DG, Nutt DJ. GABA system dysfunction in autism and related disorders: from synapse to symptoms. *Neurosci. Biobehav. Rev.* 2012; 36(9):2044–2055. [PubMed: 22841562]
- Colak D, Zaninovic N, Cohen MS, Rosenwaks Z, Yang WY, Gerhardt J, Disney MD, Jaffrey SR. Promoter-bound trinucleotide repeat RNA drives epigenetic silencing in fragile X syndrome. *Science.* 2014; 343(6174):1002–1005. [PubMed: 24578575]
- Copani A, Romano C, Di Giorgi Gerevini V, Nicosia A, Casabona G, Storto M, Mutel V, Nicoletti F. Reducing conditions differentially affect the functional and structural properties of group-I and -II metabotropic glutamate receptors. *Brain Res.* 2000; 867(1–2):165–172. [PubMed: 10837810]
- Corti C, Xuereb JH, Crepaldi L, Corsi M, Michielin F, Ferraguti F. Altered levels of glutamatergic receptors and Na⁺/K⁺ ATPase- α 1 in the prefrontal cortex of subjects with schizophrenia. *Schizophr. Res.* 2011; 128(1–3):7–14. [PubMed: 21353485]
- Crestani F, Lorez M, Baer K, Essrich C, Benke D, Laurent JP, Belzung C, Fritschy JM, Lüscher B, Mohler H. Decreased GABAA-receptor clustering results in enhanced anxiety and a bias for threat cues. *Nat. Neurosci.* 1999; 2(9):833–839. [PubMed: 10461223]
- Curia G, Papouin T, Seguela P, Avoli M. Downregulation of tonic GABAergic inhibition in a mouse model of fragile X syndrome. *Cereb. Cortex.* 2009; 19(7):1515–1520. [PubMed: 18787232]
- Darnell JC, Klann E. The translation of translational control by FMRP: therapeutic targets for FXS. *Nat. Neurosci.* 2013; 16(11):1530–1536. [PubMed: 23584741]
- Darnell JC, Van Driesche SJ, Zhang C, Hung KY, Mele A, Fraser CE, Stone EF, Chen C, Fak JJ, Chi SW, Licatalosi DD, Richter JD, Darnell RB. FMRP stalls ribosomal translocation on mRNAs linked to synaptic function and autism. *Cell.* 2011; 146(2):247–261. [PubMed: 21784246]
- D'Hulst C, De Geest N, Reeve SP, Van Dam D, De Deyn PP, Hassan BA, Kooy RF. Decreased expression of the GABA_A receptor in fragile X syndrome. *Brain Res.* 2006; 1121(1):238–245. [PubMed: 17046729]

- DeLorey TM, Handforth A, Anagnostaras SG, Homanics GE, Minassian BA, Asatourian A, Fanselow MS, Delgado-Escueta A, Ellison GD, Olsen RW. Mice lacking the beta 3 subunit of the GABA_A receptor have the epilepsy phenotype and many of the behavioral characteristics of Angelman syndrome. *J. Neurosci.* 1998; 18(20):8505–8514. [PubMed: 9763493]
- DeLorey TM, Sahbaie P, Hashemi E, Homanics GE, Clark JD. Gabrb3 gene deficient mice exhibit impaired social and exploratory behaviors, deficits in non-selective attention and hypoplasia of cerebellar vermal lobules: A potential model of autism spectrum disorder. *Behav. Brain. Res.* 2008; 187(2):207–220. [PubMed: 17983671]
- Deng PY, Sojka D, Klyachko VA. Abnormal presynaptic short-term plasticity and information processing in a mouse model of fragile X syndrome. *J. Neurosci.* 2011; 31(30):10971–10982. [PubMed: 21795546]
- Deng PY, Rotman Z, Blundon JA, Cho Y, Cui J, Cavalli V, Zakharenko SS, Klyachko VA. FMRP regulates neurotransmitter release and synaptic information transmission by modulating action potential duration via BK channels. *Neuron.* 2013; 77(4):696–711. [PubMed: 23439122]
- Deschwenden A, Karolewicz B, Feyissa AM, Treyer V, Ametamey SM, Johayem A, Burger C, Auberson YP, Sovago J, Stockmeyer CA, Buck A, Hasler G. Reduced metabotropic glutamate receptor 5 density in major depression determined by ((11)C)ABP688 PET and postmortem study. *Am. J. Psychiatry.* 2011; 168(7):724–734.
- de Vrij FM, Levenga J, van der Linde HC, Koekkoek SK, De Zeeuw CI, Nelson DL, Oostra BA, Willemsen R. Rescue of behavioral phenotype and neuronal protrusion morphology in Fmr1 KO mice. *Neurobiol. Dis.* 2008; 31(1):127–132. [PubMed: 18571098]
- Devys D, Lutz Y, Rouyer N, Bellocq JP, Mandel JL. The FMR-1 protein is cytoplasmic, most abundant in neurons and appears normal in carriers of a fragile X premutation. *Nat. Genet.* 1993; 4(4):335–340. [PubMed: 8401578]
- Dölen G, Bear MF. Role for metabotropic glutamate receptor 5 (mGluR5) in the pathogenesis of fragile X syndrome. *J. Physiol.* 2008; 586(6):1503–1508. [PubMed: 18202092]
- Duncan CE, Webster MJ, Rothmond DA, Bahn S, Elashoff M, Shannon Weickert C. Prefrontal GABA(A) receptor alpha-subunit expression in normal postnatal human development and schizophrenia. *J. Psychiatr. Res.* 2010; 44(10):673–681. [PubMed: 20100621]
- Earnheart JC, Schweizer C, Crestani F, Iwasato T, Itoharu S, Mohler H, Lüscher B. GABAergic control of adult hippocampal neurogenesis in relation to behavior indicative of trait anxiety and depression states. *J. Neurosci.* 2007; 27(14):3845–3854. [PubMed: 17409249]
- El Idrissi A, Ding XH, Scalia J, Trenkner E, Brown WT, Dobkin C. Decreased GABA_A receptor expression in the seizure-prone fragile X mouse. *Neurosci. Lett.* 2005; 377(3):141–146. [PubMed: 15755515]
- Emberger W, Windpassinger C, Petek E, Kroisel PM, Wagner K. Assignment of the human GABAA receptor delta-subunit gene (GABRD) to chromosome band 1p36.3 distal to marker NIB1364 by radiation hybrid mapping. *Cytogenet. Cell Genet.* 2000; 89(3–4):281–282. [PubMed: 10965146]
- Errington, AC. Extrasynaptic GABA_A receptors. In: Errington, AC, Di Giovanni, G., Crunelli, V., editors. *Extrasynaptic GABA_A receptors*. New York: Springer Science+Business Media; 2014. p. 1–14.
- Farrar SJ, Whiting PJ, Bonnert TP, McKernan RM. Stoichiometry of a ligand-gated ion channel determined by fluorescence energy transfer. *J. Biol. Chem.* 1999; 274(15):10100–10104. [PubMed: 10187791]
- Fatemi SH, Folsom TD. Dysregulation of fragile X mental retardation protein and metabotropic glutamate receptor 5 in superior frontal cortex of individuals with autism: a postmortem brain study. *Mol. Autism.* 2011; 2:6–16. [PubMed: 21548960]
- Fatemi SH, Folsom TD. Existence of monomer and dimer forms of mGluR5, under reducing conditions in studies of postmortem brain in various psychiatric disorders. *Schizophr. Res.* 2014; 158(1–3):270–271. [PubMed: 25043265]
- Fatemi SH, Reutiman TJ, Folsom TD, Thuras PD. GABA(A) receptor downregulation in brains of subjects with autism. *J. Autism Dev. Disord.* 2009a; 39(2) 233–230.
- Fatemi SH, Folsom TD, Reutiman TJ, Thuras PD. Expression of GABA(B) receptors is altered in brains of subjects with autism. *Cerebellum.* 2009b; 8(1):64–69. [PubMed: 19002745]

- Fatemi SH, Reutiman TJ, Folsom TD, Rooney RJ, Patel DH, Thuras PD. mRNA and protein levels for GABAA α 4, α 5, β 1, and GABABR1 receptors are altered in brains of subjects with autism. *J. Autism Dev. Disord.* 2010a; 40(6):743–750. [PubMed: 20066485]
- Fatemi SH, Kneeland RE, Liesch SB, Folsom TD. Fragile X mental retardation protein levels are decreased in major psychiatric disorders. *Schizophr. Res.* 2010b; 124(1–3):246–247. [PubMed: 20727716]
- Fatemi SH, Folsom TD, Kneeland RE, Liesch SB. Metabotropic glutamate receptor 5 upregulation in children with autism is associated with underexpression of both fragile X mental retardation protein and GABAA receptor β 3 in adults with autism. *Anat. Rec.* 2011a; 294(10):1635–1645.
- Fatemi SH, Folsom TD, Thuras PD. Deficits in GABA(B) receptor system in schizophrenia and mood disorders: a postmortem study. *Schizophr. Res.* 2011b; 128(1–3):37–43. [PubMed: 21303731]
- Fatemi SH, Folsom TD, Rooney RJ, Thuras PD. mRNA and protein expression for novel GABAA receptors θ and ρ 2 are altered in schizophrenia and mood disorders; relevance to FMRP-mGluR5 signaling pathway. *Transl. Psychiatry.* 2013a; 3:e271. [PubMed: 23778581]
- Fatemi SH, Folsom TD, Rooney RJ, Thuras PD. Expression of GABAA α 2-, β 1- and ϵ -receptors are altered significantly in the lateral cerebellum of subjects with schizophrenia, major depression and bipolar disorder. *Transl. Psychiatry.* 2013b; 3:e303. [PubMed: 24022508]
- Fatemi SH, Folsom TD, Kneeland RE, Yousefi MK, Liesch SB, Thuras PD. Impairment of fragile X mental retardation protein-metabotropic glutamate receptor 5 signaling and its downstream cognates ras-related C3 botulinum toxin substrate 1, amyloid β A4 precursor protein, striatal-enriched protein tyrosine phosphatase, and homer 1, in autism: a postmortem study in cerebellar vermis and superior frontal cortex. *Mol. Autism.* 2013c; 4:21. [PubMed: 23803181]
- Fatemi SH, Reutiman TJ, Folsom TD, Rustan OG, Rooney RJ, Thuras PD. Downregulation of GABAA Receptor Protein Subunits α 6, β 2, δ , ϵ , γ 2, θ , and ρ 2 in Superior Frontal Cortex of Subjects with Autism. *J. Autism Dev. Disord.* 2014; 44(8):1833–1845. [PubMed: 24668190]
- Frau R, Bini V, Pillolla G, Malherbe P, Pardu A, Thomas AW, Devoto P, Bortolato M. Positive allosteric modulation of GABAB receptors ameliorates sensorimotor gating in rodent models. *CNS Neurosci. Ther.* 2014; 20(7):679–684. [PubMed: 24703381]
- Frederiksen PK. Letter: Baclofen in the treatment of schizophrenia. *Lancet.* 1975; 1(7908):702.
- Gandal MJ, Sisti J, Klook K, Ortinski PI, Leitman V, Liang Y, Thieu T, Anderson R, Pierce RC, Jonak G, Gur RE, Carlson G, Siegel SJ. GABAB-mediated rescue of altered excitatory-inhibitory balance, gamma synchrony and behavioral deficits following constitutive NMDAR-hypofunction. *Transl. Psychiatry.* 2012; 2:e142. [PubMed: 22806213]
- Fromer M, Pocklington AJ, Kavanagh DH, Williams HJ, Dwyer S, Gormley P, Georgieva L, Rees E, Palta P, Ruderfer DM, Carrera N, Humphreys I, Johnson JS, Roussos P, Barker DD, Banks E, Milanova V, Grant SG, Hannon E, Rose SA, Chambert K, Mahajan M, Scolnick EM, Moran JL, Kirov G, Palotie A, McCarroll SA, Holmans P, Sklar P, Owen MJ, Purcell SM, O'Donovan MC. De novo mutations in schizophrenia implicate synaptic networks. *Nature.* 2014; 506(7487):179–184. [PubMed: 24463507]
- Gantois I, Vandescompele J, Speleman F, Reyniers E, D'Hooge R, Severijnen LA, Willemsen R, Tassone F, Kooy RF. Expression profiling suggests underexpression of the GABA $_A$ receptor subunit delta in the fragile X knockout mouse model. *Neurobiol. Dis.* 2006; 21(2):346–357. [PubMed: 16199166]
- Gerdjikov TV, Rudolph U, Keist R, Möhler H, Feldon J, Yee BK. Hippocampal alpha 5 subunit-containing GABA A receptors are involved in the development of the latent inhibition effect. *Neurobiol. Learn. Mem.* 2008; 89(2):87–94. [PubMed: 17638582]
- Glausier JR, Lewis DA. Selective pyramidal cell reduction of GABA(A) receptor α 1 subunit messenger RNA expression in schizophrenia. *Neuropsychopharmacology.* 2011; 36(10):2103–2110. [PubMed: 21677653]
- Goebel-Goody SM, Baum M, Paspalas CD, Fernandez SM, Carty NC, Kurup P, Lombroso PJ. Therapeutic implications for striatal-enriched protein tyrosine phosphatase (STEP) in neuropsychiatric disorders. *Pharmacol. Rev.* 2012; 64(1):65–87. [PubMed: 22090472]

- Goei VL, Choi J, Ahn J, Bowlus CL, Raha-Chowdhury R, Gruen JR. Human gamma-aminobutyric acid B receptor gene: complementary DNA cloning, expression, chromosomal location, and genomic organization. *Biol. Psychiatry*. 1998; 44(8):659–666. [PubMed: 9798068]
- 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]
- Goudet C, Kniazeff J, Hlavackova V, Malhaire F, Maurel D, Acher F, Blahos J, Prézeau L, Pin J-P. Asymmetric functioning of dimeric metabotropic glutamate receptors disclosed by positive allosteric modulators. *J. Biol. Chem.* 2005; 280(26):24380–24385. [PubMed: 15863499]
- Greger V, Knoll JH, Woolf E, Glatt K, Tyndale RF, DeLorey TM, Olsen RW, Tobin AJ, Sikela JM, Nakatsu Y. The gamma-aminobutyric acid receptor gamma 3 subunit gene (GABRG3) is tightly linked to the alpha 5 subunit gene (GABRA5) on human chromosome 15q11-q13 and is transcribed in the same orientation. *Genomics*. 26(2):258–264.
- Gulmann NC, Bahr B, Andersen B, Eliassen HM. A double-blind trial of baclofen against placebo in the treatment of schizophrenia. *Acta. Psychiatr. Scand.* 1976; 54(4):287–293. [PubMed: 793304]
- Gupta DS, McCullumsmith RE, Beneyto M, Haroutunian V, Davis KL, Meador-Woodruff JH. Metabotropic glutamate receptor protein expression in the prefrontal cortex and striatum in schizophrenia. *Synapse*. 2005; 57(3):123–131. [PubMed: 15945063]
- Gürkan CK, Hagerman RJ. Targeted treatments in autism and fragile X syndrome. *Res. Autism Spectr. Disord.* 2012; 6(4):1311–1320. [PubMed: 23162607]
- Gulyás B, Sovago J, Gomez-Mancilla B, Jia Z, Szigeti C, Gulya K, Schumacher M, Maguire RP, Gasparini F, Halldin C. Decrease of mGluR5 receptor density goes parallel with changes in enkephalin and substance P immunoreactivity in Huntington's disease: a preliminary investigation in the postmortem human brain. *Brain Struct. Funct.* 2015; 220(5):3043–3051. [PubMed: 24969128]
- Hagerman RJ, Des-Portes V, Gasparini F, Jacquemont S, Gomez-Mancilla B. Translating molecular advances in fragile X syndrome into therapy: a review. *J. Clin. Psychiatry*. 2014; 75(4):e294–e307. [PubMed: 24813413]
- Han Y, Qin J, Bu DF, Chang XZ, Yang ZX. Successive alterations of hippocampal gamma-aminobutyric acid B receptor subunits in a rat model of febrile seizure. *Life Sci.* 2006; 78(25):2944–2952. [PubMed: 16380138]
- Harvey VL, Duguid IC, Krasel C, Stephens GJ. Evidence that GABA rho subunits contribute to functional GABA receptors in mouse cerebellar Purkinje cells. *J. Physiol.* 2006; 577(Pt 1):127–139. [PubMed: 16945976]
- Hashimoto T, Arion D, Unger T, Maldonado-Avilés JG, Morris HM, Volk DW, Mirnics K, Lewis DA. Alterations in GABA-related transcriptome in the dorsolateral prefrontal cortex of subjects with schizophrenia. *Mol. Psychiatry*. 2008; 13(2):147–161. [PubMed: 17471287]
- Hashimoto K, Malchow B, Falkai P, Schmitt A. Glutamate modulators as potential therapeutic drugs in schizophrenia and affective disorders. *Eur. Arch. Psychiatry Clin. Neurosci.* 2013; 263(5):367–377. [PubMed: 23455590]
- Hedblom E, Kirkness EF. A novel class of GABAA receptor subunit in tissues of the reproductive system. *J. Biol. Chem.* 1997; 272(24):15346–15350. [PubMed: 9182563]
- Henderson C, Wijetunge L, Kinoshita MN, Shumway M, Hammond RS, Postma FR, Brynczka C, Rush R, Thomas A, Paylor R, Warren ST, Vanderklish PW, Kind PC, Carpenter RL, Bear MF, Healy AM. Reversal of disease-related pathologies in the fragile X mouse model by selective activation of GABAB receptors with arbaclofen. *Sci. Transl. Med.* 2012; 4(152):152ra128.
- Herman EJ, Bubser M, Conn PJ, Jones CK. Metabotropic glutamate receptors for new treatments in schizophrenia. *Hanb. Exp. Pharmacol.* 2012; 2012(213):297–365.
- Heulens I, D'Hulst C, Braat S, Rooms L, Kooy RF. Involvement and therapeutic potential of the GABAergic system in the fragile X syndrome. *Scientific World J.* 2010; 10:2198–2206.
- Heulens I, D'Hulst C, Van Dam D, De Deyn PP, Kooy RF. Pharmacological treatment of fragile X syndrome with GABAergic drugs in a knockout mouse model. *Behav. Brain. Res.* 2012; 229(1):244–249. [PubMed: 22285772]
- Hicks AA, Bailey ME, Riley BP, Kamphuis W, Siciliano MJ, Johnson KJ, Darslison MG. Further evidence for clustering of human GABAA receptor subunit genes: localization of the alpha 6-

- subunit gene (GABRA6) to distal chromosome 5q by linkage analysis. *Genomics*. 1994; 20(2): 285–288. [PubMed: 8020978]
- Hogart A, Nagarajan RP, Patzel KA, Yasui DH, Lasalle JM. 15q11–13 GABAA receptor genes are normally biallelically expressed in brain yet are subject to epigenetic dysregulation in autism-spectrum disorders. *Hum. Mol. Genet.* 2007; 16(6):691–703. [PubMed: 17339270]
- Hong A, Zhang A, Ke Y, El Idrissi A, Shen CH. Downregulation of GABA(A) β subunits is transcriptionally controlled by Fmr1p. *J. Mol. Neurosci.* 2012; 46(2):272–275. [PubMed: 21547530]
- Hou L, Antion MD, Hu D, Spencer CM, Paylor R, Klann E. Dynamic translational and proteasomal regulation of fragile X mental retardation protein controls mGluR-dependent long-term depression. *Neuron*. 2006; 51(4):441–454. [PubMed: 16908410]
- Iossifov I, Ronemus M, Levy D, Wang Z, Hakker I, Rosenbaum J, Yamrom B, Lee YH, Narzisi G, Leotta A, Kendall J, Grabowska E, Ma B, Marks S, Rodgers L, Stepansky A, Troge J, Andrews P, Bekritsky M, Pradhan K, Ghiban E, Kramer M, Parla J, Demeter R, Fulton LL, Fulton RS, Magrini VJ, Ye K, Darnell JC, Darnell RB, Mardis ER, Wilson RK, Schatz MC, McCombie WR, Wigler M. De novo gene disruptions in children on the autistic spectrum. *Neuron*. 2012; 74(2): 285–299. [PubMed: 22542183]
- Irwin SA, Idupulapati M, Gilbert ME, Harris JB, Chakravarti AB, Rogers EJ, Crisostomo RA, Larsen BP, Mehta A, Alcantara CJ, Patel B, Swain RA, Weiler IJ, Oostra BA, Greenough WT. Dendritic spine and dendritic field characteristics of layer V pyramidal neurons in the visual cortex of fragile X-knockout mice. *Am. J. Med. Genet.* 2002; 111(2):140–146. [PubMed: 12210340]
- Kasparov S, Davies KA, Patel UA, Boscan P, Garret M, Paton JF. GABA(A) receptor epsilon-subunit may confer benzodiazepine insensitivity to the caudal aspect of the nucleus tractus solitarii of the rat. *J. Physiol.* 2001; 536(Pt 3):785–796. [PubMed: 11691872]
- Kirkness EF, Kusiak JW, Fleming JT, Menninger J, Gocayne JD, Ward DC, Venter JC. Isolation, characterization, and localization of human genomic DNA encoding the beta-1 subunit of the GABA-A receptor (GABRB1). *Genomics*. 1991; 10(4):985–995. [PubMed: 1655634]
- Kelemen O, Kovács T, Kéri S. Contrast, motion, perceptual integration, and neurocognition in schizophrenia: the role of fragile X-related mechanisms. *Prog. Neuropsychopharmacol. Biol. Psychiatry*. 2013; 46:92–97. [PubMed: 23838275]
- Knoll JHM, Sinnett D, Wagstaff J, Glatt K, Wilcox AS, Whiting P, Wingrove P, Sikela J, Lalande M. FISH ordering of DNA markers within the Angelman/Prader-Willi chromosomal regions: mapping of a second GABA-A receptor subunit gene, GABRA5. (Abstract). *Am. J. Hum. Genet.* 1992; 51(suppl.):A9.
- Korpi ER, Gründer G, Lüddens H. Drug interactions at GABA(A) receptors. *Prog. Neurobiol.* 2002; 67(2):113–159. [PubMed: 12126658]
- Kovács T, Keleman O, Kéri S. Decreased fragile X mental retardation protein (FMRP) is associated with lower IQ and earlier illness onset in patients with schizophrenia. *Psychiatry Res.* 2013; 210(3):81–89.
- Kreinin A, Bawakny H, Ritsner MS. Adjunctive pregnenolone ameliorates the cognitive deficits in recent-onset schizophrenia. *Clin. Schizophr. Relat. Psychoses*. 2014; 4:1–31.
- Kuriyama K, Hirouchi M, Kimura H. Neurochemical and molecular pharmacological aspects of the GABA(B) receptor. *Neurochem. Res.* 2000; 25(9–10):1233–1239. [PubMed: 11059797]
- Laurie DJ, Seeburg PH, Wisden W. The distribution of 13 GABAA receptor subunit mRNAs in the rat brain. II. Olfactory bulb and cerebellum. *J. Neurosci.* 1992; 12(11):1063–1076. [PubMed: 1312132]
- Levkovitz Y, Mendlovich S, Riwkes S, Braw Y, Levkovitch-Verbin H, Gal G, Fennig S, Treves I, Kron S. A double-blind, randomized study of minocycline for the treatment of negative and cognitive symptoms in early-phase schizophrenia. *J. Clin. Psychiatry*. 2010; 71(2):138–149. [PubMed: 19895780]
- Li SP, Park MS, Yoon H, Rhee KH, Bahk JY, Lee JH, Park JS, Kim MO. Differential distribution of GABA(B1) and GABA(B2) receptor mRNAs in the rat brain. *Mol. Cells*. 2003; 16(1):40–47. [PubMed: 14503843]

- Lohith TG, Osterweil EK, Fujita M, Jenko KJ, Bear MF, Innis RB. Is metabotropic glutamate receptor 5 upregulated in prefrontal cortex in fragile X syndrome. *Mol. Autism*. 2013; 4(1):15. [PubMed: 23706040]
- Luo L, Hensch TK, Ackerman L, Barbel S, Jan LY, Jan YN. Differential effects of the Rac GTPase on Purkinje cell axons and dendritic trunks and spines. *Nature*. 1996; 379(6568):837–840. [PubMed: 8587609]
- Luscher B, Shen Q, Sahir N. The GABAergic deficit hypothesis of major depressive disorder. *Mol. Psychiatry*. 2011; 16(4):383–406. [PubMed: 21079608]
- Ma DQ, Whitehead PL, Menold MM, Martin ER, Ashley-Koch AE, Mei H, Ritchie MD, DeLong GR, Abramson RK, Wright HH, Cuccaro ML, Hussman JP, Gilbert JR, Pericak-Vance MA. Identification of significant association and gene-gene interaction of GABA receptor subunit genes in autism. *Am. J. Hum. Genet*. 2005; 77(3):377–388. [PubMed: 16080114]
- Maier K, Merkler D, Gerber J, Taheri N, Kuhnert AV, Williams SK, Neusch C, Bähr M, Diem R. Multiple neuroprotective mechanisms of minocycline in autoimmune CNS inflammation. *Neurobiol. Dis*. 2007; 25(3):514–525. [PubMed: 17239606]
- Maldonado-Avilés JG, Curley AA, Hashimoto T, Morrow AL, Ramsey AJ, O'Donnell P, Volk DW, Lewis DA. Altered markers of tonic inhibition in the dorsolateral prefrontal cortex of subjects with schizophrenia. *Am. J. Psychiatry*. 2009; 166(4):450–459. [PubMed: 19289452]
- Martin, BS., Huntsman, MM. Tonic GABA_A-receptor mediated inhibition in fragile X syndrome: a cause of dysfunction or a pathway for a cure?. In: Errington, AC, Di Giovanni, G., Crunelli, V., editors. *Extrasynaptic GABA_A receptors*. New York: Springer Science+Business Media; 2014. p. 271-284.
- Martin BS, Corbin JG, Huntsman MM. Deficient tonic GABAergic conductance and synaptic balance in the fragile X syndrome amygdala. *J. Neurophysiol*. 2014; 112(4):890–902. [PubMed: 24848467]
- Martin SC, Russek SJ, Farb DH. Molecular identification of the human GABA(B)R1: cell surface expression and coupling to adenylyl cyclase in the absence of GABA(B)R2. *Molec. Cell. Neurosci*. 1999; 13(3):180–191. [PubMed: 10328880]
- Martínez-Cué C, Martínez P, Rueda N, Vidal R, García S, Vidal V, Corrales A, Montero JA, Pazos Á, Flórez J, Gasser R, Thomas AW, Honer M, Knoflach F, Trejo JL, Wettstein JG, Hernández MC. Reducing GABA α 5 receptor-mediated inhibition rescues functional and neuromorphological deficits in a mouse model of down syndrome. *J. Neurosci*. 2013; 33(9):3953–3966. [PubMed: 23447605]
- Marx CE, VanDoren MJ, Duncan GE, Lieberman JA, Morrow AL. Olanzapine and clozapine increase the GABAergic neuroactive steroid allopregnanolone in rodents. *Neuropsychopharmacology*. 2003; 28(1):1–13. [PubMed: 12496935]
- Marx CE, Shampine LJ, Khisti RT, Trost WT, Bradford DW, Grobin AC, Massing MW, Madison RD, Butterfield MI, Lieberman JA, Morrow AL. Olanzapine and fluoxetine administration and coadministration increase rat hippocampal pregnenolone, allopregnanolone and peripheral deoxycorticosterone: implications for therapeutic actions. *Pharmacol. Biochem. Behav*. 2006a; 84(4):609–617. [PubMed: 16996120]
- Marx CE, Shampine LJ, Duncan GE, VanDoren MJ, Grobin AC, Massing MW, Madison RD, Bradford DW, Butterfield MI, Lieberman JA, Morrow AL. Clozapine markedly elevates pregnenolone in rat hippocampus, cerebral cortex, and serum: candidate mechanism for superior efficacy? *Pharmacol. Biochem. Behav*. 2006b; 84(4):598–608. [PubMed: 16962649]
- Marx CE, Keefe RS, Buchanan RW, Hamer RM, Kilts JD, Bradford DW, Strauss JL, Naylor JC, Payne VM, Lieberman JA, Savitz AJ, Leimone LA, Dunn L, Porcu P, Morrow AL, Shampine LJ. Proof-of-concept trial with the neurosteroid pregnenolone targeting cognitive and negative symptoms in schizophrenia. *Neuropsychopharmacology*. 2009; 34(8):1885–1903. [PubMed: 19339966]
- Matosin N, Frank E, Deng C, Huang X-F, Newell KA. Metabotropic glutamate receptor 5 binding and protein expression in schizophrenia and following antipsychotic drug treatment. *Schizophr. Res*. 2013; 146(1–3):170–176. [PubMed: 23462049]
- Matosin N, Fernandez-Enright F, Frank E, Deng C, Wong J, Huang XF, Newell KA. Metabotropic glutamate receptor mGluR2/3 and mGluR5 binding in the anterior cingulate cortex in psychotic

and nonpsychotic depression, bipolar disorder and schizophrenia: implications for novel mGluR-based therapeutics. *J. Psychiatry Neurosci.* 2014; 39(4):130242.

- McCauley JL, Olson LM, Delahanty R, Amin T, Nurmi EL, Organ EL, Jacobs MM, Folstein SE, Haines JL, Sutcliffe JS. A linkage disequilibrium map of the 1-Mb 15q12 GABA(A) receptor subunit cluster and association to autism. *Am. J. Med. Genet. B Neuropsychiatr. Genet.* 2004; 131(1):51–59.
- McLean PJ, Farb DH, Russek SJ. Mapping of the alpha(4) subunit gene (GABRA4) to human chromosome 4 defines an alpha(2)-alpha(4)-beta(1)-gamma(1) gene cluster: further evidence that modern GABA(A) receptor gene clusters are derived from an ancestral cluster. *Genomics.* 1995; 26(3):580–586. [PubMed: 7607683]
- Miyaoka T, Yasukawa R, Yasuda H, Hayashida M, Inagaki T, Horiguchi J. Minocycline as adjunctive therapy for schizophrenia: an open-label study. *Clin Neuropharmacol.* 2008; 31(5):287–292. [PubMed: 18836347]
- Miyashiro KY, Beckel-Mitchener A, Purk TP, Becker KG, Barret T, Liu L, Carbonetto S, Weiler IJ, Greenough WT, Eberwine J. RNA cargoes associating with FMRP reveal deficits in cellular functioning in *Fmr1* null mice. *Neuron.* 2003; 37(3):417–431. [PubMed: 12575950]
- Mizoguchi H, Yamada K. Pharmacologic treatment with GABA(B) receptor agonist of methamphetamine-induced cognitive impairment in mice. *Curr. Neuropharmacol.* 2011; 9(1):109–112. [PubMed: 21886573]
- Möhler H. The GABA system in anxiety and depression and its therapeutic potential. *Neuropharmacology.* 2012; 62(1):42–53. [PubMed: 21889518]
- Moragues N, Ciofi P, Tramu G, Garret M. Localisation of GABA(A) receptor epsilon-subunit in cholinergic and aminergic neurones and evidence for co-distribution with the theta-subunit in rat brain. *Neuroscience.* 2002; 111(3):657–669. [PubMed: 12031352]
- Nakayama AY, Harms MB, Luo L. Small GTPases Rac and Rho in the maintenance of dendritic spines and branches in hippocampal pyramidal neurons. *J. Neurosci.* 2000; 20(14):5329–5338. [PubMed: 10884317]
- Nalavadi VC, Muddashetty RS, Gross C, Bassell GJ. Dephosphorylation-induced ubiquitination and degradation of FMRP in dendrites: a role in immediate early mGluR-stimulated translation. *J. Neurosci.* 2012; 32(8):2582–2587. [PubMed: 22357842]
- Oblak AL, Gibbs TT, Blatt GJ. Decreased GABA(B) receptors in the cingulate cortex and fusiform gyrus in autism. *J. Neurochem.* 2010; 114(5):1414–1423. [PubMed: 20557420]
- Oblak AL, Gibbs TT, Blatt GJ. Reduced GABA(A) receptors and benzodiazepine binding sites in the posterior cingulate cortex and fusiform gyrus in autism. *Brain Res.* 2011; 1380:218–228. [PubMed: 20858465]
- Ohnuma T, Tessler S, Arai H, Faull RL, McKenna PJ, Emson PC. Gene expression of metabotropic glutamate receptor 5 and excitatory amino acid transporter 2 in the schizophrenic hippocampus. *Brain Res. Mol. Brain Res.* 85(1–2):24–31.
- Oka A, Takashima S. The up-regulation of metabotropic glutamate receptor 5 (mGluR5) in Down's syndrome brains. *Acta Neuropathol.* 1999; 97(3):275–278. [PubMed: 10090675]
- Olmos-Serrano JL, Paluszkiwicz SM, Martin BS, Kaufmann WE, Corbin JG, Huntsman MM. Defective GABAergic neurotransmission and pharmacological rescue of neuronal hyperexcitability in the amygdala in a mouse model of fragile X syndrome. *J. Neurosci.* 2010; 30(29):9929–9938. [PubMed: 20660275]
- Ota VK, Noto C, Gadelha A, Santoro ML, Ortiz BB, Andrade EH, Tasso BC, Spindola LM, Silva PN, Abílio VC, Smith MD, Sato JR, Brietzke E, Cordeiro Q, Bressan RA, Belangero SI. Evaluation of neurotransmitter receptor gene expression identifies GABA receptor changes: A follow-up study in antipsychotic-naïve patients with first-episode psychosis. *J. Psychiatr. Res.* 2014; S0022-3956(14):00150–00152.
- Paribello C, Tao L, Folino A, Berry-Kravis E, Tranfaglia M, Ethell IM, Ethell DW. Open-label add-on treatment trial of minocycline in fragile X syndrome. *BioMed. Central Neurology.* 2010; 10:91. [PubMed: 20937127]

- Pi R, Li W, Lee NT, Chan HH, Pu Y, Chan LN, Sucher NJ, Chang DC, Li M, Han Y. Minocycline prevents glutamate-induced apoptosis of cerebellar granule neurons by differential regulation of p38 and Akt pathways. *J. Neurochem.* 2004; 91(5):1219–1230. [PubMed: 15569265]
- Pieretti M, Zhang FP, Fu YH, Warren ST, Oostra BA, Caskey CT, Nelson DL. Absence of expression of FMR-1 gene in fragile X syndrome. *Cell.* 1991; 66(4):817–822. [PubMed: 1878973]
- Pinna G, Costa E, Guidotti A. Fluoxetine and norfluoxetine stereospecifically and selectively increase brain neurosteroid content at doses that are inactive on 5-HT reuptake. *Psychopharmacology (Berl).* 2006; 186(3):362–372. [PubMed: 16432684]
- Pinna G, Costa E, Guidotti A. SSRIs act as selective brain steroidogenic stimulants (SBSSs) at low doses that are inactive on 5-HT reuptake. *Curr. Opin. Pharmacol.* 2009; 9(1):24–30. [PubMed: 19157982]
- Pirker S, Schwarzer C, Wieselthaler A, Sieghart W, Sperk G. GABA(A) receptors: immunocytochemical distribution of 13 subunits in the adult rat brain. *Neuroscience.* 2000; 101(4):815–850. [PubMed: 11113332]
- Pirker S, Schwarzer C, Czech T, Baumgartner C, Pockberger H, Maier H, Hauer B, Sieghart W, Furtinger S, Sperk G. Increased expression of GABA(A) receptor beta-subunits in the hippocampus of patients with temporal lobe epilepsy. *J. Neuropathol. Exp. Neurol.* 2003; 62(8):820–834. [PubMed: 14503638]
- Pretto DI, Kumar M, Cao Z, Cunningham CL, Durbin-Johnson B, Qi L, Berman R, Noctor SC, Hagerman RJ, Pessah IN, Tassone F. Reduced excitatory amino acid transporter 1 and metabotropic glutamate receptor 5 expression in the cerebellum of fragile X mental retardation gene 1 premutation carriers with fragile X-associated tremor/ataxia syndrome. *Neurobiol. Aging.* 2014; 35(5):1189–1197. [PubMed: 24332449]
- Priller C, Bauer T, Mitteregger G, Krebs B, Kretschmar HA, Herms J. Synapse formation and function is modulated by the amyloid precursor protein. *J. Neurosci.* 2006; 26(27):7212–7221. [PubMed: 16822978]
- Princiville AP, Richards DA, Duncan JS, Spreafico R, Bowery NG. Modification of GABA(B1) and GABA(B2) receptor subunits in the somatosensory cerebral cortex and thalamus of rats with absence seizures (GAERS). *Epilepsy Res.* 2003; 55(1–2):39–51. [PubMed: 12948615]
- Purcell SM, Moran JL, Fromer M, Ruderfer D, Solovieff N, Roussos P, O'Dushlaine C, Chambert K, Bergen SE, Kähler A, Duncan L, Stahl E, Genovese G, Fernández E, Collins MO, Komiyama NH, Choudhary JS, Magnusson PK, Banks E, Shakir K, Garimella K, Fennell T, DePristo M, Grant SG, Haggarty SJ, Gabriel S, Scolnick EM, Lander ES, Hultman CM, Sullivan PF, McCarroll SA, Sklar P. A polygenic burden of rare disruptive mutations in schizophrenia. *Nature.* 2014; 506(7487):185–190. [PubMed: 24463508]
- Richardson-Burns SM, Haroutunian V, Davis KL, Watson SJ, Meador-Woodruff JH. Metabotropic glutamate receptor mRNA expression in the schizophrenic thalamus. *Biol. Psychiatry.* 2000; 47(1):22–28. [PubMed: 10650445]
- Ritsner MS, Gibel A, Shleifer T, Boguslavsky I, Zayed A, Maayan R, Weizman A, Lerner V. Pregnenolone and dehydroepiandrosterone as an adjunctive treatment in schizophrenia and schizoaffective disorder: an 8-week, double-blind, randomized, controlled, 2-center, parallel-group trial. *J. Clin. Psychiatry.* 2010; 71(10):1351–1362. [PubMed: 20584515]
- Ritsner MS, Bawakny H, Kreinin A. Pregnenolone treatment reduces severity of negative symptoms in recent-onset schizophrenia: An 8-week, double-blind, randomized add-on two-center trial. *Psychiatry Clin. Neurosci.* 2014; 68(8):432–440. [PubMed: 24548129]
- Romano C, Miller JK, Hyrc K, Dikranian S, Mennerick S, Takeuchi Y, Goldberg MP, O'Malley KL. Covalent and noncovalent interactions mediate metabotropic glutamate receptor mGluR5 dimerization. *Mol. Pharmacol.* 2001; 59(1):46–53. [PubMed: 11125023]
- Russek SJ, Farb DH. Mapping of the beta 2 subunit gene (GABRB2) to microdissected human chromosome 5q34-q35 defines a gene cluster for the most abundant GABAA receptor isoform. *Genomics.* 1994; 23(3):528–533. [PubMed: 7851879]
- Rustan OG, Folsom TD, Yousefi MK, Fatemi SH. Phosphorylated fragile X mental retardation protein at serine 499, is reduced in cerebellar vermis and superior frontal cortex of subjects with autism: implications for fragile X mental retardation protein-metabotropic glutamate receptor 5 signaling. *Mol. Autism.* 2013; 4(1):41. [PubMed: 24180586]

- Samaco RC, Hogart A, LaSalle JM. Epigenetic overlap in autism-spectrum neurodevelopmental disorders: MECP2 deficiency causes reduced expression of UBE3A and GABRB3. *Hum. Mol. Genet.* 2005; 14(4):483–492. [PubMed: 15615769]
- Sanchez-Pernaute R, Wang JQ, Kuruppu D, Cao L, Tueckmantel W, Kozikowski A, Isacson O, Brownell AL. Enhanced binding of metabotropic glutamate receptor type 5 (mGluR5) PET tracers in the brain of parkinsonian primates. *Neuroimage.* 2008; 42(1):248–251. [PubMed: 18501638]
- Schroer RJ, Phelan MC, Michaelis RC, Crawford EC, Skinner SA, Cuccaro M, Simensen RJ, Bishop J, Skinner C, Fender D, Stevenson RE. Autism and maternally derived aberrations of chromosome 15q. *Am. J. Med. Genet.* 1998; 76(4):327–336. [PubMed: 9545097]
- Schüle C, Northdurfte C, Rupprecht R. The role of allopregnanolone in depression and anxiety. *Prog. Neurobiol.* 2014; 113:79–87. [PubMed: 24215796]
- Schwarzer C, Berresheim U, Pirker S, Wieselthaler A, Fuchs K, Sieghart W, Sperk G. Distribution of the major gamma-aminobutyric acid(A) receptor subunits in the basal ganglia and associated limbic brain areas of the adult rat. *J. Comp. Neurol.* 2001; 433(4):526–549. [PubMed: 11304716]
- Schwendt M, McGinty JF. Regulator of G-protein signaling 4 interacts with metabotropic glutamate receptor 5 in rat striatum: Relevance to amphetamine behavioral sensitization. *J. Pharmacol. Exp. Ther.* 2007; 323(2):650–657. [PubMed: 17693584]
- Stell BM, Brickley SG, Tang CY, Farrant M, Mody I. Neuroactive steroids reduce neuronal excitability by selectively enhancing tonic inhibition mediated by delta subunit-containing GABA_A receptors. *Proc. Natl. Acad. Sci. USA.* 2003; 100(24):14439–14444. [PubMed: 14623958]
- Straessle A, Loup F, Arabadzisz D, Ohning GV, Fritschy JM. Rapid and long-term alterations of hippocampal GABAB receptors in a mouse model of temporal lobe epilepsy. *Eur. J. Neurosci.* 2003; 18(8):2213–2226. [PubMed: 14622182]
- Sur C, Wafford KA, Reynolds DS, Hadingham KL, Bromidge F, Macaulay A, Collinson N, O'Meara G, Howell O, Newman R, Myers J, Attack JR, Dawson GR, McKernan RM, Whiting PJ, Rosahl TW. Loss of the major GABA(A) receptor subtype in the brain is not lethal to mice. *J. Neurosci.* 2001; 21(10):3409–3418. [PubMed: 11331371]
- Szumliński KK, Kalivas PW, Worley PF. Homer proteins: implications for neuropsychiatric disorders. *Curr. Opin. Neurobiol.* 2006; 16(3):251–257. [PubMed: 16704932]
- Thompson SA, Bonnert TP, Cagetti E, Whiting PJ, Wafford KA. Overexpression of the GABA(A) receptor epsilon subunit results in insensitivity to anesthetics. *Neuropharmacology.* 2002; 43(4):662–668. [PubMed: 12367611]
- Threadgill R, Bobb K, Ghosh A. Regulation of dendritic growth and remodeling by Rho, Rac, and Cdc42. *Neuron.* 1997; 19(3):625–634. [PubMed: 9331353]
- Tsamis KI, Mytilinaios DG, Njau SN, Baloyannis SJ. Glutamate receptors in human caudate nucleus in normal aging and Alzheimer's disease. *Curr. Alzheimer Res.* 2013; 10(5):469–475. [PubMed: 23627706]
- Tuchman R, Rapin I. Epilepsy in autism. *Lancet Neurol.* 2002; 1(6):352–358. [PubMed: 12849396]
- Turner PR, O'Connor K, Tate WP, Abraham WC. Roles of amyloid precursor protein and its fragments in regulating neural activity, plasticity and memory. *Prog. Neurobiol.* 2003; 70(1):1–32. [PubMed: 12927332]
- Vollenweider I, Smith KS, Keist R, Rudolph U. Antidepressant-like properties of α -containing GABA(A) receptors. *Behav. Brain. Res.* 2011; 217(1):77–80. [PubMed: 20965216]
- Volk DW, Egan SM, Lewis DA. Alterations in metabotropic glutamate receptor 1 α and regulator of G protein signaling 4 in the prefrontal cortex in schizophrenia. *Am J Psychiatry.* 2010; 167(10):1489–1498. [PubMed: 20889653]
- Wang H, Westin L, Nong Y, Birnbaum S, Bendor J, Brismar H, Nestler E, Aperia A, Flajolet M, Greengard P. Norbin is an endogenous regulator of metabotropic glutamate receptor 5 signaling. *Science.* 2009; 326(5959):1554–1557. [PubMed: 20007903]
- Wafford, K. The pharmacology of extrasynaptic GABA_A receptors. In: Errington, AC, Di Giovanni, G., Crunelli, V., editors. *Extrasynaptic GABA_A receptors*. New York: Springer Science+Business Media; 2014. p. 51–74.

- Wafford KA, Ebert B. Gaboxadol-a new awakening in sleep. *Curr. Opin. Pharmacol.* 2006; 6(1):30–36. [PubMed: 16368265]
- Wang LW, Berry-Kravis E, Hagerman RJ. Fragile X: leading the way for targeted treatments in autism. *Neurotherapeutics.* 2010; 7(3):264–274. [PubMed: 20643379]
- Weiler IJ, Greenough WT. Synaptic synthesis of the fragile X protein: possible involvement in synapse maturation and elimination. *Am J. Med. Genet.* 1999; 83(4):248–252. [PubMed: 10208156]
- Whiting PJ, Bonnert TP, McKernan RM, Farrar S, le Bourdelles B, Heavens RP, Smith DW, Hewson L, Rigby MR, Sirinathsinghji DJS, Thompson SA, Wafford KA. Molecular and functional diversity of the expanding GABA-A receptor gene family. *Ann. N.Y. Acad. Sci.* 1999; 868:645–653. [PubMed: 10414349]
- Wilcox AS, Warrington JA, Gardiner K, Berger R, Whiting P, Altherr MR, Wasmuth JJ, Patterson D. Human chromosomal localization of genes encoding the gamma 1 and gamma 2 subunits of the gamma-aminobutyric acid receptor indicates that members of this gene family are often clustered in the genome. *Proc. Natl. Acad. Sci. USA.* 1992; 89(13):5857–5861. [PubMed: 1321425]
- Wisden W, Laurie DJ, Monyer H, Seeburg PH. The distribution of 13 GABA_A receptor subunit mRNAs in the rat brain. I. Telencephalon, diencephalon, mesencephalon. *J. Neurosci.* 1992; 12(3):1040–1062. [PubMed: 1312131]
- Wong P, Chang CC, Marx CE, Caron MG, Wetsel WC, Zhang X. Pregnenolone rescues schizophrenia-like behavior in dopamine transporter knockout mice. *PLoS One.* 2012; 7(12):e51455. [PubMed: 23240026]
- Yee BK, Keist R, von Boehmer L, Studer R, Benke D, Hagenbuch N, Dong Y, Malenka RC, Fritschy JM, Bluethmann H, Feldon J, Möhler H, Rudolph U. A schizophrenia-related sensorimotor deficit links alpha 3-containing GABAA receptors to a dopamine hyperfunction. *Proc. Natl. Acad. Sci. USA.* 2005; 102(47):17154–17159. [PubMed: 16284244]

Summary of GABA_A and GABA_B receptor expression changes in major psychiatric disorders**Table 1**

Receptor Subunit	Autism	Schizophrenia	Bipolar Disorder	Major Depression	Reference
GABRA1	— mRNA, ↓ protein in BA9, BA40, Cer	No change in protein in Cer; ↓ mRNA in Cer ↓ mRNA in DLPFC ↓ mRNA in PFC pyramidal cells No change in mRNA in PFC No change in mRNA in DLPFC	No change in mRNA or protein in Cer	↑ protein in Cer ↓ mRNA in Cer	Fatemi et al., 2009a, 2013b Fatemi et al., 2013b Beneyto et al., 2011; Hashimoto et al., 2008 Glausier and Lewis, 2011 Akbarian et al., 1995 Duncan et al., 2010
GABRA2	↓ protein in BA40; no change in Cer or BA9 ↓ mRNA in BA9; ↑ mRNA in Cer; no change in BA40	↑ protein in Cer ↓ mRNA in Cer ↑ mRNA in DLPFC No change in mRNA in DLPFC No change in mRNA in PFC	↑ protein in Cer No change in mRNA in Cer	↑ protein in Cer No change in mRNA in Cer	Fatemi et al., 2009a, 2013b Fatemi et al., 2013b, 2014 Beneyto et al., 2011 Duncan et al., 2010 Akbarian et al., 1995
GABRA3	↓ protein in BA40; no change in BA9 or Cer ↓ mRNA in BA9 and BA40; ↑ mRNA in Cer	No change in mRNA or protein in Cer No change in mRNA in DLPFC	No change in mRNA or protein in Cer	No change in mRNA or protein in Cer	Fatemi et al., 2009a Fatemi et al., 2014 Fatemi et al., 2013b Beneyto et al., 2011; Duncan et al., 2010
GABRA4	↓ protein in BA9; no change in BA40 or Cer				Fatemi et al., 2010b

Receptor Subunit	Autism	Schizophrenia	Bipolar Disorder	Major Depression	Reference
	↓ mRNA in BA9; ↑ mRNA in Cer; no change in BA40				Fatemi et al., 2010b
		ND	ND	ND	Fatemi et al., 2013b
		↓ gene transcript in DLPFC;			Hashimoto et al., 2008
		medication-dependent ↓ mRNA in BA9			Maldonado-Avilés et al., 2009
		No change in mRNA in DLPFC			Duncan et al., 2010
GABRα5	↓ protein in BA9 and BA40; no change in Cer				Fatemi et al., 2010b
	↓ mRNA in BA9; ↑ mRNA in Cer; no change in BA40				Fatemi et al., 2010b
		No change in mRNA or protein in Cer	No change in mRNA or protein in Cer	No change in mRNA or protein in Cer	Fatemi et al., 2013b
		↓ mRNA in DLPFC			Beneyto et al., 2011; Duncan et al., 2010
	No change in mRNA in PFC				Akbarian et al., 1995
GABRα6	↓ protein in BA9; no change in BA40 or Cer			↑ protein in Cer	Fatemi et al., 2013b, 2014
	↑ mRNA in BA9; ↓ mRNA in Cer	↑ mRNA in Cer	No change in mRNA or protein in Cer	No change in mRNA or protein in Cer	Bullock et al., 2008
		No change in mRNA or protein in Cer	No change in mRNA or protein in Cer	No change in mRNA or protein in Cer	Fatemi et al., 2013b, 2014
GABRβ1	↓ protein in BA9; no change in BA40 or Cer	↓ protein in Cer	↓ protein in Cer	↓ protein in Cer	Fatemi et al., 2010b
	↓ mRNA in BA9; ↑ mRNA in Cer; no change in BA40	No change in mRNA in Cer	No change in mRNA in Cer	No change in mRNA in Cer	Fatemi et al., 2010b, 2013b
		No change in mRNA in DLPFC			Beneyto et al., 2011
		No change in mRNA in PFC			Akbarian et al., 1995
GABRβ2	↓ protein in BA9; no	No change in mRNA	↓ protein in Cer;	No change in mRNA	Fatemi et al., 2013b, 2014

Receptor Subunit	Autism	Schizophrenia	Bipolar Disorder	Major Depression	Reference
	change in BA40 or Cer ↓ mRNA in Cer; no change in BA9 or BA40	or protein in Cer ↓ mRNA in DLPFC No change in mRNA in PFC	no change in mRNA	or protein in Cer	Fatemi et al., 2014 Beneyto et al., 2011 Akbarian et al., 1995
GABRβ3	↓ protein in BA40 and Cer; no change in BA9 ↓ protein in BA9 ↓ mRNA in BA9; ↑ mRNA in Cer; no change in BA40	↑ mRNA and no change in protein in Cer No change in mRNA in Cer	No change in mRNA or protein in Cer	No change in mRNA or protein in Cer	Fatemi et al., 2009a, 2013b Bullock et al., 2008 Samaco et al., 2005 Fatemi et al., 2013b, 2014
		↓ gene transcript in DLPFC No change in mRNA in DLPFC			Hashimoto et al., 2008 Beneyto et al., 2011
GABRδ	↓ protein in BA9; no change in BA40 or Cer; No change in mRNA in BA9, BA40, Cer	No change in mRNA or protein in Cer ↑ mRNA in Cer ↓ mRNA in DLPFC ↓ mRNA in BA9	No change in mRNA or protein in Cer	No change in mRNA or protein in Cer	Fatemi et al., 2013b, 2014 Bullock et al., 2008 Hashimoto et al., 2008 Maldonado-Avilés et al., 2009
GABRe	↓ protein in BA9; no change in BA40 or Cer; No change in mRNA in BA9, BA40, Cer	↑ protein in Cer; no change in mRNA in Cer	↑ protein in Cer; no change in mRNA in Cer	↑ protein in Cer; no change in mRNA in Cer	Fatemi et al., 2013b, 2014
GABRγ2	↓ protein in BA9; No change in mRNA in BA9, BA40, Cer ↑ mRNA in Cer; no change in BA9 and BA40	No change in mRNA or protein in Cer ↓ gene transcript in	No change in mRNA or protein in Cer	No change in mRNA or protein in Cer	Fatemi et al., 2013b, 2014 Fatemi et al., 2014 Hashimoto et al., 2008

Receptor Subunit	Autism	Schizophrenia	Bipolar Disorder	Major Depression	Reference
		DLPFC			
		No change in mRNA in PFC			Akbarian et al., 1995
GABRγ3	No change in protein in BA9, BA40, Cer ↓ mRNA in BA9; ↑ mRNA in BA40 and Cer	No change in mRNA or protein in Cer	No change in mRNA or protein in Cer	↑ protein in Cer; no change in mRNA in Cer	Fatemi et al., 2013b, 2014 Fatemi et al., 2014
GABRπ	No change in mRNA or protein in BA9, BA40, and Cer	No change in mRNA or protein in Cer	No change in mRNA or protein in Cer	No change in mRNA or protein in Cer	Fatemi et al., 2013b, 2014
GABRθ	No change in protein in BA9, BA40, Cer ↓ mRNA in BA9; ↑ mRNA in Cer; no change in BA40	↓ protein in BA9 and Cer ↑ mRNA in BA9; ↓ mRNA in Cer	↓ protein in BA9 and Cer No change in mRNA in Cer	↓ protein in Cer No change in mRNA in Cer	Fatemi et al., 2013a, 2014 Fatemi et al., 2013a, 2014
GABRρ2	↓ protein in BA9; No change in mRNA in BA9, BA40, Cer	No change in mRNA or protein in BA9 or Cer	↑ protein in Cer; No change in protein in BA9 ↑ mRNA in BA9 and Cer	↑ protein in Cer No change in mRNA in Cer	Fatemi et al., 2013a, 2014 Fatemi et al., 2013a Ota et al., 2014
		↓ mRNA in blood of subjects on risperidone			
GABBR1	↓ protein in BA9, BA40, Cer ↑ mRNA in BA40; ↓ mRNA in Cer	↓ protein in BA9 and Cer; no change in mRNA in Cer	↓ protein in BA9 and Cer; no change in mRNA in Cer	↓ protein in Cer; no change in mRNA in Cer	Fatemi et al., 2009b, 2011b Fatemi et al., 2010b, 2014
GABBR2	↓ protein in Cer; No change in BA9 or BA40; no mRNA changes in BA9, BA40, Cer	↓ protein in Cer; no change in mRNA in Cer	↓ protein in Cer; no change in mRNA in Cer	↓ protein in Cer; no change in mRNA in Cer	Fatemi et al., 2009b, 2011b

↑, significant increase; ↓ significant decrease; —, no change; BA9, Brodmann Area 9; Cer, cerebellum; DLPFC, dorsolateral prefrontal cortex; ND, not determined; PFC, prefrontal cortex

Table 2

Summary of changes in GABA receptor mRNA and protein expression in subjects with schizophrenia

Receptor	Protein		mRNA	
	Fatemi	Others	Fatemi	Others ^a
GABRα1	— Cer	ND	↓ Cer	↓/— DLPFC, ↓/— PFC
GABRα2	↑ Cer	ND	↓ Cer	↑/— DLPFC, — PFC
GABRα3	— Cer	ND	— Cer	— DLPFC
GABRα4	ND	ND	ND	↓/— DLPFC, ↓ BA9
GABRα5	— Cer	ND	— Cer	↓ DLPFC, — PFC
GABRα6	— Cer	ND	— Cer	↑ Cer
GABRβ1	↓ Cer	ND	— Cer	— DLPFC, — PFC
GABRβ2	— Cer	ND	— Cer	↓ DLPFC, — PFC
GABRβ3	— Cer	ND	↑ Cer	↓/— DLPFC; — Cer
GABRδ	— Cer	ND	— Cer	↓DLPFC, ↓BA9; ↑Cer
GABRe	↑ Cer	ND	— Cer	ND
GABRγ2	— Cer	ND	— Cer	↓ DLPFC, — PFC
GABRγ3	— Cer	ND	— Cer	ND
GABRπ	— Cer	ND	— Cer	ND
GABRθ	↓ BA9 and Cer	ND	↑ BA9, ↓ Cer	ND
GABRρ2	— Cer	ND	— Cer and BA9	↓ Blood
GABRR1	↓ BA9 and Cer	ND	ND	ND
GABRR2	↓ Cer	ND	ND	ND

↑, increase; ↓, decrease; —, no change; BA9, Brodmann Area 9;; Cer, cerebellum; DLPFC, dorsolateral prefrontal cortex; ND, not determined; PFC, prefrontal cortex

^aPlease see Table 1 for specific references

Table 3

Summary of changes in GABA receptor mRNA and protein expression in subjects with bipolar disorder

Receptor	Protein		mRNA	
	Fatemi	Others	Fatemi	Others
GABRα1	— Cer	ND	— Cer	ND
GABRα2	↑ Cer	ND	— Cer	ND
GABRα3	— Cer	ND	— Cer	ND
GABRα4	ND	ND	ND	ND
GABRα5	— Cer	ND	— Cer	ND
GABRα6	— Cer	ND	— Cer	ND
GABRβ1	↓ Cer	ND	— Cer	ND
GABRβ2	↓ Cer	ND	— Cer	ND
GABRβ3	— Cer	ND	— Cer	ND
GABRδ	— Cer	ND	— Cer	ND
GABRϵ	↑ Cer	ND	— Cer	ND
GABRγ2	— Cer	ND	— Cer	ND
GABRγ3	— Cer	ND	— Cer	ND
GABRπ	— Cer	ND	— Cer	ND
GABRθ	↓ BA9 and Cer	ND	— BA9 and Cer	ND
GABRρ2	↑ Cer	ND	↑ BA9 and Cer	ND
GABRR1	↓ BA9 and Cer	ND	ND	ND
GABRR2	↓ Cer	ND	ND	ND

↑, increase; ↓, decrease; —, no change; BA9, Brodmann Area 9; Cer, cerebellum; DLPFC, dorsolateral prefrontal cortex; ND, not determined; PFC, prefrontal cortex

Table 4

Summary of changes in GABA receptor mRNA and protein expression in subjects with major depression

Receptor	Protein		mRNA	
	Fatemi	Others	Fatemi	Others
GABRα1	↑ Cer	ND	↓ Cer	ND
GABRα2	↑ Cer	ND	— Cer	ND
GABRα3	— Cer	ND	— Cer	ND
GABRα4	ND	ND	ND	ND
GABRα5	— Cer	ND	— Cer	ND
GABRα6	↑ Cer	ND	— Cer	ND
GABRβ1	↓ Cer	ND	— Cer	ND
GABRβ2	— Cer	ND	— Cer	ND
GABRβ3	— Cer	ND	— Cer	ND
GABRδ	— Cer	ND	— Cer	ND
GABRe	↑ Cer	ND	— Cer	ND
GABRγ2	— Cer	ND	— Cer	ND
GABRγ3	↑ Cer	ND	— Cer	ND
GABRπ	— Cer	ND	— Cer	ND
GABRθ	↓ Cer	ND	— Cer	ND
GABRρ2	↑ Cer	ND	— Cer	ND
GABRR1	↓ Cer	ND	ND	ND
GABRR2	↓ Cer	ND	ND	ND

↑, increase; ↓, decrease; —, no change; BA9, Brodmann Area 9; Cer, cerebellum; DLPFC, dorsolateral prefrontal cortex; ND, not determined; PFC, prefrontal cortex

Table 5

Summary of changes in GABA receptor mRNA and protein expression in subjects with autism

Receptor	Protein		mRNA	
	Fatemi	Others ^a	Fatemi	Others
GABRα1	↓ BA9, BA40, Cer	ND	— BA9, BA40, Cer	ND
GABRα2	↓ BA40; — BA9, Cer	ND	↓BA9, ↑Cer, —BA40	ND
GABRα3	↓ BA40; — BA9, Cer	ND	↓BA9, BA40; ↑Cer	ND
GABRα4	↓ BA9; — BA40, Cer	ND	↓BA9, ↑Cer, —BA40	ND
GABRα5	↓ BA9, BA40; — Cer	ND	↓BA9, ↑Cer, —BA40	ND
GABRα6	↓ BA9; — BA40, Cer	ND	↑BA9, ↓Cer, —BA40	ND
GABRβ1	↓ BA9; — BA40, Cer	ND	↓BA9, ↑Cer, —BA40	ND
GABRβ2	↓ BA9; — BA40, Cer	ND	↓Cer; —BA9, BA40	ND
GABRβ3	↓ BA40, Cer; — BA9	↓ BA9	↓BA9, ↑Cer, —BA40	ND
GABR6	↓ BA9; — BA40, Cer	ND	— BA9, BA40, Cer	ND
GABRe	↓ BA9; — BA40, Cer	ND	— BA9, BA40, Cer	ND
GABRγ2	↓ BA9; — BA40, Cer	ND	↑Cer; —BA9, BA40	ND
GABRγ3	— BA9, BA40, Cer	ND	↓BA9; ↑BA40, Cer	ND
GABRπ	— BA9, BA40, Cer	ND	— BA9, BA40, Cer	ND
GABRθ	— BA9, BA40, Cer	ND	↓BA9, ↑Cer, —BA40	ND
GABRρ2	↓ BA9; — BA40, Cer	ND	— BA9, BA40, Cer	ND
GABRR1	↓ BA9, BA40, Cer	ND	↑BA40; ↓Cer; —BA9	ND
GABRR2	↓ Cer; — BA9, BA40	ND	— BA9, BA40, Cer	ND

↑, increase; ↓, decrease; —, no change; BA9, Brodmann Area 9; BA40, Brodmann Area 40; Cer, cerebellum; DLPFC, dorsolateral prefrontal cortex; ND, not determined; PFC, prefrontal cortex

^aPlease see Table 1 for specific references

Table 6

Summary of changes in expression of FMRP-mGluR5 signaling molecules in major psychiatric disorders

Protein of Interest	Autism	Schizophrenia ^a	Bipolar Disorder ^a	Major Depression ^a	Reference
FMRP ^a	↓ protein in BA9 and Cer; No change in mRNA in BA9 and Cer	↓ protein in BA9 and Cer; No change in mRNA in BA9 and Cer ↓ protein in peripheral lymphocytes	↓ protein in BA9 and Cer; No change in mRNA in BA9 and Cer	↓ protein in Cer; No change in mRNA in Cer	Fatemi and Folsom, 2011; Fatemi et al., 2010a, 2011a, 2013a Kelenen et al., 2013; Kóvacs et al., 2013
mGluR5	↑ dimerized protein in BA9 and Cer of children; no change in monomer in BA9 or Cer of children or adults.	↓ monomeric protein in BA9 and Cer of adults No change in protein in BA10 No change in protein in PFC or striatum No change in protein in DLPFC or ACC	↓ monomeric protein in BA9 and Cer of adults No change in protein in ACC	↓ monomeric protein in Cer of adults No change in protein in ACC	Fatemi and Folsom, 2011; Fatemi et al., 2011a, 2013a Corti et al., 2011 Gupta et al., 2005 Matosin et al., 2013, 2014
		↓ mRNA in Cer; no change in BA9 No change in mRNA in hippocampus No change in mRNA in thalamus No change in mRNA in BA9 or BA42	↓ mRNA in BA9; no change in Cer	↓ protein in PFC, CC, insula, thalamus, hippocampus ↓ mRNA in Cer	Deschwandt et al., 2011 Fatemi et al., 2013a Ohnuma et al., 2000 Richardson-Burns et al., 2000 Volk et al., 2010
APP 120 kDa	↑ protein in BA9 of children and ↓ protein in Cer of adults	↓ protein in BA9; no change in Cer	↓ protein in BA9; no change in Cer	No change in protein in Cer	Fatemi et al., 2013c, unpublished observations
APP 88 kDa	↑ protein in BA9 of children	↓ protein in BA9; no change in Cer	↓ protein in BA9; no change in Cer	No change in protein in Cer	Fatemi et al., 2013c, unpublished observations
RAC1	↑ protein in BA9 of adults and children and Cer of adults	↑ protein in Cer; no change in BA9	↑ protein in Cer; no change in BA9	↑ protein in Cer	Fatemi et al., 2013c, unpublished observations

Protein of Interest	Autism	Schizophrenia ^a	Bipolar Disorder ^a	Major Depression ^a	Reference
Homer 1	↓ protein in BA9 of adults	No change in protein in BA9 or Cer	↓ protein in BA9	No change in protein in Cer	Fatemi et al., 2013c, unpublished observations
STEP 61 kDa	↓ in BA9 of children	↓ protein in BA9 ↑ protein in DLPFC and ACC	No change in protein in BA9 or Cer	No change in protein in Cer	Fatemi et al., 2013c, unpublished observations Carty et al., 2012
STEP 33 kDa	↓ in Cer of adults	↓ protein in BA9; no change in Cer	No change in protein in BA9 or Cer	No change in protein in Cer	Fatemi et al., 2013c, unpublished observations

^a adults;

↓, significant decrease; ↑, significant increase; ACC, anterior cingulate cortex; CC, cingulate cortex; Cer, cerebellum; DLPFC, dorsolateral prefrontal cortex; PFC, prefrontal cortex