GABA System in Schizophrenia and Mood Disorders: A Mini Review on Third-Generation Imaging Studies

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Third-generation neuroimaging research has been enriched by advances in magnetic resonance spectroscopy (MRS) measuring the concentration of important neurotransmitters, such as the inhibitory amino acid GABA. Here, we performed a systematic mini-review on brain MRS studies measuring GABA concentration in patients affected by schizophrenia (SZ), bipolar disorder (BD), and major depressive disorder (MDD). We wondered whether multimodal investigations could overcome intrinsic technical limits of MRS giving a broader view of mental disorders pathogenesis. In SZ, unimodal studies gave mixed results, as increased, decreased, or unaltered GABA levels were reported depending on region, disease phase, and treatment. Conversely, multimodal results showed reduced level of glutamate, but not of GABA, in patients mirrored by in vitro biochemical findings revealing hippocampal reduction in glutamate signaling in SZ, and no deficits in GABA synthesis. Moreover, a mouse model confirmed the unique pathological characteristic of glutamate function in SZ. Unimodal studies in BD revealed again, inconsistent results, while no multimodal investigations including MRS on GABA exist. In MDD, unimodal studies could not differentiate patients from controls nor characterize high-risk subjects and remitted patients. However, a multimodal study combining functional magnetic resonance imaging and MRS revealed that cingulate cortex activity is related to glutamate, N-acetylaspartate levels and anhedonia in patients, and to GABA concentration in healthy subjects, improving the distinction between MDD and physiology. Overall, our results show that unimodal studies do not indicate GABA as a biomarker for the psychiatric disorders considered. Conversely, multimodal approaches seem promising for moving from GABA MRS unimodal-descriptive to causal level, and for integrating GABA results into a more comprehensive interpretation of mental disorder pathophysiology.

Keywords: GABA, MRS, multimodal imaging, schizophrenia, bipolar disorder, major depressive disorder
INTRODUCTION

An imbalance between excitation and inhibition in brain neuronal transmission has been hypothesized as one of the molecular mechanisms responsible for psychiatric disorders (1–5). In this context, multimodal studies coupling the continuous technical progresses in neuroimaging to methods for measuring neurotransmitter concentrations may represent a turning point for in vivo evidence of postmortem (6–8) and animal model (9–12) results. Moreover, the chance to link psychopathology, genetics, neuroanatomy, and functional–biochemical brain activity may take psychiatric research to the causal understanding of patients’ illness.

The support given by newly developed improvements in well known technologies, such as proton magnetic resonance spectroscopy (MRS) (13–15), has been fundamental to encourage in vivo research on gamma-aminobutyric acid (GABA) in brain physiology and pathology (16–18). GABA is the primary inhibitory neurotransmitter in the mammalian central nervous system. Theories on its dysfunction in schizophrenia (SZ) assume that alterations in the neural circuitry involving GABA have a role in the mechanisms of the disorder and associated cognitive deficits (19–21). The role of GABA dysfunction in different psychiatric disorders such as bipolar disorder (BD), or major depressive disorder (MDD) is also established (3, 22, 23).

Magnetic resonance spectroscopy is the election technique to non-invasively measure in vivo GABA concentration in selected brain regions (18, 24). However, direct interpretation of MRS results is limited by intrinsic features of the technique. In particular, acquisition of GABA signal is restricted to large (e.g., 3x3x3 cm³) single voxels, since multi-voxel spectroscopy usually measures metabolites with longer T2 relaxation, such as N-acetylaspartate (NAA), choline (Cho), and creatine (Cr). This results in a broad between-studies heterogeneity in the anatomical region investigated. Moreover, MRS can only detect total concentration of neurochemicals and cannot distinguish between separate functional pools, thus impeding conclusions on neurotransmitters availability.

In this context, multimodal approaches, combining MRS with other complementary techniques, would lead to a solid and comprehensive interpretation of neurochemical underpinnings of brain pathologies. As a case in point, multimodal MRS and functional magnetic resonance imaging (fMRI) would help in depicting the neurochemical and functional pathological mechanisms responsible for complex disorders. The support from electrophysiological measurements such as electroencephalography (EEG) or magnetoencephalography (MEG), measuring the oscillatory activity in brain neuronal ensembles, could be fundamental in interpreting results on GABA concentration since the latter has been shown to be positively correlated with stimulus specific neuronal oscillations (25–27). Similarly, findings from in vitro tissue biochemistry, animal models, and genetics could provide data at higher spatial resolution and further mechanistic insights into the interpretation of GABA concentration (28).

On the basis of these considerations, we reviewed research articles focusing on GABA as measured by MRS in SZ and mood disorders (i.e., BD and MDD). In particular, we analyzed whether studies combining different approaches could overcome the technical limits intrinsic to MRS and give a broader view of the mechanisms involved into mental disorders.

METHODS

To investigate recent MRS studies evaluating GABA level in the brain, we performed a systematic literature search on PubMed, PsycNET (including PsycINFO, PsycBOOKS, PsycCRITIQUES, PsycARTICLES, and PsyEXTRA databases), and Scopus database till November 2015 using the keywords “GABA” AND “spectroscopy” AND any of the following terms: “schizophrenia,” “bipolar disorder,” “major depressive disorder.” The reference list of identified articles and review papers was also hand searched to obtain additional articles. Inclusion criteria for studies selection were (1) English language, (2) articles published in peer-reviewed journals after 2000, (3) original research article (comments, letters to editors and review articles were excluded), (4a) inclusion of patients diagnosed with the specific neuropsychiatric disorder of interest according to ICD or DSM criteria or (4b) inclusion of high risk (HR) subjects, (5) inclusion of at least 10 patients, (6) comparison between patients and healthy controls (HC), (7) performance of MRS using a magnetic field of at least 3 T (to have a good signal-to-noise ratio and to resolve GABA peak from those of other more concentrated molecular compounds, e.g., NAA or Cr).

In the search for SZ studies, 72 papers were initially identified. Among them, 11 were not original researches (9 reviews, 1 comment, and 1 letter), 2 studies did not consider HC and 9 did not include SZ patients, 22 papers did not include humans (e.g., studies on animal models and in vitro measurements), 9 studies measured the unresolved glutamate + glutamine (Glx) with GABA contamination peak as a proxy of GABA concentration, 1 study included less than 10 patients and 6 studies were published before 2000. At the end of the selection process, 12 studies on SZ fulfilled the inclusion criteria.

In the search for BD studies, 21 papers were screened, but we excluded 7 reviews, 3 studies not performing in vivo MRS on humans, 1 on healthy men only, 1 not measuring GABA, 3 studies considering Glx, and 1 including less than 10 patients. Only five studies survived the selection process for BD.

At last, 53 studies were initially identified for MDD, but only 11 studies were eligible for the review, and 42 were excluded (6 studies without a control group, 5 not focusing on MDD patients, 6 not using in vivo MRS on humans, 11 reviews, 1 comment, 5 measuring Glx, 4 considering less than 10 patients, 3 not in English, and 1 published before 2000).

RESULTS

Schizophrenia

GABA MRS results in SZ are very scattered, since GABA concentration was found reduced, increased, or unaltered in patients (see Table 1). Such heterogeneity is mostly due to the different methodological approaches used, as studies vary in terms of patients’ clinical characteristics, brain region under investigation, and aims of the studies. Indeed, while most authors evaluated the
| Reference             | Sociodemographic characteristics | Clinical characteristics | Probed brain region | Brain region of altered GABA in patients | Additional findings | Other techniques |
|-----------------------|----------------------------------|--------------------------|---------------------|-----------------------------------------|--------------------|-----------------|
|                       | Sample size                      | Age [mean (SD) or years range] | Illness duration [mean (SD) or years range] | GMM [no. patients (%)] | Antipsychotics [no. patients (%)] |                     |
|                       | Patients | HC | Patients | HC |                            |
| **SZ < HC**           |          |    |          |    |                            |                     |
| Rowland et al. (30)   | 31 older | 37 older | 48.3 (5.8) | 51.0 (6.0) | 24.0 (9.8) | Anticholinergics: 1 (3) | Typ: 4 (13); Atyp: 18 (58); Both: 6 (19); none: 3 (10) | MFC | MFC |
|                       | 29 younger | 40 younger | 25.7 (4.3) | 25.3 (4.6) | 5.6 (4.6) | Anticholinergics: 2 (7) | Typ: 1 (3); Atyp: 25 (87); Both: 1 (3); None: 2 (7) | MFC | |
| Rowland et al. (29)   | 11 younger | 10 younger | 30.2 (6.6) | 33.4 (6.5) | 7.7 (4.1) | Benzodiazepines or mood stabilizers free at scan time | Atyp: 11 (100) | ACC, CSO | ACC |
|                       | 10 older | 10 older | 51.1 (4.0) | 49.4 (3.9) | 25.5 (6.5) | Benzodiazepines or mood stabilizers free at scan time | Typ: 2 (20); Atyp: 9 (80) | ACC, CSO | |
| Marsman et al. (31)   | 17 | 23 | 27.6 (6.1) | 27.7 (5.3) | 6.4 (6.8) | Benzodiazepines current: 6 (35); Benzodiazepines lifetime: 11 (65) | Typ: 3 (18); Atyp: 10 (59); Both: 4 (23) | PFC, POC | PFC |
| Kelemen et al. (32)   | 28 | 20 | 24.9 (8.3) | 24.2 (6.9) | <1 | T0: drug naive: 28 (100); FU: anticholinergics: 5 (18); benzodiazepines: 16 (57); mood stabilizers: 5 (18) | T0: None: 28 (100); FU: Typ: 3 (11); Atyp: 25 (89) | OC | OC |
| Yoon et al. (33)      | 13 | 13 | 27.5 (8.8) | 28.1 (8.2) | Na | Na | Typ: 1 (8); Atyp: 7 (54); None: 5 (38) | OC | OC |
| Goto et al. (34)      | 16 | 18 | 30 (11) | 15–49 | <0.5 | Na | T0: None: 16 (100); FU: Atyp: 16 (100) | MFC, ltBG, POC | ltBG | GABA_SZ_T0 = GABA_SZ_FU |
| **SZ = HC**           |          |    |          |    |                            |                     |                     |
| Stan et al. (28)      | 18 | 16 | 41.94 (8.5) | 35.63 (11.74) | Na | Anticonvulsants: 1 (5); benzodiazepines: 2 (11), valproic acid: 2 (11) | Typ, Atyp, Both: Na; None: 7 (39) | Hippocampus | |

(Continued)
### Reference Sociodemographic characteristics Clinical characteristics Probed brain region Brain region of altered GABA in patients Additional findings Other techniques

| Reference                  | Sample size | Age [mean (SD) or years range] | Illness duration [mean (SD) or years range] | GMM [no. patients (%)] | Antipsychotics [no. patients (%)] | DLPFC | ACC, ltBG | Correlation between GABA levels and gamma band oscillation in SZ and HC | EEG at rest during a working memory task |
|---------------------------|-------------|---------------------------------|---------------------------------------------|-------------------------|------------------------------------|-------|-----------|-------------------------------|---------------------------------------|
| Chen et al. (36)          | 12          | 31.00 (10.79)                   | Na                                          | Na                      | Atyp: 9 (75); None: 3 (25)         |       |           |                               |                                       |
| Tayoshi et al. (35)       | 38          | 34.0 (10.0)                     | 11.1 (9.4)                                  | Benzodiazepines: 16 (42)| Typ: 16 (42); Atyp: 22 (58)        |       |           |                               |                                       |
| De la Fuente-Sandoval et al. (39) | 23 UHR | 20.7 (4.1)                      | <1                                          | Medication free for T >12 weeks: 23 (100) | None: 23 (100)                  | Dorsal caudate, MPFC | |                               |                                       |
| Kegeles et al. (37)       | 16 unmed*, 22 unmed: 32 (11), med: 32 (10) | 33 (8)                                     | Benzodiazepines free at scan time: 32 (100) | med: Atyp: 16 (100) |                                               | MPFC, DLPFC | |                               |                                       |
| Ongür et al. (38)         | 21          | 39.0 (10.8)                     | 36.3 (9.8)                                  | Na                      | Anticonvulsants: 6 (28); benzodiazepines: 10 (48); lithium: 4 (19) |                 | ACC, POC | ACC + POC, averaged          |                                       |

*Patients free of antipsychotic medication treatment for a minimum of 14 days prior to the scan.

ACC, anterior cingulate cortex; Atyp, patients taking atypical antipsychotics; CSO, centrum semiovale region; DG, dentate gyrus; DLPFC, dorsolateral prefrontal cortex; EEG, electroencephalography; FU, follow up; GMM, GABA-modulating medication; HC, healthy controls; ltBG, left basal ganglia; med, medicated; MFC, medial frontal cortex; MPFC, medial prefrontal cortex; Na, not available; OC, occipital cortex; PFC, prefrontal cortex; POC, parieto-occipital cortex; SD, standard deviation; SZ, schizophrenia patients; T, time; T0, baseline; Typ, patients taking typical antipsychotics; UHR, ultra high risk patients; unmed, unmedicated.
diagnosis effect on GABA concentration, others considered the
effect of age, of antipsychotics, and the role of GABA in different
illness phases.

The most reported result (i.e., replicated in six studies) is that
GABA concentration is reduced in SZ patients with respect to
HC (29–34). Specifically, GABA was reduced in medial frontal
cortex (MFC) (29, 30) and occipital cortex (OC) (32, 33), and the
result was modulated by age in MFC (29, 30) and not affected by
current medication type or dosage in OC (32, 33). The observed
reduction in MFC GABA level in old SZ subjects as compared to
age-matched HC suggests that GABA concentration decreases as
age increases in patients and not in controls (29, 30). The inde-
pendence from medication dosage in the OC (33) was further
extended to the basal ganglia (34) suggesting that GABA reduc-
tion in these areas is driven by the disorder, being observable
also in first-episode patients (32), and not an effect of treatment.
A reduced GABA level in prefrontal areas of SZ patients was
described only performing MRS at very high (7 T) magnetic field
(31). Conversely, three studies (34–36) failed to find alterations
in GABA level in SZ with respect to HC in any of the considered
regions. Among them, one study found that patients taking only
typical antipsychotics had higher GABA concentration than
those taking only atypical antipsychotics (35). The other two
studies failing to find GABA alterations in SZ, probed the hip-
campus and the dorsolateral prefrontal cortex (DLPFC) (28,
36). These studies are of particular interest since they combined
MRS with different experimental techniques. In particular, one
correlated GABA levels in DLPFC to gamma oscillations, as
measured by EEG during a working memory task, and found that
both baseline and working memory-induced gamma oscil-
lations were strongly dependent on GABA levels either in patients
and controls (36). Within a data rich experimental design, the
second multimodal study integrated in vivo MRS measurements
of hippocampal GABA (and glutamate) concentration in patients
with in vitro tissue biochemistry (sampling postmortem human
hippocampal tissue) and MRS on a mouse model recapitulating
symptoms of SZ (dentate gyrus-selective knockout of the GRIN1
gene, encoding a critical unit of N-methyl-D-aspartate receptors)
(28). Looking at in vivo MRS results, authors found no global dif-
ference in GABA level between SZ and HC both in humans and
animals, while they found decreased glutamate in SZ. Looking at
in vitro results, authors found reduced level of GluN1 protein, a
marker of the glutamatergic system, in SZ, but no alterations with
respect to HC in the level of GAD67, the main enzyme in the
GABAergic system. The combination of such findings provides
evidence that the excitatory, but not the inhibitory, system within
the hippocampus is implicated in SZ pathogenesis.

Finally, three studies found increased GABA concentration
in SZ with respect to HC. One of them compared unmedicated
SZ and patients medicated only with atypical antipsychotics
to HC (37). Authors showed increased prefrontal GABA in
unmedicated SZ patients with respect to both medicated and
HC samples. Such results partially confirmed those presented
in a previous research in which, averaging GABA concentra-
tion in anterior cingulate cortex (ACC) and parieto-occipital
cortex (POC), authors found increased GABA in chronic SZ
(38). More recently, an increased GABA concentration in dorsal
caudate area and medial prefrontal cortex has been observed
also considering ultra HR patients free from GABA modulating
medications (GMM) (i.e., benzodiazepines, mood stabilizers, or
antidepressants) and antipsychotics (39).

Bipolar Disorder
Among the few studies using MRS to measure GABA concen-
tration in BD, three reported no difference between patients and
HC (40–42). However, papers contributing to such evidence are
very heterogeneous in terms of localization of MRS voxel,
clinical characteristics of BD samples, and GMM (see Table 2),
which were scarcely considered in the analyses. Their effect was
specifically taken into account in a study indicating an increased
GABA in BD as a whole, with respect to HC. However, within the
patients group, there was a reduction of GABA in those taking
GMM (43). To clarify the impact of medication dosage and life-
time exposure on GABA concentration, some authors considered
only drug free patients (for at least 3 months before MR scan)
who however, had lifetime exposure to lithium, antidepressants,
or mood stabilizers (44). Results indicated decreased GABA level
in recovered unmedicated BD patients with respect to HC.

No study using multimodal techniques has been published so
far on BD patients.

Unipolar Major Depressive Disorder
Studies investigating unipolar MDD patients showed either no
difference in GABA concentration between patients and HC (45–
50), either a reduction of GABA in MDD (44, 51–54). A decreased
GABA level has been observed mainly in patients depressed at scan
time (51–53), but some authors found a reduction also in remitted
patients (44, 54). One study comparing GABA level between HR
subjects (i.e., having a family history of parental depression) and
a control group without a family history of depression described
negative results (45). Among studies failing to find an alteration
of GABA in MDD, one combined genotyping with MRS in
order to test the effect of common variants of the tryptophan
hydroxylase isoform 2 (TPH2) gene, modulating serotonergic
neurotransmission and brain circuits for emotion and adapta-
tion, on GABA concentration in the prefrontal cortex (PFC) (47).
Authors found a significant association between increased GABA
concentration in the PFC and the allele frequencies of three
TPH2 SNPs in female subjects, independently from diagnosis.
Along with MRS, another research focused on remitted, formerly
severe MDD patients and HC using MEG to measure the induced
gamma oscillation frequency (IGF), a reliable surrogate marker
of postsynaptic GABA function, in the OC (49). Authors found
that MDD have normal IGF and GABA concentration in the OC.
In a further multimodal investigation, MRS quantifying GABA,
glutamate, and NAA concentrations was combined with fMRI
measuring blood oxygenation level-dependent (BOLD) response
to emotional stimuli in the pregenual ACC, part of the default
mode network, related to anhedonia (48). MRS results showed
no alteration in metabolites concentration in MDD patients,
while fMRI indicated that negative BOLD responses, as well as
glutamate and N-acetylaspartate concentrations, correlated with
emotional intensity ratings, an anhedonia surrogate, in MDD
but not in HC. Differently, negative BOLD responses in HC
### TABLE 2 | Studies comparing GABA concentration between mood disorders patients (BD and MDD) and HC.

| Reference                                    | Sociodemographic characteristics | Clinical characteristics | Probed brain region | Brain region of altered GABA in patients | Additional findings | Other techniques |
|----------------------------------------------|----------------------------------|--------------------------|---------------------|------------------------------------------|---------------------|-----------------|
| **Patients**                                 | **Age [mean (SD) or years range]** | **Illness duration**     | **GMM**             | **Antipsychotics**                        |                     |                 |
| **BD**                                       | **[mean (SD) or years range]**   | **[no. patients (%)]**   |                     | **[no. patients (%)]**                     |                     |                 |
| **BD < HC**                                  |                                   |                          |                     |                                          |                     |                 |
| Bhagwagar et al. (44)                        | 16 BD-I, 15 rMDD                 | 37.0 (13.8)              | BD-I = 0.5–10.1     | 11 (69); lithium: 6 (37); mood stabilizers: 3 (19) | Na                  | OC              | GABA_rMDD = GABA_BD-I |
| Soeiro-de-Souza et al. (40)                  | 50 38                            | 31.7 (9.1)               | Na                  | anticonvulsants: 23 (46); antidepressants: 8 (16); benzodiazepines: 1 (2); lithium: 29 (58) | Atyp: 23 (46), Typ: 0 (0) | ACC             |                 |
| Godlewska et al. (41)                        | 13 11                            | 23.8 (3.6)               | Na                  | Mood stabilizers naive: 13 (100)          | None: 13 (100)      | MPFC, OC        |                 |
| Kaufman et al. (42)                          | 13 11                            | 40.5 (12.5)              | Antidepressants: 6 (46), mood stabilizers: 12 (92) | Typ, Atyp, Both: Na; None: 0 (0) | POC, Thal, whole brain | Whole brain: GABA_BD_antipsy < GABA_BD_noantipsy |
| **BD > HC**                                  |                                   |                          |                     |                                          |                     |                 |
| Brady et al. (43)                            | 14 BD-I                          | 32.6 (13.6)              | Anticonvulsants: 5 (36); antidepressants: 7 (50); benzodiazepines: 6 (43); lithium: 4 (29) | Typ: 2 (14); Atyp: 9 (64); Both: Na; None: 0 (0) | ACC, POC           | GABA_HC < GABA_BD-I, GMM < GABA_BD-I, rGMM |
| **MDD**                                      |                                   |                          |                     |                                          |                     |                 |
| **MDD = HC**                                 |                                   |                          |                     |                                          |                     |                 |
| Taylor et al. (45)                           | 24 HR                            | 18.9 (16–21)             | Drug naive: 24 (100) | None: 24 (100)                           | POC                |                 |
| Godlewska et al. (46)                        | 39 31                            | 29.9 (10.6)              | 6 weeks FU: antidepressant (escitalopram): 39 (100) | T0: None: 39 (100) | OC                |                 |
| Preuss et al. (47)                           | 19 cMDD, 16 rMDD, 9 PD           | 31.5 (9), rMDD: 40.8 (11.7), PD = 33.8 (12.8) | Psychotropic medication free for T > 4 weeks: 44 (100) | None | PFC | GABA level differs between female carrier/non-carrier of 3 nuclear polymorphysms |

(Continued)
**TABLE 2 | Continued**

| Reference          | Sample size | Age [mean (SD) or years range] | Illness duration [mean (SD) or years range] | GMM [no. patients (%)] | Antipsychotics [no. patients (%)] | Probed brain region | Brain region of altered GABA in patients | Additional findings | Other techniques |
|--------------------|-------------|--------------------------------|---------------------------------------------|-------------------------|-------------------------------------|---------------------|------------------------------------------|-------------------|------------------|
| Walter et al. (48) | Patients: 19 (11 with MRS GABA level) | 40.0 (Na) | Na | Psychotropic medication free for T > 1 week: 19 (100) | Na | ACC | GABA_HC correlated with NBR, but not GABA_MDD | fMRI |
| Patients remitted at scan time | HC: 24 (13 with MRS GABA level) | 34.6 (Na) | | | | | | | |
| Shaw et al. (49)   | Patients: 19 | 23 (2.6) | 21 (1.5) | Na | Medication free: 19 (100) | Na | PFC, OC, ltBG | OC: IGF_rMDD = IGF_HC | MEG |
| Hasler et al. (50) | Patients: 16 | 41.0 (11.6) | 41.7 (12.4) | Na | Antidepressant medication free for T ≥ 3 months: 16 (100) | Na | DM/DA-PF, VM-PF |
| MDD < HC Patients depressed at scan time | HC: 15 | 16.7 (2.7) | 16.2 (1.6) | 11.7 (8.6) months | Psychotropic medication free for T ≥ 3 months: 20 (100) | Na | ACC | ACC |
| Gabbay et al. (51) | Patients: 20 | 21 | 16.3 (1.0) | 16.2 (1.6) | 11.7 (8.6) months | Psychotropic medication free for T ≥ 3 months: 20 (100) | Na | ACC | ACC |
| Price et al. (52)  | Patients: 15 TRD | 24 | TRD = 46.8 (11.9), nTRD = 38.3 (12.3) | TRD: 26.93 (10.8), nTRD: 21.80 (16.4) | TRD: 26.93 (10.8), nTRD: 21.80 (16.4) | Na | OC, ACC | OC | OC: GABA_MDD (TRD + nTRD) < GABA_HC |
| Patients remitted at scan time | HC: 18 nTRD | 37.25 (13.5) | | | | | | | |
| Hasler et al. (53) | Patients: 20 | 34.0 (11.2) | 34.8 (12.4) | 18.8 (13.5) | Medication free for T > 4 weeks or medication naie: 20 (100) | Na | DM/DA-PF, VM-PF | DM/DA-PF |
| Bhagwagar et al. (54) | Patients: 12 | 40.6 (4.2) | 43.3 (4.1) | Na | Medication free for T > 6 months: 12 (100) | Na | ACC, POC | ACC, POC |
| Bhagwagar et al. (44) | Patients: 16 BD-I | 18 | BD = 37.0 (13.8), rMDD = 42.1 (14.6) | BD-I: 0.5-10.1, rMDD: 1-18.4 | BD-I: 0.5-10.1, rMDD: 1-18.4 | Na | OC | OC | GABA_rMDD = GABA_BD-I |

GABA, anterior cingulate cortex; Atyp, patients taking atypical antipsychotics; BD, bipolar disorder patients; BD_antipsy, patients taking antipsychotics; BD-I_GMM, BD-I patients taking GABA modulating medications; BD-I, patients with bipolar disorder type I; BD_noantipsy, patients not taking antipsychotics; BD-I, nGMM, BD-I patients not taking GABA modulating medications; rMDD, patients with a current episode of major depressive disorder; DM/DA-PF, dorsomedial/dorsal anterolateral prefrontal region; fMRI, functional magnetic resonance imaging; FU, follow up; GMM, GABA-modulating medication; HC, healthy controls; HR, high risk patients; IGF, induced γ frequency; ltBG, left basal ganglia; MEG, magnetoencephalography; MDD, major depressive disorder patients; MPFC, medial prefrontal cortex; Na, not available; NBR, negative blood response; nTRD, non-treatment-resistant depression; OC, occipital cortex; PD, panic disorder; PFC, prefrontal cortex; POC, parieto-occipital cortex; rMDD, individuals with remitted major depressive disorder; SD, standard deviation; T, time; T0, baseline; Thal, thalamic region; TRD, treatment-resistant depression; Typ, patients taking typical antipsychotics; VM-PF, ventromedial prefrontal region.
correlated with GABA. The fact that GABA concentration could not differentiate between MDD patients and HC together with the absence of GABA modulating effects on anhedonia were interpreted as secondary outcomes consequent to a primary deficit in glutamatergic metabolism, which may lead to a distortion of the excitation–inhibition balance and cause anhedonic depression.

**DISCUSSION**

The involvement of GABA abnormalities in the mechanisms of psychiatric disorders is strongly debated. In particular, recent developments in MRS sequences allow discriminating the peak of GABA from those of more concentrated metabolites in the brain, thus permitting its measurement. However, despite postmortem evidence and preclinical studies highlighting GABAergic abnormalities in patients with mental disorders, the connection between these abnormalities and categorical/diagnostic or dimensional/symptomatic characteristics is still unclear. In this framework, we reviewed the body of evidence on GABA concentration, as measured by MRS in localized brain regions of SZ, BD, and MDD patients, particularly highlighting results obtained by multimodal methods and multiple experimental techniques.

Although this topic is under continuous development, some conclusions can be drawn from the present results.

**Schizophrenia**

First, the reduction of GABA level in SZ (the most frequent reported result) seems to occur in specific brain areas (frontal, occipital, and basal ganglia) and in old age, being probably a mixed effect of chronicity, lifetime exposure (more than current type or dosage) to antipsychotics, and GMM, particularly benzodiazepines (17). The latter is known to allosterically increase GABAA receptor activation, but available experimental techniques are still too coarse to detect circuit-specific perturbations in GABA levels as induced by benzodiazepines (or other medications modulating neuronal transmission), and results are not concordant. From our review, a slight majority of authors failed to find a link between GABA level and medications. Such heterogeneous results might be reconciled performing technically more precise experiments (e.g., MRS at ultra high magnetic field) and enrolling HR subjects in their pre-clinical stage or drug naive patients to be followed longitudinally.

The second interesting conclusion derived from multimodal studies on SZ is that GABA concentration alone cannot be considered a biomarker for this disorder, while a potential perturbation in the balance between excitation and inhibition, measurable through glutamate/GABA ratio, needs to be more deeply investigated in SZ (28). The latter should be the target for studies aimed at clarifying mechanisms and/or novel therapeutic strategies.

**Bipolar Disorder**

Unfortunately, GABA cannot be considered a biomarker of BD yet. Indeed, the only study including young and drug naive patients failed to find differences with respect to HC (41). From the other few studies, it appears that both current and lifetime exposure to GMM tend to reduce GABA level in BD patients, especially in the OC (43, 44). However, heterogeneity of patients’ clinical characteristics, illness phase at scan time, number of previous manic/depressive episodes, and eventual action of the complex mixtures of GMM (not only benzodiazepines but also antidepressants, lithium, mood stabilizers, etc.) justify the need to start multimodal researches focused on more homogeneous clinical subsamples.

**Major Depressive Disorder**

Research on neurotransmission in MDD is truly promising and intriguing in the hunt for innovative approaches to prevention. Understanding whether eventual changes in GABA reflect an underlying trait vulnerability to depression, or can be considered “scars” of depressive episodes or treatment effects, may have implications for preventative strategies in HR subjects (55). The only study measuring GABA concentration with MRS in subjects at risk of depression did not find differences in the parieto-occipital cortex with respect to subjects not at risk, indicating that, at the actual level of accuracy, GABA level in such brain region cannot be considered an endophenotype for depression (45). Moreover, the study including genotyping showed that GABA concentration in PFC is associated with allele frequencies of three polymorphisms linked to anxiety only in women, independently from the diagnosis (47). This result reinforces the notion that GABA levels are not a marker of MDD (at least in the POC and PFC). The other two multimodal studies associating MRS with fMRI (48) and MEG (49) failed to find differences in GABA concentration in diffuse brain regions between MDD and HC. However, the classification of studies in terms of patients state (i.e., depressed/remitted) at scan time (see Table 2) allows us to support the idea that GABA level identifies the state of being ill, and is not a trait marker for diagnosis, since physiological concentration has been described in the majority of studies including MDD patients during the remission phase (44, 49, 50, 53, 54). Conversely, a primary deficit in glutamatergic metabolism may cause aberrant neuronal activation patterns in regions specifically relevant for the expression of anhedonic behavior in MDD.

**CONCLUSION**

Complex and multimodal researches looking at GABA in psychiatric populations are still a minority. Our review shows that fMRI, in vitro biochemistry, genotyping, EEG, and MEG have been combined to MRS, and each of them adds a piece to the puzzle depicting the role of GABA abnormalities in psychiatric disorders. Indeed, fMRI can differentiate neural response patterns induced by stimulation (56), in vitro biochemistry allows higher resolution spatial information and correlations between MRS results and biochemical activity of the brain, while genotyping can elucidate the genetic correlates of GABAergic transmission. Furthermore, as EEG reflects voltage changes resulting from the synchronous firing of groups of neurons (57), and MEG describes the effects of synchronous postsynaptic activity (58), when combined with MRS they allow the in vivo investigation of GABA effect on neuronal transmission. Thus, from studies using a multimodal approach, it appears that GABA level alone may not be the best biomarker for the psychiatric disorders here considered. However, it is a promising parameter, particularly for the stratification of patients in more homogeneous subtypes.
sharing specific biological features. The possibility to reduce heterogeneity in psychiatric patients is fundamental both in research (giving the opportunity to gain new insight in the underlying pathophysiology of different mental disorders) and in clinical practice (allowing the prescription of effective and tailored medical treatments).

 Conversely, although still scarce, the so-called third-generation paradigms will be the turning point of neuroimaging research on neurotransmission in general, and on GABA dysfunctions in particular. The effort spent in the design and realization of multimodal studies, as well as multicentre ones to include larger samples, would then be rewarded by the strong translational impact of such researches. This approach would support clinicians in the design of preventative interventions with defined, expected outcomes for specific types of psychiatric patients making “precision medicine” a more realistic medical model. The precise medicine is the final end.

**AUTHOR CONTRIBUTIONS**

CCh and GS conceived the paper and performed literature search. CCh, FeP, FaP, and GS wrote the paper. All authors critically reviewed the manuscript and agreed on its final version.

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