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CRITICAL REVIEW

Potential TMS biomarkers for $GABA_B$ receptor engagement in alcohol use disorder: A systematic review of existing evidence

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Abstract

Alcohol use disorder (AUD) is a major global health issue, with current treatments often limited in efficacy and patient acceptance. The gamma-aminobutyric acid (GABA) system, particularly $GABA_B$ receptors ($GABA_BR$), is crucial in the pathophysiology of AUD. This review aimed to evaluate the potential of transcranial magnetic stimulation (TMS) as a tool for identifying neurophysiological biomarkers of $GABA_BR$ engagement in AUD. Two independent systematic literature reviews were conducted using MEDLINE, PsychINFO, and EMBASE databases to evaluate: (1) the neurophysiological effects of $GABA_BR$ pharmacological manipulation, and (2) the neurophysiological alterations linked to alcohol consumption and addiction. Studies included human subjects and assessed cortical excitability using TMS-EMG or TMS-EEG. Data on study design, sample characteristics, TMS protocols, and neurophysiological outcomes were extracted and analyzed. The final analysis included 13 studies evaluating the effects of $GABA_BR$ agonism (mainly baclofen administration) and 16 studies on acute and chronic alcohol consumption. The $GABA_BR$ agonism studies were primarily randomized, placebo-controlled experimental medicine studies in healthy controls. Results showed that $GABA_BR$ agonism enhanced long-interval intracortical inhibition (LICI) and increased post-TMS N100 amplitude, indicating the sensitivity of these parameters to $GABA_BR$ manipulation. The alcohol consumption studies were mostly case–control or within-subject designs, with fewer randomized controlled trials. Acute and chronic alcohol consumption was found to alter LICI, N100 amplitude, and the cortical silent period (CSP). However, no alcohol-induced changes were observed in short-interval intracortical inhibition (SICI), which depends on $GABA_AR$ activation. Despite limitations, this review indicates $GABA_BR$ functioning to be measurable and different in AUD compared to healthy controls. Overall, the reviewed literature supports the hypothesis that $GABA_BR$ is involved in the neurotransmission imbalances induced by both acute and chronic alcohol intake, with potential regional differences

Sara Terrezza, Federico Maruottolo, and Andrea Costumati contributed equally to this study.

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that warrant further investigation. Standardized protocols and larger studies are needed to validate these findings and their clinical relevance.

KEYWORDS
alcohol use disorder, baclofen, cortical inhibition, gamma-aminobutyric acid, transcranial magnetic stimulation

INTRODUCTION

Alcohol use accounts for about 5% of the global disease burden (World Health Organization [WHO], 2019), with people suffering from alcohol use disorder (AUD) or very heavy drinking (HD, >100 or 60 g of alcohol/day for males and females, respectively) disproportionately affected (Rehm et al., 2018). Despite this, less than 20% of people with AUD ever receive treatment, and then with a lag from diagnosis of about a decade (Mekonen et al., 2021). The limited efficacy and patient acceptance of existing pharmacotherapies further exacerbate this gap (Jonas et al., 2014).

Among the various neurotransmitter systems involved in the pathophysiology of AUD, the gamma-aminobutyric acid (GABA) system is of particular interest. GABA is the primary inhibitory neurotransmitter of the central nervous system (CNS), and disruptions in GABAergic signaling have been implicated in several neuropsychiatric disorders, including AUD (Shaye et al., 2021). Among GABAergic receptors, $GABA_B$ metabotropic receptors ($GABA_BR$) are widely expressed in the CNS at both pre- and postsynaptic sites, and also in astroglia (Shaye et al., 2021). Among their diverse functions, such as nociception, cortical excitability, and neuroplasticity, $GABA_BR$ have been linked to dopaminergic signaling in the midbrain and the nucleus accumbens (Lalive & Lüscher, 2016). Dysregulation of GABA transmission at $GABA_BR$ in the central nucleus of the amygdala (CeA) has also been linked to alcohol use disorders (Gilpin et al., 2015). Recent work in animal models has also found that the choice of alcohol over natural reward and compulsive alcohol use can be rescued by activation of $GABA_BR$ in the central nucleus of the amygdala (Augier et al., 2017, 2018; Domi et al., 2023). These findings provide insight into the mechanisms by which GABAergic drugs exert beneficial effects in AUD (Addolorato et al., 2007, 2009), suggesting that $GABA_BR$ activation could be a promising neurobiological target for novel treatments.

While electrophysiological measures of neuronal excitability and synaptic inhibition can provide direct and reliable indicators of $GABA_BR$ activation in preclinical models (Domi et al., 2023), objective biomarkers of $GABA_BR$ engagement in humans are currently lacking. In fact, there are no widely available magnetic resonance spectroscopy (MRS) or positron emission tomography (PET) imaging techniques capable of directly measuring $GABA_BR$ engagement in humans (McGinnity et al., 2017; Murrell et al., 2020), and developing PET radiotracers for $GABA_BR$ has proven challenging due to issues related to specificity, blood–brain barrier penetration, and binding affinity (Murrell et al., 2020). Although some studies have pointed to potential biomarkers that may be detected in the cerebrospinal fluid of patients with anti-$GABA_BR$ encephalitis, these markers currently only reflect disease severity and prognosis, rather than direct receptor activation (Li et al., 2023). Computational models have provided valuable insights by simulating $GABA_BR$ signaling pathways and downstream effects, yet they do not offer practical, in vivo biomarkers for receptor engagement (Mäki-Marttunen et al., 2025). Hence, despite promising avenues, a dependable, noninvasive biomarker for $GABA_BR$ engagement remains an unmet need in both clinical and research settings.

Transcranial magnetic stimulation (TMS), widely recognized for its therapeutic use in Major Depression and Substance Use Disorders (Sabé et al., 2024), offers a promising noninvasive approach for assessing brain function and neurophysiology (Di Lazzaro et al., 2004). By combining TMS with electromyography (TMS-EMG) and electroencephalography (TMS-EEG), researchers can obtain objective neurophysiological measures that reflect neurotransmitter and receptor activity (Di Lazzaro et al., 2000; Ziemann, 2004, 2013; Ziemann et al., 1996). These approaches have been utilized to aid in diagnosing neurological disorders (Chu et al., 2009), studying psychiatric conditions (Bunse et al., 2014), and investigating the effects of CNS-active drugs (Paulus et al., 2008). Specifically, both TMS-EMG and TMS-EEG offer valuable experimental probes of GABAergic functioning, such as the cortical silent period (CSP), the long-interval intracortical inhibition (LICI), and the short-interval intracortical inhibition (SICI; Ziemann, 2013). CSP refers to the transient (up to 300 ms) suppression of muscle activations or cortical responses observed after a TMS-evoked motor (MEPs) or cortical (TEPs) potential, linked to both spinal and cortical inhibitory circuits. This measure, and especially its duration, is likely due to presynaptic $GABA_BR$-mediated inhibition (Chu et al., 2008). Also linked to the activation of $GABA_BR$ (McDonnell et al., 2006; Müller-Dahlhaus et al., 2008), LICI is the suppression of the cortical or motor output induced by the pairing of suprathreshold conditioning and test stimuli with a 50–200 ms interstimuli interval. LICI is usually observed as the reduction in MEP amplitude and the suppression of late TEPs components (i.e., N100 and/or the P180), as well as the overall reduction in the oscillatory power in beta and low-gamma bands. $GABA_BR$ that are located postsynaptically on cortical output neurons are thought to be responsible for the suppression of cortical and motor outputs through LICI, while presynaptic $GABA_BR$ on inhibitory interneurons are thought to be responsible for a reduction of GABA release and the prolongation of the CSP (Chu et al., 2008). On the

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other hand, SICI is the phenomenon observed after the pairing of one below-threshold conditioning and one suprathreshold test stimuli separated by 1–6 ms. This leads to the suppression of the output expected after the TS alone, such as a reduction in the amplitude of MEPs or the suppression of early TEP components (i.e., N45 and P60). This effect is increased by benzodiazepines and has been linked to the activation of postsynaptic GABA$_A$ receptors in response to GABA released by cortical interneurons (Di Lazzaro et al., 2005, 2007). Further details on TMS-EMG and TMS-EEG procedures of interest are provided in Appendix S1.

To explore whether these measures may serve as reliable tools for probing GABA$_B$R activity, and as feasible, noninvasive biomarkers of receptor engagement in research and clinical settings, we systematically reviewed studies evaluating the neurophysiological effects of the direct pharmacological modulation of GABA$_B$R.

Our primary objective was to identify neurophysiological measures that can clarify the roles of GABA$_B$R in chronic alcohol use and addiction. These measures may also serve as biomarkers of target engagement for novel GABA-ergic treatments. To achieve this, we systematically reviewed the existing evidence of neurophysiological alterations in AUD, with a particular focus on markers of GABAergic neurotransmission throughout the manuscript.

METHODS

Two independent systematic reviews were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA; Page et al., 2021) guidelines on July 15 2025. Two authors (CM, FM) independently searched all the relevant articles using three different electronic databases: MEDLINE, PsychINFO, and EMBASE. We also conducted targeted searches of ClinicalTrials.gov using search terms relevant to our review to identify unpublished or ongoing studies, reducing potential publication bias. Complete search strings used for each database are reported in Tables S3 and S4.

To evaluate the neurophysiological effects of GABA$_B$R pharmacological manipulation, we included all original articles written in English, in which healthy human subjects were included and tested with TMS-EMG or TMS-EEG with the aims to assess the effects of acute oral administration of a single dose of GABAergic drugs on cortical excitability. Specifically, we focused on the administration of baclofen—the only GABA$_B$R agonist currently approved for use in humans—and other GABAergic drugs that exert effects at least in part through GABA$_B$R, such as vigabatrin, tiagabine, and γ-hydroxybutyric acid (GHB). Notably, we excluded gabapentin and pregabalin, as their mechanisms involve GABA analogues that do not directly activate GABAergic signaling (Bockbrader et al., 2010).

To evaluate the neurophysiological alterations linked to alcohol consumption and addiction, we included all original articles written in English, in which subjects with different levels of alcohol consumption and/or AUD patients were tested with TMS-EMG or TMS-EEG with the aims to assess the effects of acute and/or chronic alcohol consumption on cortical excitability.

Reviews, preprints, studies enrolling patients with predominant medical and psychiatric comorbidity, and studies not including a TMS-based neurophysiological assessment were excluded (Figure 1). Given that our main objective was to explore the neurophysiological underpinning of alcohol use and GABAergic drug actions, publications in which TMS served as a treatment tool for any condition were excluded. Also, publications using neurostimulation techniques different from TMS-EMG and TMS-EEG, or evaluating any pharmacological treatment with more than a single GABAergic drug administration, were excluded.

Four authors (CM, FM, AC, and ST) independently evaluated and examined all the included studies, and a qualitative synthesis was performed. The following variables were collected for each study: year of publication, country, aims, study design (randomization, blinding), sample size and characteristics (age, gender, handedness), diagnostic and psychometric tools, experimental manipulation, TMS protocol and parameters (including machine and coil type), EEG and EMG methods, and parameters of interest, results (*p*-values and effect's size). The synthesis involved systematically summarizing and integrating the findings from individual studies to identify common themes, patterns, and discrepancies. The rationale for choosing a qualitative synthesis was based on the heterogeneity of the study designs, populations, interventions, and outcome measures.

The same authors assessed the quality of the studies through validated instruments: methodological details and results of the quality assessment are reported in Appendix S1: Results.

RESULTS

Changes in cortical excitability in response to GABA$_B$R manipulation

The searches for the effects of GABAergic drugs targeting GABA$_B$R on cortical excitability yielded 51 publications and seven registered clinical trials; 12 studies were selected after screening (Figure 1). After full-text review, one study was excluded because it only tested the effects of pregabalin, the mechanism of action of which falls outside of the scope of this review. Two additional studies were identified through manual search. Ultimately, 13 studies were included: five focusing on TMS-EMG and eight on TMS-EEG correlates following single oral administration of GABAergic drugs (Table 1). Notably, the majority of the included studies investigated the neurophysiological effects of baclofen (*n*: 11/13), while no studies investigating the neurophysiological effects of GHB administration on cortical excitability in healthy subjects were found (specifically, all the retrieved studies about GHB did not meet the inclusion criteria given their focus on the succinic semialdehyde dehydrogenase [SSADH] deficiency).

Studies on GABAergic drugs included healthy controls (sample size: 5–19) in randomized or pseudo-randomized, double-blind,

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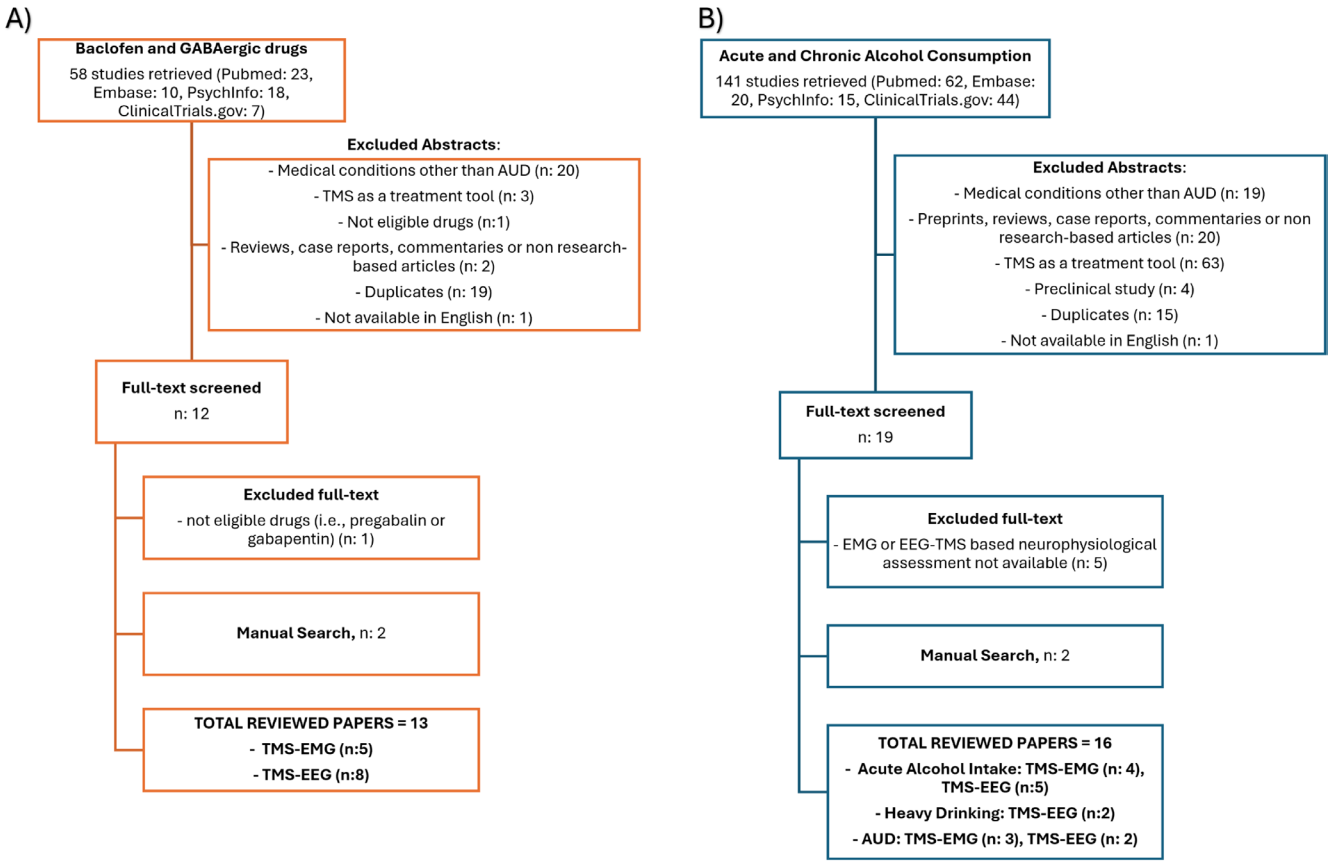

FIGURE 1 Flowchart regarding (A) the search for the effects of GABAergic drugs targeting $GABA_BR$ on cortical excitability, and (B) the search about the effects of alcohol consumption on cortical excitability.

placebo-controlled, cross-over designs (Darmani et al., 2019; Hui et al., 2020; McDonnell et al., 2006; Müller-Dahlhaus et al., 2008; Premoli et al., 2017, 2018; Premoli, Castellanos, et al., 2014; Premoli, Rivolta, et al., 2014; Salavati, Daskalakis, et al., 2018; Salavati, Rajji, et al., 2018; Werhahn et al., 1999; Ziemann et al., 1996), often comparing baclofen to placebo (McDonnell et al., 2006) or placebo and other active compounds with a different mechanism of action (i.e., dextromethorphan, L-dopa, and rivastigmine (Hui et al., 2020; Salavati, Daskalakis, et al., 2018; Salavati, Rajji, et al., 2018); diazepam (Müller-Dahlhaus et al., 2008; Premoli et al., 2017, 2018; Premoli, Castellanos, et al., 2014; Premoli, Rivolta, et al., 2014); other antiepileptic drugs (Ziemann et al., 1996)). For a summary, see Table 1.

$GABA_BR$ agonism: baclofen

As the only selective $GABA_BR$ agonist approved in humans, baclofen has been widely used as an off-label treatment in AUD (de Beaurepaire et al., 2019). Despite the clinical evidence of its efficacy in severe AUD (Addolorato et al., 2007; Agabio et al., 2018; Garbutt et al., 2021; Pierce et al., 2018), the mechanism of action and the optimal dose needed to treat AUD remain unclear. Eleven studies evaluated neurophysiological correlates of baclofen administration in healthy subjects. In all of these studies, baclofen 50 mg was administered orally, and its effects were assessed 60 (Hui et al., 2020; Salavati, Daskalakis, et al., 2018; Salavati, Rajji, et al., 2018) or 90 min (McDonnell et al., 2006, 2007; Müller-Dahlhaus et al., 2008; Premoli et al., 2017, 2018; Premoli, Castellanos, et al., 2014; Premoli, Rivolta, et al., 2014), and in one case at 2, 5, and 24 h after drug administration (Ziemann et al., 1996).

GABAergic neurotransmission

Consistent with its role as a $GABA_BR$ agonist, baclofen reliably enhanced LICI. Specifically, LICI of the motor cortex was found to be enhanced by baclofen administration compared to both placebo (McDonnell et al., 2006, 2007) and diazepam (Müller-Dahlhaus et al., 2008; Table 1). Additionally, baclofen was found to enhance LICI-induced contralateral N45 and ipsilateral N100 TEPs in the motor cortex, as well as the P180 component of TEPs in frontal and right-central regions (Premoli, Rivolta, et al., 2014). These findings suggest an overall enhancement of inhibitory cortical activity. Moreover, baclofen increased the N100 component of the TEPs after spTMS (Premoli et al., 2018; Premoli, Castellanos, et al., 2014). Also, LICI over the left DLPFC was enhanced after baclofen administration (Salavati, Rajji, et al., 2018). However, these effects showed high interindividual variability, with some subjects showing opposite effects of LICI suppression after baclofen intake (Premoli, Rivolta, et al., 2014).

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TABLE 1 Effects of drugs with specific effects on GABA$_B$Rs on cortical excitability.

Authors (year) (ref.)	Study design	Sample	Experimental manipulation	Neurophysiological assessment	Site	TMS protocol	Results
Müller-Dahlhaus et al. (2008)	Randomized, double-blind, PBO-controlled, cross-over study	HC: 8 (5 M) Age: 27.6 (2.5)	BAC 50 mg DZP: 20 mg PBO	TMS-EMG at baseline and 90 min ADI and after	M1	SICI: 3 ms ISI LICI: intensity = inhibition 50%, 100 ms ISI, SIHI: 12 ms ISI	BAC vs. diazepam: enhanced LICI, no changes RMT
McDonnell et al. (2006)	Randomized, double-blind, PBO-controlled, cross-over study	HC: 9 (4 M) Age: 21–41	BAC: 50 mg PBO	TMS-EMG at baseline and 90 min ADI Two sessions at least 1 week apart	M1	LICI: 120%RMT, 100 ms ISI SICI: 3 ms ISI	BAC vs. PBO: suppressed SICI, enhanced LICI, no changes RMT
McDonnell et al. (2007)	Randomized, double-blind, PBO-controlled, cross-over study	HC: 7 (3 M) Age: 28 (7.9)	BAC: 50 mg PBO	TMS-EMG at baseline and 90 min ADI Two sessions at least 1 week apart	M1	LICI: 120%RMT, 100 ms ISI SICI: 3 ms ISI PAS: 0.25 Hz TMS left M1 + median nerve	BAC vs. PBO: no changes RMT, enhanced LICI, trend towards suppressed SICI, reduced PAS-induced LTP-like plasticity (6/7 subs, LTP → LTD)
Ziemann et al. (1996)	Randomized, double-blind, cross-over study	HC: 5–8 Age: 28.1 (4)	VGB: 2000 mg GBP: 1200 mg BAC: 50 mg CBZ: 600 mg LTG: 300 mg LSG: 1000 mg	TMS-EMG at baseline + 6, 24, 48, 96 h post VGB 2, 5, 24 h post GBP, BAC, LTG, LSG 2, 5, 24, 48, 96 h post CBZ	M1	ICF/SICI: 95% AMT—1 mV, 1–30 ms CSP: 110%–140% AMT	VGB, BAC: no changes RMT, suppressed ICF BAC: enhanced SICI
Werhahn et al. (1999)	Randomized, within subjects study	HC: 8 (6 M) Age: 31.7 (25–41 range)	TGB: 5–10–15 mg	TMS-EMG at baseline and 90 min ADI	M1	SICI: 70% RMT + 1 mV, 3 ms ISI ICF: 70% RMT + 1 mV, 10 ms ISI LICI: 130% RMT, 160 ms ISI CSP: 130% RMT	TGB: suppressed SICI, enhanced LICI, increased ICF, prolonged CSP (dose-dep), no changes RMT
Darmani et al. (2019)	Randomized, double-blind, PBO-controlled, cross-over study	HC: 15 (only M) Age: 28 (2.6)	PBO TGB: 15 mg CBZ: 600 mg Brivaracetam: 100 mg	TMS-EEG at baseline—after 150 min ADI Four sessions, 1 week apart	M1	SICI: 50%–100% RMT + 1 mV, 2 ms ISI	TGB: no changes RMT, no modulation of any TEP component, increased delta, theta, alpha and beta (spontaneous oscillatory power)
Salavati, Rajji, et al. (2018)	Randomized, double-blind, PBO-controlled, cross-over study	HC: 13 (9 M) Age: 31.3 (10.5)	BAC: 50 mg (1 h) DXT: 150 mg (3 h) L-DOPA: 100 mg (1 h) RVS: 3 mg (2 h) PBO	TMS-EEG at baseline—drug peak	Left DLPFC	LICI 100: 120%RMT, 100 ms ISI, 5 s ITI	BAC vs. other drugs: enhanced LICI over the left DLPFC
Salavati, Daskalakis, et al. (2018)	Randomized, double-blind, PBO-controlled, cross-over study	HC: 13 (9 M) Age 31.3 (10.5)	BAC: 50 mg (1 h) DXT: 150 mg (3 h) L-DOPA: 100 mg (1 h) RVS: 3 mg (2 h) PBO	TMS-EEG at baseline—drug peak PAS (180 pairs of PNS + TMS 0.1 HZ)	Left DLPFC (F5, F6, F7)	PAS-induced LTP: CEA at 0, 17, 34 and 60 min post-PAS/ CEA pre-PAS	BAC vs. other drugs: no effect of on PAS

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TABLE 1 (Continued)

Authors (year) (ref.)	Study design	Sample	Experimental manipulation	Neurophysiological assessment	Site	TMS protocol	Results
Hui et al. (2020)	Randomized, double-blind, PBO-controlled, cross-over study	HC: 12 (9 M) Age: 31.3 (10.5)	BAC: 50 mg (1 h) DXT: 150 mg (3 h) L-DOPA: 100 mg (1 h) RVS: 3 mg (2 h) PBO	TMS-EEG at baseline—drug peak	M1 left DLPFC	SP: 120% RMT ISP: signal propagation C3 → C4, F5 → F6	BAC vs. other drugs: reduced ISP in response to M1 stimulation
Premoli, Rivolta, et al. (2014)	Pseudo-randomized, double-blind, PBO-controlled, cross-over study	HC: 19 (only M) Age: 26.4 (3.5)	BAC: 50 mg DZP: 20 mg PBO	TMS-EEG at drug peak (90 min)	M1	LICI: 100% RMT, 100 ms ISI, 5 s ITI	BAC vs. other drugs: enhanced LICI-induced N45 contralateral and N100 ipsilateral M1, enhanced P180 in frontal and right-central regions
Premoli, Castellanos, et al. (2014)	Pseudo-randomized, double-blind, PBO-controlled, cross-over study	HC: 19 (only M) Age: 26.4 (3.5)	BAC: 50 mg DZP: 20 mg PBO	TMS-EEG at drug peak (90 mins)	M1	SP: 100% RMT, 5 s ITI	BAC vs. other drugs: increased N100, no effect on N45, other components, or oscillatory activity
Premoli et al. (2017)	Pseudo-randomized, double-blind, PBO-controlled, cross-over study (Exp. 2)	HC: 19 (only M), Age: 26.4 (3.5)	BAC: 50 mg DZP: 20 mg PBO	TMS-EEG at drug peak (90 min)	M1	SP: 100% RMT, 5 s ITI	BAC vs. other drugs: increased RMT, increased α-band synchronization 30–200 ms, decreased β-band synchronization 30–200 ms, enhanced α and β-band desynchronization 200–400 ms
Premoli et al. (2018)	Pseudo-randomized, double-blind, PBO-controlled, cross-over study	HC: 16 (only M), Age: 25.6 (4.5)	BAC: 50 mg DZP: 20 mg PBO	TMS-EEG at drug peak (90 min)	M1	SP: 70%–100% RMT SICI: 70 + 100% RMT, 2 ms ISI	BAC vs. other drugs: increased RMT and N100 component on frontal sites in both hemispheres

Abbreviations: ADI, after drug intake; AMT, active motor threshold; BAC, baclofen; BRV, brivaracetam; CBZ, carbamazepine; CEA, cortical evoked activity; CS, conditioned stimulus; CSP, cortical silent period; DLPFC, dorso-lateral prefrontal cortex; DXT, dextromethorphan; DZP, diazepam; EEG, electroencephalography; EMG, electromyography; Exp, experiment; F, females; GBP, gabapentin; HC, healthy controls; ISI, inter-stimulus interval; ISP, interhemispheric signal propagation; ITI, inter-train interval; LICI, long-interval cortical inhibition; LTP, long-term potentiation; M, males; M1, motor cortex; MEP, motor-evoked potentials; ms, milliseconds; NA, not available; PAS, paired associative stimulation; PBO, placebo; PGB, pregabalin; RMT, resting motor threshold; RVS, rivastigmine; SICI, short interval intracortical inhibition; SIHI, short-latency interhemispheric inhibition; SP, single pulse; TEP, TMS-evoked potentials; TGB, tiagabine; TMS, transcranial magnetic stimulation; TS, test stimulus; VGB, vigabatrin.

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Results were less consistent when examining other measures of cortical inhibition. For example, the CSP was tested only in one of the studies and was not affected by baclofen administration (Ziemann et al., 1996). SICI was suppressed (McDonnell et al., 2006, 2007) or unaltered (Müller-Dahlhaus et al., 2008) 90 min after baclofen administration but increased after 2 and 5 h (Ziemann et al., 1996). Moreover, SICI was increased bilaterally on frontal sites 90 min after baclofen administration (Premoli et al., 2018). Although the different timings of assessment may have contributed to this variability, SICI response to baclofen administration also showed high interindividual variability in all studies (Table 1).

Other neurophysiological measures of interest The effects of baclofen on motor cortical excitability varied across studies, with most reporting no changes between 90 min and 5 h postadministration (McDonnell et al., 2006, 2007; Müller-Dahlhaus et al., 2008; Ziemann et al., 1996), and only two studies found increased RMT 90 min after baclofen administration (Premoli et al., 2017, 2018).

In terms of intracortical facilitation, baclofen significantly suppressed ICF in the motor cortex at 2 and 5 h after administration (Ziemann et al., 1996) and reduced LTP-like plasticity induced by paired associative stimulation (PAS), often shifting into depression rather than facilitation (McDonnell et al., 2007). Notably, in the majority of subjects, LTP was not only reduced but shifted into depression (McDonnell et al., 2007). Additionally, baclofen decreased early beta oscillations and induced desynchronization in alpha and beta bands during later phases, indicating a possible shift toward less coordinated neural activity due to altered inhibitory-excitatory balance (Premoli et al., 2017). One study also assessed TMS-evoked interhemispheric signal propagation (ISP), finding that baclofen uniquely reduced ISP over the motor cortex, although this effect was not consistent across the DLPFC due to interindividual variability (Hui et al., 2020).

Other GABAergic drugs

Tiagabine blocks GAT-1, the primary transporter responsible for clearing GABA from the synaptic cleft and extracellular space. By doing so, it increases extracellular GABA levels, particularly in the forebrain and hippocampus. It is primarily used as an antiepileptic drug acting by enhancing the inhibitory effects of GABA in the CNS. Its effects are to a large extent blocked by selective GABA$_B$R antagonists, suggesting a possible role of GABA$_B$R in its mechanism of action (Ipponi et al., 1999), but there is contrasting evidence (Thompson & Gahwiler, 1992). In line with the hypotheses of a GABA$_B$R-related mechanism of action, in a randomized, within-subject study, tiagabine (5–15 mg) did not induce any change in RMT but suppressed SICI, increased LICI, and dose-dependently prolonged CSP, while increasing ICF 90 min after drug intake (Werhahn et al., 1999). Notably, no modulation of any TEP components was observed 150 min after the administration of 15 mg of tiagabine (vs. placebo) (Darmani et al., 2019).

While the effects of tiagabine might be attributed to an increased release of GABA in the central nervous system rather than a direct effect on GABA$_B$R, vigabatrin, an antiepileptic drug known to inhibit the GABA-transaminase and therefore increase GABA concentrations in the CNS (Petroff et al., 1996), showed no effects on the motor cortical excitability between 6 and 96 h after drug administration (Ziemann et al., 1996). This finding suggests that GABA concentrations may not be the sole factor influencing the neurophysiological effects observed with tiagabine. However, the evidence remains limited and varies across studies, which complicates the ability to draw definitive conclusions.

Changes in cortical excitability in response to acute alcohol intake and chronic alcohol misuse

The literature searches regarding the effects of alcohol consumption on cortical excitability identified a total of 97 publications and 44 clinical trial registrations. After screening titles and abstracts, 19 publications were selected (Figure 1). Following full-text reviews, 14 papers were included, with an additional two studies added through manual search. Among these 16 studies, nine focused on TMS-EMG and TMS-EEG correlations related to acute alcohol intake (Table 2), two examined TMS-EEG correlates of heavy drinking (Table 3), and five explored TMS-EMG and TMS-EEG correlates of AUD (see Table 3).

Acute alcohol administration

The effects of acute alcohol administration were assessed in healthy individuals (sample sizes 6–20) using within-subject, pre-/postdesigns (Conte et al., 2008; Hamel et al., 2022; Kähkönen et al., 2001, 2003; Kähkönen & Wilenius, 2007; Loheswaran et al., 2017, 2018; Ziemann et al., 1995) or over two sessions, in a randomized, placebo-controlled, cross-over design (Hamel et al., 2022; Hoppenbrouwers et al., 2010; Loheswaran et al., 2017, 2018). Acute alcohol effects in healthy subjects were evaluated before and 30 min (Conte et al., 2008; Hoppenbrouwers et al., 2010; Kähkönen et al., 2001, 2003; Kähkönen & Wilenius, 2007; Loheswaran et al., 2017, 2018; Ziemann et al., 1995), or before and 15, 45, 75, and 105 min after acute alcohol administration (Hamel et al., 2022). TMS was delivered over the primary motor cortex (Conte et al., 2008; Hamel et al., 2022; Hoppenbrouwers et al., 2010; Kähkönen et al., 2001; Kähkönen & Wilenius, 2007; Ziemann et al., 1995) or the left prefrontal cortex (Kähkönen et al., 2003; Loheswaran et al., 2017, 2018). Main results have been summarized in Table 2 and details about the alcohol administration procedures are available in Appendix S1: Results.

GABAergic neurotransmission

In terms of TMS-EMG (Conte et al., 2008; Hamel et al., 2022; Ziemann et al., 1995), the main effects of acute alcohol intake on

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TABLE 2 Cortical excitability in acute alcohol intoxication.

Authors (year)	Study design	Sample	Alcohol-related diagnosis	Experimental manipulation	Neurophysiological assessment	Site	TMS protocol	Results
Ziemann et al. (1995)	Within-subjects study	HC: 6 (4 M), 26.8 (3.6) years		Acute alcohol intake (0.7 L bottle of red wine [12 vol %])	TMS-EMG baseline and 30 min after alcohol	Left M1	CSP: 110%–140%AMT ICF, SICI: ISI range 1–30 ms, CS 95% AMT	Alcohol: prolonged CSP duration (dose-dep)
Conte et al. (2008)	Exp 1: within-subjects study Exp2: case–control study	HC: 10 (7 M), 50 (4) years AUD: 13 (11 M), 49 (6) years	Chronic alcoholism (DSM-IV) CIWA = 2.8 (range 0–8)	Acute alcohol intake (ethanol 24 g M, 12 g F)—HC only	TMS-EMG baseline and 30 min after alcohol BrAC = 0 in AUD	Left M1	CSP: 120% RMT, 10 sp. 5 Hz × 10 SICI: 80%–120% RMT, 2 ms ISI ICF: 80%–120% RMT, 10 ms ISI	Alcohol (HC only): prolonged CSP duration AUD (vs. HC): prolonged CSP duration, decreased MEP
Hamel et al. (2022)	Randomized, PBO-controlled, cross-over design	HC: 20 (11 M), 22 (0.9) years	AUDIT <8	Acute alcohol intake (1 mL/kg M, 0.85 mL/kg F; max BrAC = 0.095%) vs. PBO	TMS-EMG at baseline and 15, 45, 75 and 105 min after alcohol	Left M1	SICI: CS 70%—TS 120% RMT, 2 ms ISI ICF: CS 70%—TS 120% RMT, 10 ms ISI	Alcohol: prolonged CSP duration
Hoppenbrouwers et al. (2010)	Within-subject study	HC 22 (10 M), 22.5 (0.8) years	AUDIT <8	Acute alcohol intake (BAC: 0.05%) vs. PBO (peppermint oil)	TMS-EMG baseline and 30 min after alcohol	Concurrent Left and right M1	sp-TMS: 120% RMT spTMS over left or right M1 TCI: left + right M1, 120%RMT	Alcohol (vs. PBO): reduced MEP amplitude (M + F), reduced TCI (F, not M)
Kähkönen et al. (2001)	Within-subject study	HC: 10 (only M), 24 (3.7) years		Acute alcohol intake (0.8 g/kg to all subjects)	TMS-EEG before and after alcohol	M1	sp-TMS: 120 pulses, ISI: 1.5–2.5 s, 100% RMT Active TMS (*n*: 10), control condition (*n*: 6)	Alcohol: change in GMFA after real TMS in left parietal and right frontal areas
Kähkönen et al. (2003)	Within-subject study	HC: 9 (only M), 25 (3.7) years		Acute alcohol intake (0.8 g/kg to all subjects)	TMS-EEG before and after alcohol	Left DLPFC	sp-TMS: 120 pulses, ISI: 1.5–2.5 s, 100% RMT Active TMS (*n*: 10) vs. control (*n*: 6)	Alcohol: reduced GMFA at 30–130 ms after TMS (anterior electrodes)
Kähkönen and Wilenius (2007)	Within-subject study	HC: 10 (only M), 25 (3.7)		Acute alcohol intake (0.8 g/kg to all subjects)	TMS-EEG baseline, 30 min after alcohol	M1	sp-TMS: 120 pulses, ISI: 1.5–2.5 s, 100% RMT Active TMS (*n*: 10) vs. control (*n*: 6)	Alcohol: decreased N100 at stimulation site, contralateral sensorimotor area, and frontal electrodes
Loheswaran et al. (2018)	Randomized, PBO-controlled, cross-over study	HD: 15 (10 M), 33.4 (7.5) years	Binge drinking: >1 heavy drinking episode/month (NIAAA Guidelines, 2004)	Acute alcohol intake (95% USP alcohol mixed in a ratio 1:5 to orange juice) vs. PBO (0.2 mL vodka)	TMS-EEG pre- and postalcohol	M1, Left DLPFC (F5)	sp-TMS: 100 pulses, 0.1 Hz, 120% RM	Alcohol (vs. PBO): reduced N100 amplitude in response to left DLPC stimulation
Loheswaran et al. (2017)	Within-subject, PBO-controlled randomized cross-over	HD: 15 (10 M), 33.4 (7.5) years	Binge drinking: >1 heavy drinking episode/month (NIAAA Guidelines, 2004)	Acute alcohol intake (95% USP alcohol mixed in a ratio 1:5 to orange juice) vs. PBO (0.2 mL vodka)	TMS-EEG, pre- and postalcohol	M1, left DLPFC (F5)	RMT, MEP (peak-to-peak 1 mV) PAS: 180 pulses, 0.1 Hz CEA: 100 pulses, 0.1 Hz, pre- and post-PAS	Beverage-by-time interaction on CEA Alcohol (vs. PBO): decreased DLPFC PAS-induced neuroplasticity decreased post-PAS potentiation of theta-gamma coupling

Abbreviations: AMT, active motor threshold; AUD, alcohol use disorder; AUDIT, alcohol use disorders identification test; AUDIT-c, AUDIT concise; CEA, cortical evoked activity; CIWA, clinical institute withdrawal assessment for alcohol; CSP, cortical silent period; DLPFC, dorso-lateral prefrontal cortex; EEG, electroencephalography; EMG, electromyography; Exp, experiment; F, females; GMFA, global mean field amplitude; HC, healthy controls; HD, heavy drinkers; Hz, hertz; ICF, intracortical facilitation; ISI, inter-stimulus interval; ITI, inter-train interval; LICI, long-interval cortical inhibition; M, males; M1, motor cortex; MEP, motor-evoked potentials; ms, milliseconds; NA, not available; PAS, paired associative stimulation; PBO, placebo; RMT, resting motor threshold; SICI, short interval intracortical inhibition; sp, single pulse; TCI, trans-callosal inhibition; TMS, transcranial magnetic stimulation.

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TABLE 3 Cortical excitability in chronic alcohol consumption and alcohol use disorder.

Authors (year)	Study design	Sample	Alcohol-related diagnosis	Experimental manipulation	Neurophysiological assessment	Site	TMS protocol	Results
Kaarre et al. (2018)	Case–control study	HC: 25 (12 M) HD: 27 (11 M)	HC: AUDIT <2 HD: AUDIT-c 21.1 (3.9)		TMS-EEG	M1	150 pulses, 90% RMT, 3–5 ISI + white noise with TMS clicks	HD (vs. HC): higher GMFP activity between 54 and 74 ms after TMS
Juntunen et al. (2023)	Case–control study	HC: 21 (12 F), 24.8 (1.4) years HD: 26 (16 F), 25.6 (1.3) years	HC: AUDIT <2 HD: AUDIT-c 6.4 (2.0)		TMS-EEG	Left M1 Frontal—AP1 Central—AP2 Parietal—AP3	RMT spTMS: 150 pulses, 90% RMT, 3–5 s ISI → N45 (35–60 ms after TMS)	HD (vs. HC): Increased N45—significantly larger frontally (AP1). Lower cortical thickness (left angular gyrus, right frontal and left temporal) inversely correlated with N45
Nardone et al. (2010)	Three-arms, case–control study	AWS: 13 (8 M), 48.4 years AUD: 12 (8 M), 47.6 years HC: 15 (8 M), 46.8 years	AWS (DSM-IV, CIWA) AUD (DSM-IV)		TMS-EMG	Left M1	RMT, AMT CMCT SICI: 90% AMT-1 mV, 2–3 ms ISI ICF: 90% AMT-1 mV, 7–10 ms ISI	AWS (vs. AUD and HC): increased ICF and a trend towards a decreased SICI No significant difference in RMT, AMT, CMCT and CSP duration
Peng et al. (2021)	Case–control study	AUD: 19 (M), 51 (1.5) HC: 14 (M), 53.8 (2.4) years	AUD (ICD-10) Michigan alcoholism screening test ≥6		TMS-EMG	Left M1	RMT LICI: 120%–130% RMT, 100 ms ISI	AUD (vs. HC): decreased LICI-induced inhibition
Quoilin et al. (2023)	Case–control study	AUD: 15 (12 M), 45.6 (2.1) HC: 13 (7 M), 46.0 (3.0)	AUD (DSM-5) (severe: 13, moderate: 2) detox program (18–20 days abstinent) HC: AUDIT <8 M, <7 F	Instructed-delay choice RT task	TMS-EMG	Bilateral M1	RMT LICI: 120% RMT, 100 ms ISI SICI: 80%–120% RMT, 2 ms ISI ICF: 80%–120% RMT, 10 ms ISI spTMS during task: 120% RMT	AUD (vs. HC): increased RMT, decreased suppression of MEPs in task-irrelevant muscles
Naim-Feil et al. (2022)	Case–control study	AUD: 11 (7 M), 32 (6) HC: 16 (8 M), 40 (14)	AUD: 2 years after detox TLFB OCDS SADQ		TMS-EEG	M1 and bilat. DLPFC (AF4-F4, AF3-F3)	RMT, AMT spTMS: 1 mV, 3 s ITI LICI: 1 mV, 100 ms ISI	AUD (vs. HC): alteration of global network response to left DLPFC LICI
Naim-Feil et al. (2016)	Case–control study	AUD: 12 (8 M), 40.1 (13.4) HC: 14 (7 M), 31.1 (5.3)	AUD: 2 years after detox TLFB OCDS SADQ		TMS-EEG	M1 DLPFC (right: AF4-F4, left: AF3-F3)	RMT, AMT, CSP: 125% AMT, 20 p SICI: 90% AMT—1 mV, 2 ms ISI ICF: 90% AMT-1 mV, 15 ms ISI LICI: 1 mV, 100 ms ISI	AUD (vs. HC): reduced RMT, suppressed LICI right and left DLPC

Abbreviations: AMT, active motor threshold; AUD, alcohol use disorder; AUDIT, alcohol use disorders identification test; AUDIT-c, AUDIT concise; CIWA, clinical institute withdrawal assessment for alcohol; CMCT, central motor conduction time; CSP, cortical silent period; DLPFC, dorso-lateral prefrontal cortex; EEG, electroencephalography; EMG, electromyography; Exp, experiment; F, females; GMFP, global mean field power; HC, healthy controls; HD, heavy drinkers; Hz, hertz; ICF, intracortical facilitation; ISI, inter-stimulus interval; ITI, inter-train interval; LICI, long-interval cortical inhibition; M, males; M1, motor cortex; MEP, motor-evoked potentials; ms, milliseconds; NA, not available; OCDS, Obsessive-Drinking Scale; PBO, placebo; RMT, resting motor threshold; SADQ, Severity of Alcohol Dependence Questionnaire; SICI, short interval intracortical inhibition; SP, single pulse; TCI, trans-callosal inhibition; TLFB, timeline follow back; TMS, transcranial magnetic stimulation.

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GABAergic neurotransmission were observed on the CSP, which was prolonged after alcohol intake, suggesting increased cortical inhibition mediated by presynaptic $GABA_BR$ (Table 2). Although measured, SICI and LICI did not show any specific effects of acute alcohol administration (vs. placebo) at any time point. Nevertheless, SICI was positively associated with alcohol-induced feelings of sedation (Hamel et al., 2022), and CSP showed a positive correlation with the activating effects of alcohol (Hamel et al., 2022), suggesting cortical inhibitory circuits are correlated with alcohol-induced symptoms.

One single study evaluated the effects of alcohol (vs. placebo) on transcallosal inhibition (TCI; Hoppenbrouwers et al., 2010), the process by which one hemisphere of the brain inhibits the activity of the other, mediated by inhibitory interneurons using $GABA_BR$ neurotransmission (Daskalakis et al., 2002). Notably, a significant alcohol-induced reduction in TCI was observed in females (all taking oral contraceptives) but not in males after acute alcohol intake (Hoppenbrouwers et al., 2010).

In terms of TMS-EEG measures, the amplitude of the N100 after TMS pulses delivered on either M1 or DLPFC was reduced by acute alcohol intake (Kähkönen et al., 2001, 2003; Kähkönen & Wilenius, 2007; Loheswaran et al., 2018). Also, a reduction in the early components was observed after M1 stimulation (Kähkönen et al., 2001), suggesting an imbalance in GABAergic/glutamatergic dynamics.

Other neurophysiological parameters of interest Notably, acute alcohol intake did not alter short-term neuroplasticity of the motor cortex in healthy subjects, with no change in MEP facilitation induced by rTMS stimulation (5 Hz-rTMS) (Conte et al., 2008), nor in any other cortical or peripheral component of motor activation (Conte et al., 2008; Hamel et al., 2022). However, one study using cortical evoked activity measures—assessing responses to 100 TMS pulses before and after paired associative stimulation (PAS)—found that alcohol impaired long-term potentiation in prefrontal areas (Loheswaran et al., 2017). Specifically, alcohol reduced PAS-induced neuroplasticity in the DLPFC and decreased mean and maximum theta-gamma coupling potentiation following PAS (Loheswaran et al., 2017).

Chronic alcohol use

Most studies investigating the neurophysiological effects of chronic alcohol consumption involved small sample sizes (11–27 patients with alcohol-related diagnoses vs. 9–25 controls) in case–control study designs (Conte et al., 2008; Juntunen et al., 2023; Kaarre et al., 2018; Naim-Feil et al., 2016, 2022; Nardone et al., 2010; Peng et al., 2021; Quoilin et al., 2023). For a summary, see Table 3.

Two TMS-EEG studies, both based on one larger cohort but including two different datasets, compared subjects with long-term binge drinking and heavy alcohol use to a matched sample of controls with little or no alcohol use (Juntunen et al., 2023; Kaarre et al., 2018). However, alcohol history was only assessed through a shortened 3-item version of the Alcohol Use Disorder Identification Test (AUDIT; Saunders et al., 1993) and heavy and social drinkers were not separated on the basis of standardized cut-offs but according to the scores distribution in the sample. Alcohol intoxication on the day of the study was excluded using specific questionnaires (Juntunen et al., 2023; Kaarre et al., 2018).

Six studies included AUD patients and compared them to healthy controls (Conte et al., 2008; Naim-Feil et al., 2016, 2022; Nardone et al., 2010; Peng et al., 2021; Quoilin et al., 2023). Notably, alcohol-related diagnosis varied from DSM-IV alcohol dependence (Conte et al., 2008; Naim-Feil et al., 2016, 2022; Nardone et al., 2010), DSM-5 moderate-to-severe AUD as diagnosed (Quoilin et al., 2023), and ICD-10 criteria combined with a Michigan alcoholism screening test equal to or above 6 (Peng et al., 2021). Also, two studies recruited patients within 2 years after successfully completing a detoxification program (Naim-Feil et al., 2016, 2022), and one more study included patients between day 18 and 20 of the detoxification program, without the need for any medication for withdrawal symptoms (Quoilin et al., 2023). One single study evaluated AUD patients during withdrawal (with average withdrawal symptoms duration of 1.7 ± 1.3 days) and AUD patients without withdrawal symptoms (Nardone et al., 2010). Two studies included subjects with active diagnosis who did not undergo treatment nor detoxification (Conte et al., 2008; Peng et al., 2021). Although alcohol diagnosis criteria were not homogeneous, for the benefit of the readers, in the current manuscript, subjects with any alcohol-related diagnosis are referred to as AUD patients.

GABAergic neurotransmission

Heavy drinkers exhibited higher global mean field potential (GMFP) activity in an early time window (54–74 ms post-TMS) (Kaarre et al., 2018) and increased N45 amplitudes (Juntunen et al., 2023; Kaarre et al., 2018) in response to TMS compared to controls, indicating heightened cortical excitability—although typical TEP components were recorded in both groups (Kaarre et al., 2018). Notably, an inverse correlation between cortical thickness and N45 amplitudes was observed in heavy drinkers, who also presented reduced cortical thickness at the level of the left angular gyrus, the right frontal cortex and left temporal cortex (Juntunen et al., 2023). Topographical differences were also observed in P60 and N100 components (Kaarre et al., 2018), suggesting alterations in cortical connectivity.

Patients with active AUD demonstrated reduced efficacy in inhibitory protocols, showing less suppression of MEPs in both LICI (Peng et al., 2021) and CSP (Conte et al., 2008), with less effective MEP suppression in both inhibitory protocols. Following 5 Hz-rTMS over the motor cortex, AUD patients exhibited increased CSP duration and MEP inhibition, reflecting heightened cortical inhibition contrary to the facilitation seen in healthy individuals (Conte et al., 2008).

These results were, however, not replicated in AUD patients during withdrawal (Nardone et al., 2010). Although a trend toward a decreased SICI was observed under these conditions, these patients did not differ from nonwithdrawing AUD and healthy controls in terms of other inhibitory measures (Nardone et al., 2010). Similarly, AUD patients during early (approx. 20 days) detoxification without

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any withdrawal symptoms did not show any significant alteration of intracortical inhibition (Quoilin et al., 2023).

Nevertheless, patients undergoing more prolonged detoxification showed a significant suppression of LICI in both the right and left DLPFC compared to healthy controls, although no difference in frontal response to sp-TMS was observed, and LICI was preserved in the motor cortex (Naim-Feil et al., 2016). Also, in terms of network connectivity, these patients showed a broadly altered global network response to inhibitory pp-TMS applied to the left DLPFC compared to healthy controls (Naim-Feil et al., 2022). Notably, although measures of alcohol dependence were related to bilateral sp-TMS network response measures, no correlations were observed between network metrics and cortical inhibition (Naim-Feil et al., 2022).

Other neurophysiological measures of interest Patients with current AUD showed similar corticomotor excitability (RMT and MEP amplitude) to controls (Conte et al., 2008; Nardone et al., 2010; Peng et al., 2021), and withdrawing patients did not differ significantly from nonwithdrawing AUD or healthy subjects (Nardone et al., 2010). However, recently detoxified AUD patients exhibited increased motor-cortical excitability, with steeper MEP recruitment curves (Quoilin et al., 2023), and a significant RMT reduction after 2 years of detoxification (Naim-Feil et al., 2016). During a choice reaction task, these long-term abstinent patients showed a trend toward decreased suppression of MEPs in task-irrelevant muscles—more pronounced in the nondominant hand—indicating impaired inhibitory control (Quoilin et al., 2023).

Additionally, intracortical facilitation was elevated in withdrawal patients compared to both nonwithdrawing AUD individuals and controls; riluzole administration reversed this effect (Nardone et al., 2010), supporting the role of glutamatergic dysfunction in alcohol withdrawal (Hermann et al., 2012).

DISCUSSION

Disruptions in GABAergic signaling have long been implicated in AUD (Colombo et al., 2004), with GABA$_B$R recently identified as significant contributors to the development and persistence of this condition in preclinical models (Augier et al., 2018; Domi et al., 2023). Activation of GABA$_B$R has thus emerged as a promising neurobiological target for novel therapeutic interventions. However, a significant obstacle is the absence of reliable, noninvasive biomarkers capable of accurately monitoring GABA$_B$R engagement in humans, which limits our capacity to assess target engagement during alcohol consumption and pharmacological treatment effectively.

Among different neurophysiological measures of cortical inhibition, enhanced LICI emerged as a key effect of GABA$_B$R agonism, as demonstrated by baclofen and tiagabine administration (for a summary, see Table 4 and Figure 2). However, LICI has never been assessed in the context of acute alcohol intake and rarely tested in studies evaluating the effects of chronic alcohol misuse. From the scarce evidence collected, LICI on the motor cortex (assessed through TMS-EMG) seems to be impaired in patients with an active AUD versus healthy controls, but these alterations are undetectable in patients during early detoxification and persist unaltered during more prolonged abstinence. However, responses from TMS delivered over the bilateral prefrontal cortex suggest long-term consequences of AUD may be specific to certain brain regions, with impaired bilateral inhibition over the frontal regions in 2-year abstinent AUD patients. However, no study evaluated the relationship between LICI and AUD's severity or duration. So, whether these long-term effects vary on the basis of the duration of illness or measures of alcohol exposure remains unknown.

Although the evidence is limited, parameters such as CSP and N100 show promise as markers related to GABA$_B$R activity. Post-TMS N100 amplitude increases after administration of GABA$_B$R agonists such as baclofen and tiagabine, and correlates positively with GABA$_B$R-mediated inhibition in deeper cortical layers and long-range cortical interactions (Premoli, Castellanos, et al., 2014). And although CSP has shown inconsistent effects being increased after tiagabine but unchanged by baclofen, CSP duration is believed to indicate prolonged inhibition potentially mediated by presynaptic GABA$_B$R (Chu et al., 2008). In the context of alcohol consumption, a few studies tested for CSP or N100 in the context of AUD. In fact, although a reduction in N100 amplitude and prolonged CSP have been observed following acute alcohol intake in healthy subjects and binge drinkers, data in chronic alcohol use are lacking.

Overall, the reviewed literature supports the hypothesis that GABA$_B$R are involved in the neurotransmission imbalances induced by both acute and chronic alcohol intake, with potential regional differences that warrant further investigation. Notably, neurophysiological parameters associated with GABA$_B$R function—such as LICI, N100, and CSP—are affected in the context of alcohol use, whereas measures primarily reflecting GABA$_A$ receptor activity—such as SICI—appear unaffected. This is consistent with findings that alcohol exposure induces transient plastic changes in GABA$_A$R subunit levels, composition, and localization, which may not directly impact SICI (Olsen & Liang, 2017). The findings reviewed here imply that chronic alcohol exposure may impair the overall inhibitory tone, with this effect being related to GABA$_B$R functioning. Importantly, some alcohol-induced neurophysiological changes appear to be reversible following long-term detoxification programs. However, it is essential to note that GABA$_B$R activation in the prefrontal cortex remains impaired even after 2 years of successful abstinence and clinical recovery (Naim-Feil et al., 2016, 2022), indicating long-lasting changes in specific regions.

Our review also highlights significant gaps in current literature and underscores important avenues for future research. First, no studies have yet examined how these neurophysiological alterations relate to AUD severity, duration, or any other clinical parameter. Furthermore, long-term, prospective monitoring of these measures—particularly in relation to treatment progress or relapse—is lacking. Moreover, the limited number of studies involving AUD patients and the high variability in AUD definition are notable limitations, restricting the extent to which these findings can be generalized to the AUD population. From a study design perspective,

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TABLE 4 Summary of TMS-EMG correlates of GABAergic drugs and alcohol consumption.

References	MEP	RMT	CSP	SICI	LICI	ICF	Gender	Condition
Changes in cortico-motor excitability in response to baclofen and other GABAergic drugs administration								
Müller-Dahlhaus et al. (2008)	≈	≈		≈	↑		5 M, 3 F	Baclofen 50 mg
McDonnell et al. (2006)	≈	≈		↓	↑		4 M, 5 F	Baclofen 50 mg
McDonnell et al. (2007)	≈	≈		↓	↑		3 M, 4 F	Baclofen 50 mg
Ziemann et al. (1996)	≈	≈	≈	↑		↓		Baclofen 50 mg
Ziemann et al. (1996)	≈	≈	≈	≈		↓		Vigabatrin 2000 mg
Werhahn et al. (1999)	≈	≈	↑	↓	↑	↑	6 M, 2 F	Tiagabine 5–15 mg
Changes in cortico-motor excitability in response to acute and chronic alcohol consumption								
Conte et al. (2008)	≈	≈	↑	≈		≈	7 M, 3 F	Acute alcohol intake
Ziemann et al. (1995)	≈	≈	↑				4 M, 2 F	Acute alcohol intake
Hamel et al. (2022)			↑	≈		≈	11 M, 9 F	Acute alcohol intake
Nardone et al. (2010)	≈	≈	≈	≈		≈	8 M, 4 F 8 M, 7 F	AUD
Conte et al. (2008)	↑	≈	≈	≈		≈	11 M, 2 F 7 M, 3 F	AUD
Peng et al. (2021)	≈	≈			↓		19, only M 14, only M	AUD
Nardone et al. (2010)	≈	≈	≈	↓		↑	8 M, 5 F 8 M, 7 F	Alcohol withdrawal
Quoilin et al. (2023)	↑	↓		≈	≈	≈	12 M, 3 F 7 M, 6 F	AUD—20 days after detox

Note: ≈: no significant differences, ↓: decreased, ↑: increased.

Abbreviations: AUD, alcohol use disorder; CSP, cortical silent period; HC, healthy controls; ICF, intracortical facilitation; LICI, long-interval intracortical inhibition; MEP, motor evoked potential; RMT, resting motor threshold; SICI, short-interval intracortical inhibition.

while case–control studies provide valuable insights into differences between populations, they are limited in their ability to produce prospective, causal conclusions. The generalizability of findings is further constrained by high variability in methodology and inclusion criteria across studies. TMS-EMG and TMS-EEG have been used in small-size ($N < 60$) samples to evaluate either the neurophysiological effects of directly modulating $GABA_BR$ (Table 1) and the neurophysiological alterations linked to acute (Table 2) and chronic alcohol consumption (Table 3). Also, the included studies varied considerably in demographic characteristics and, although some studies included female participants, only one explicitly evaluated the effect of gender on neurophysiological measures, indicating a need for more gender-specific research to understand potential differences in $GABA_BR$ functioning in both healthy subjects and AUD patients. Additionally, methodological discrepancies concerning TMS parameters, such as pulse frequency and choice of stimulation sites, may have contributed to some of the observed variability.

While limitations exist, this review highlights measurable differences in $GABA_BR$ functioning between individuals with AUD and healthy controls, reinforcing the potential of $GABA_BR$ as a potential therapeutic target (Maccioni & Colombo, 2019). Although baclofen's use is restricted by side effects (Garbutt et al., 2021), and positive allosteric modulators show limited efficacy in humans despite their improved side effect profile (Augier et al., 2017; Schacht et al., 2024), further research into $GABA_BR$-targeted therapies for AUD is warranted. Also, no study reported adverse effects of TMS-based assessments in AUD patients or controls, and TMS measures appear to be effective tools for assessing GABAergic function in AUD, with a potential for safe application during different phases of AUD. Future research should prioritize standardized protocols and larger, more homogeneous sample populations in order to better understand the neurophysiological underpinnings of AUD and alcohol consumption.

In conclusion, our review highlights the significance of neurophysiological measures derived from TMS-based studies in providing insights into $GABA_BR$ engagement and its possible implications for AUD. Identifying standardized neurophysiological markers may facilitate advancements in pharmacotherapies and provide insights into the complexities of GABAergic transmission in alcohol addiction. As we continue to unravel the complexities of GABAergic transmission in AUD, TMS-based neurophysiological measures could serve as objective endpoints in clinical trials, ultimately accelerating the development of targeted pharmacotherapies.

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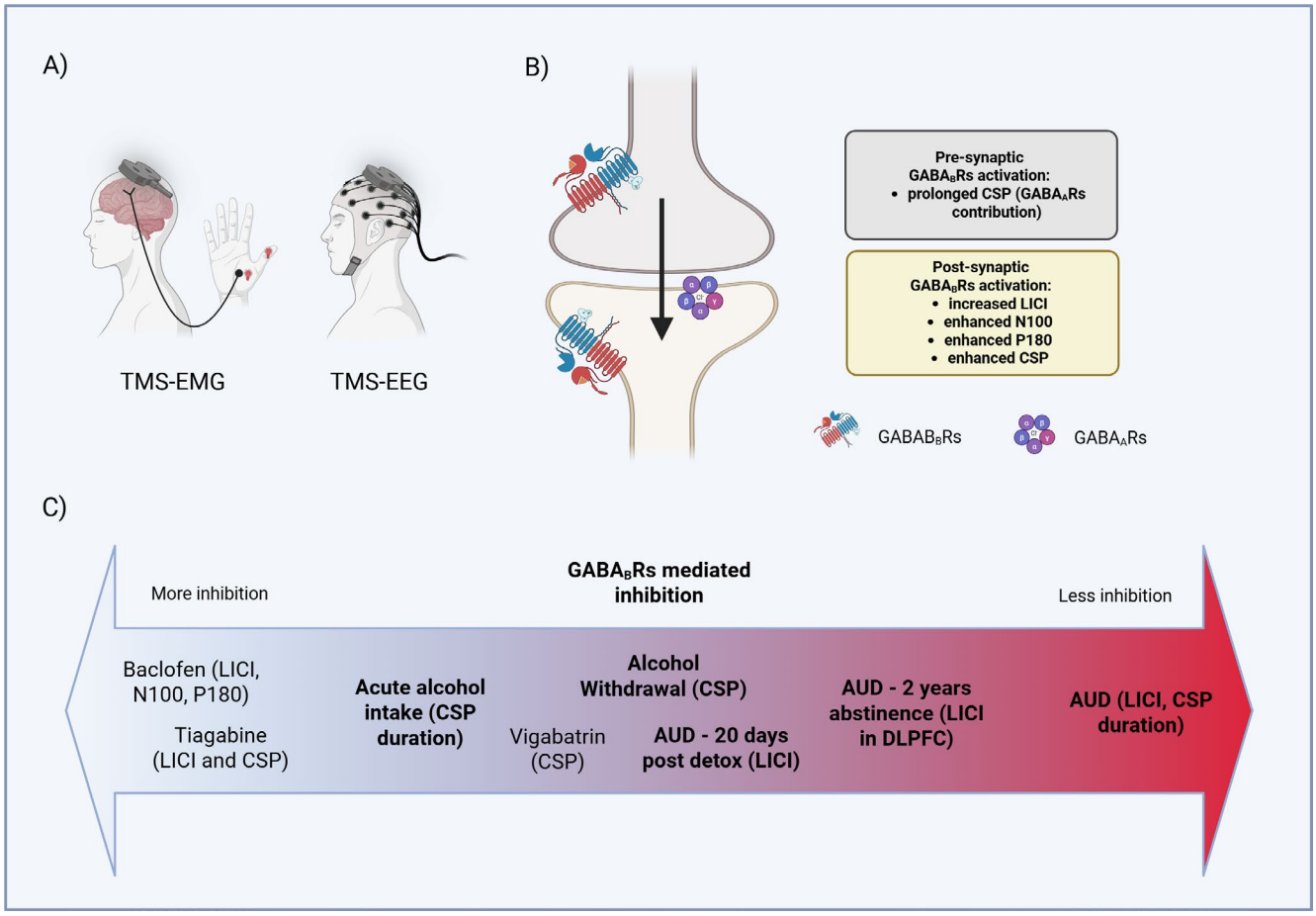

FIGURE 2 Neurophysiological biomarkers of GABA$_B$Rs mediated inhibition collected through TMS-manipulation (A) depend on both pre- and postsynaptic GABA$_B$Rs (B). These measures are enhanced by GABABRs agonists, such as baclofen and tiagabine, while the inhibitory mechanisms result to be impaired by AUD, even after detoxification (C). CSP, cortical silent period; LICI, long intracortical inhibition; N100, negative EEG-peak approx. 100 ms after TMS pulse; P180, positive EEG-peak approx. 180 ms after TMS pulse.

AUTHOR CONTRIBUTIONS

CM and MH conceptualized and designed the study. CM, ST, FM, and AC contributed to data acquisition and analysis. CM drafted the initial manuscript. CM and MH revised the manuscript for intellectual content. All authors read and approved the final version before submission.

CONFLICT OF INTEREST STATEMENT

MH has received consulting fees, research support, or other compensation from Indivior, Nordic Drugs, Camurus, BrainsWay, Aelis Farma, and Janssen Pharmaceuticals.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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