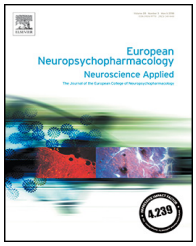
European Neuropsychopharmacology (2019) 29, 539–548

www.elsevier.com/locate/euroneuro



Effects of gamma-hydroxybutyrate on neurophysiological correlates of performance and conflict monitoring

Dario A. Dornbierer[a,e,*], Michael Kometer[b], Robin Von Rotz[a], Erich Studerus[c], Jürg Gertsch[d], M. Salomé Gachet[d], Franz X. Vollenweider[b,f], Erich Seifritz[a,f], Oliver G. Bosch[a], Boris B. Quednow[a,f]

[a] *Experimental and Clinical Pharmacopsychology, Department of Psychiatry, Psychotherapy and Psychosomatics, Psychiatric Hospital, University of Zurich, Lenggstrasse 31, CH-8032 Zurich, Switzerland*
[b] *Neuropsychopharmacology and Brain Imaging Research Unit, Department of Psychiatry, Psychotherapy and Psychosomatics, University Hospital of Psychiatry Zurich, Lenggstrasse 31, 8032 Zurich, Switzerland*
[c] *Center for Gender Research and Early Detection, Kornhausgasse 7, 4051 Basel, Switzerland*
[d] *Institute of Biochemistry and Molecular Medicine, University of Bern, Bühlstrasse 28, 3012 Bern, Switzerland*
[e] *Institute of Pharmacology and Toxicology, University of Zurich, Winterthurerstrasse 190, 8057 Zürich, Switzerland*
[f] *Neuroscience Center Zurich, University and ETH Zurich, Zurich, Switzerland*

Received 23 April 2018; received in revised form 31 January 2019; accepted 2 February 2019

KEYWORDS
Gamma-hydroxybutryrate;
GHB;
Error processing;
Performance monitoring;
Conflict monitoring;
EEG

Abstract
Performance and conflict monitoring (PM and CM) represent two essential cognitive abilities, required to respond appropriately to demanding tasks. PM and CM can be investigated using event-related brain potentials (ERP) and associated neural oscillations. Namely, the error-related negativity (ERN) represents a correlate of PM, whereas the N2 component reflects the process of CM. Both ERPs originate in the anterior cingulate cortex (ACC) and PM specifically has been shown to be susceptible to *gamma*-aminobutyric acid (GABA) A receptor activation. Contrarily, the specific effects of $GABA_B$ receptor ($GABA_BR$) stimulation on PM and CM are unknown. Thus, the effects of *gamma*-hydroxybutyrate (GHB; 20 and 35 mg/kg), a predominant $GABA_BR$

* Corresponding author at: Experimental and Clinical Pharmacopsychology, Department of Psychiatry, Psychotherapy and Psychosomatics, Psychiatric Hospital, University of Zurich, Lenggstrasse 31, CH-8032 Zurich, Switzerland.
E-mail address: dornbierer@pharma.uzh.ch (D.A. Dornbierer).

https://doi.org/10.1016/j.euroneuro.2019.02.004

agonist, on behavioral and electrophysiological correlates of PM and CM were here assessed in 15 healthy male volunteers, using the Eriksen-Flanker paradigm in a randomized, double-blind, placebo-controlled, cross-over study. Electroencephalographic (EEG) data were analyzed in the time and time-frequency domains. GHB prolonged reaction times, without affecting error rates or post-error slowing. Moreover, GHB decreased ERN amplitudes and associated neural oscillations in the theta/alpha1 range. Similarly, neural oscillations associated with the N2 were reduced in the theta/alpha1 range, while N2 amplitude was conversely increased. Hence, GHB shows a dissociating effect on electrophysiological correlates of PM and CM. Reduced ERN likely derives from a $GABA_BR$-mediated increase in dopaminergic signaling, disrupting the generation of prediction errors, whereas an enhanced N2 suggests an increased susceptibility towards external stimuli. Conclusively, GHB is the first drug reported, thus far, to have opposite effects on PM and CM, underlined by its unique electrophysiological signature.

1. Introduction

Performance and conflict monitoring (PM and CM, respectively) represent two vital cognitive processes, required to appropriately interact with a continuously changing and demanding environment. On the one hand, PM is engaged in evaluating the accordance between an ongoing action and its original intent. Thus, erroneous actions can be readily detected and behavior can be adjusted in order to improve performance in response to future events (Devinsky et al., 1995). PM is typically investigated in terms of the error-related negativity (ERN), an event-related potential (ERP) elicited in the electroencephalogram (EEG), when subjects commit errors in speeded two-choice tasks (Falkenstein et al., 2000; Gehring et al., 1995). More precisely, the ERN originates from a phase-resetting of frontomedial delta and theta oscillations and, accordingly, these oscillations were also found to be increased after error commission (Luu et al., 2004; Yordanova et al., 2004; Munneke et al., 2015).

On the other hand, CM serves in the evaluation of conflicting response alternatives, enabling a dynamic recruitment of top-down neural resources that are needed to choose the most appropriate response (Yeung et al., 2004). CM can be assessed by means of the stimulus-locked N2 ERP and associated frontal theta oscillations. Specifically, the amplitude of the N2 is thought to reflect the conflict load arising from simultaneously active response tendencies, as its amplitude was repeatedly found to increase proportionally with the strength of the conflict (Yeung et al., 2004; Cavanagh et al., 2009).

Both the ERN and the N2 reflect similar processes of a complex neural control system, with the anterior cingulate cortex (ACC) representing its core neural generator. The ACC is influenced by the striatal dopaminergic reward system and implements behavioral adjustments during PM and CM in conjunction with the dorsolateral prefrontal cortex (DLPFC) (Botvinick et al., 2001; Veen and Carter, 2002; Holroyd et al., 2004; MacDonald 2000). Importantly, the mesencephalic dopamine system (MCDS) plays a critical role in the activation of the ACC during error commission and response conflict. As proposed by the reinforcement learning theory, a "prediction error" is generated, when outcomes are worse than expected. This prediction error signal is then transmitted to the ACC via a phasic dip in the tonic activity of the MCDS, disinhibiting the ACC and thereby enabling behavioral adjustment (Holroyd et al., 2002; Schultz et al., 1997). Based on this notion of dopaminergic involvement in the generation of the ERN, many pharmacological studies have investigated the effects of drugs on PM and CM. Interestingly, while the ERN shows a high susceptibility to a wide range of pharmacological manipulations, the N2 seems to be more resistant to such interventions (Spronk et al., 2011, 2014). ERN amplitudes were found to be enhanced in subjects treated with the indirect dopamine agonist D-amphetamine, but N2 amplitudes remained unaffected (Bruijn et al., 2004). In contrast, administration of antipsychotics such as haloperidol and olanzapine – both antagonists at dopaminergic receptors – reduced ERN amplitude, but again without affecting N2 magnitude (Bruijn et al., 2006). Additionally, the involvement of *gamma*-aminobutyric acid-A receptors ($GABA_AR$) in the process of PM has been demonstrated repeatedly, as indicated by reduced ERN amplitudes after treatment with positive $GABA_AR$ modulatory benzodiazepines or the full $GABA_AR$ agonist muscimol (Riba et al., 2005; Bruijn et al., 2004; Shima 1998). Likewise, ethanol, with its modulatory effects on $GABA_A$ergic transmission, shows a blunting effect on the ERN (Spronk et al., 2014; Ridderinkhof et al., 2002). However, despite their effects on the ERN, neither benzodiazepines nor ethanol significantly affect N2 magnitude (Bruijn et al., 2004; Riba et al., 2005).

To our knowledge, no data are available that elucidate a role for $GABA_B$ergic transmission in the processes of PM and CM. Therefore, we investigated the effects of gamma-hydroxybutyrate (GHB), an endogenous short-chain fatty acid, on the behavioral and electrophysiological correlates of PM and CM in healthy volunteers. GHB has an agonistic action at $GABA_B$ and GHB receptors and its subjective and behavioral effects were shown to be predominantly mediated by $GABA_BR$ (Nissbrandt and Engberg 1996; Carter et al., 2009). Given the similarity between GHB and $GABA_A$ergic drugs, we expected comparable effects on PM and CM to those reported for ethanol and benzodiazepines. Consequently, we hypothesized a blunting effect of GHB on PM indicated by reduced ERN amplitudes and a decreased spectral power in associated neural oscillations in the theta range. Given the repeatedly reported insusceptibility of the N2 to pharmacological manipulations, we expected no

effects on CM, indicated by unaffected N2 amplitudes and spectral power in associated neural theta oscillations. As GHB has been reported to have both stimulant and sedative effects (Abanades et al., 2006; Bosch et al., 2018), no specific drug effects on behavioral outcomes were expected. Besides the relevance of this study for increased understanding of the role of $GABA_BR$ in the processes of PM and CM, it is also of clinical relevance, as GHB has become a repurposing candidate for the treatment of major depressive disorder (Bosch et al., 2012), Parkinson's (Ondo et al., 2008) and Alzheimer's disease (Mamelak, 2007), which in turn have all been shown to be associated with altered PM and CM processes (Ullsperger, 2006).

2. Experimental procedures

2.1. Permission

The study was approved by Swissmedic and Cantonal Ethics Committee of Zurich and registered at ClinicalTrials.gov (NCT02342366). According to the declaration of Helsinki all participants provided written informed consent.

2.2. Study design

The study followed a placebo-controlled, randomized, balanced, cross-over design. Each subject attended a screening, two experimental days and a follow-up session, wherein experimental days were separated by a washout phase of seven days.

2.3. Participants

Twenty healthy, male volunteers (mean age 25.8 ± 5.1 years) participated in the study. The following criteria were required for inclusion: (i) male sex in order to avoid the potential impact of menstrual cycle, (ii) age within the range of 18–40 years, (iii) absence of any somatic or psychiatric disorders, (iv) no first-degree relatives with a history of psychiatric disorders, (v) non-smoking, given the effects of nicotine on EEG signals (Franken et al., 2010), (vi) without a history of drug abuse (lifetime use $>$ 5 occasions, with exception of occasional cannabis use). None of the participants reported previous experiences with GHB in their life. Participants were instructed to abstain from ethanol 24 h before the session and were asked to neither have breakfast nor drink caffeinated beverages in the morning of an experimental session, as bioavailability of GHB is markedly reduced when taken together with food (Borgen et al., 2004). Urine samples were collected on the two experimental days in order to ensure that all participants abstained from illegal substance use. All participants were instructed about potential risks concerning the administered substance and were monetarily compensated for the completion of the study. We previously reported effects of GHB on resting state EEG, pharmacokinetics, social cognition and mood in the same study sample (Rotz et al., 2017; Liechti et al., 2016; Bosch et al., 2015).

2.4. Drug administration

Each subject received either 20 mg/kg ($N = 10$) or 35 mg/kg ($N = 10$) of GHB (Xyrem®) dissolved in 3dl of orange juice and a placebo, matched in appearance and taste. The doses used were safe and tolerable and can be regarded as intermediate in intensity, characterized by significant subjective and cognitive effects. Undesired side effects such as vomiting or narcosis are unlikely to occur in this dosage range (Palatini et al., 1993; Abanades et al., 2006).

2.4.1. Eriksen-Flanker task

In a modified version of the Eriksen-Flanker task (Eriksen and Eriksen, 1974) subjects were required to respond as fast and accurately as possible according to the direction pointed by a centrally presented arrow with either the index finger of the left hand (←) or the right hand (→), respectively. Two additional arrows flanking the target arrow on the left as well as the right side either favored the target response (congruent trials, ←←←←← or →→→→→) or primed the other response (incongruent trials, ←←→←← or →→←→→). The stimuli were presented on a black background for 650 ms. In order to assure a constant error rate throughout participants and to ensure a sufficient number of incorrect responses, the difficulty level during the task was programmed in a dynamic way. In the case of an error commission, presentation time was prolonged by 15 ms for the subsequent trial; in the case of a correct response, presentation time was shortened by 30 ms. Furthermore, visual feedback about the correctness of the response was given 3000 ms after the response, indicated by smiling (☺) or sad faces (☹), or by a question mark (?) if a response was too slow. The task consisted of 240 trials (120 congruent, 120 incongruent) and each of the four stimuli were presented in a randomized order. The task was performed between 70 and 90 min after GHB/placebo administration, which is shortly after peak drug effects (Abanades et al., 2006; Liechti et al., 2016).

2.5. Blood samples

To determine the plasma kinetics of GHB post-administration, blood was withdrawn at minutes t_{-20}, t_{35}, t_{60}, t_{100}, t_{140}, and t_{200} with the help of a permanent peripheral venous catheter. GHB was quantified in the plasma by liquid chromatography-mass spectrometry, according to the procedure of Meyer et al. (2011). As blood sampling was not feasible during the task execution, plasma values for the task time point (t_{70}-t_{90}) were estimated by averaging the plasma values at t_{60} and t_{100} (see supplementary Fig. 1).

2.6. Subjective measurement

Subjective drug effects were monitored with a 4-dimensional Visual Analog Scale (VAS). Therein, the dimensions *"general drug effect", "sedation", "stimulation"* and *"dizziness"* were assessed on a scale ranging from zero ("no effect") to ten ("strong effect"). The VAS was applied at time points t_{-15}, t_{40}, t_{60}, t_{100}, t_{120}; and t_{180} min.

2.7. EEG data acquisition

A BioSemi ActiveTwo electrode system (BioSemi, Netherlands) including 64 scalp electrodes was used for EEG recording. Additional electrooculographic electrodes were placed superior and lateral to the eyes in order to detect horizontal and vertical eye movements. EEG signals were sampled at a rate of 2048 Hz.

2.8. EEG data preprocessing

EEG data preprocessing was performed using the Brain Vision Analyzer 2 software (Brain Products GmBH). First, channels with bad data quality were interpolated using spherical splines. Second, the

EEG data were re-referenced to the average of all scalp electrodes. Third, EEG data were bandpass-filtered from 0.5 to 40 Hz in order to attenuate channel drifts and to satisfy the stationarity assumption necessary for computing independent component analysis (ICA). Fourth, an Ocular Correction ICA was applied to remove eye blinks as well as vertical and horizontal eye movements.

2.9. ERN, correct-related negativity (CRN), N2

Response-locked ERP segments were generated based on the marker position of incorrect response (ERN) and correct responses (CRN) (−1500 ms to 1500 ms). Moreover, stimulus-locked ERP segments were generated based on the marker position for congruent trials and for incongruent trials (−1500 ms to 1500 ms). The analysis was restricted to N2s preceding correct trials, wherein congruent (N2-con) and incongruent trials (N2-inc) were differentiated. Artifact-containing segments (maximal allowed amplitude difference: +/−100 μV, maximal allowed voltage step: 50 μV/ms, Lowest allowed activity: 0.5 μV) were automatically rejected from the data set. The remaining single trials were averaged within subjects (Avg_ERN, Avg_CRN, Avg_N2-con, Avg_N2-inc). Furthermore, to ensure interpretable ERPs, only subjects with at least 24 clean segments were included in the analysis. Therefore, one subject had to be excluded due to low data quality and 4 subjects due to a low number of incorrect trials (<24). The final number of segments which were included in the analysis was: ERN (39.2 ± 14.2), CRN (43.4 ± 9.5), N2-con (74.8 ± 15.3), N2-inc (42 ± 7.1). The number of segments did not significantly differ between the drug conditions ($p>0.05$). Fifteen subjects thus entered the final analysis (low dose $N=6$, high dose $N=9$).

ERN and CRN amplitudes were quantified by subtracting the most negative peak between 0 and 150 ms post-response from the most positive peak −150 to 0 ms pre-response at electrode FCz, where ERN/CRN amplitudes were largest. For the N2 component, amplitudes were quantified by subtracting the most negative peak between 200 and 350 ms post-stimulus from the most positive peak 0–200 ms post-stimulus at the FCz electrode, where N2 amplitudes were largest.

2.10. Time-frequency analysis

To assess the time-frequency of neural oscillations, a continuous Morlet Complex Wavelet Transformation was applied to the 3 s segments (segment window: −1500 to 1500 ms around stimuli (N2-con/N2-inc) or response (ERN/CRN)) at the FCz electrode. Spectral power was calculated between 1 and 12 Hz (Delta (1–4 Hz), Theta (5–7 Hz), Alpha1 (8–10), Alpha2 (11–12 Hz)) using a Morlet parameter of 5.5 and Gabor-normalized instantaneous amplitudes. Single trial values were averaged within subjects and condition. Peak spectral values for each frequency band during a +/−100 ms time-window around the ERN/CRN or N2 peaks were exported for further analysis. Furthermore, the extent of normalized phase variability across trials for each condition was quantified by the phase-locking value (Lachaux et al., 1999). This results in values ranging from 0 (randomized phases across trials) to 1 (consistent phase across trial).

2.10.1. Prestimulus activity

To determine pre-stimuli frequency power, a continuous Morlet Complex Wavelet Transformation was applied to a 0.8 s epoch prior to stimulus presentation (segment window: −600 to 200 ms before stimulus presentation) at the FCz electrode. Spectral power was calculated between 1 and 12 Hz, using a Morlet parameter of 5.5 and Gabor-normalized instantaneous amplitudes. Single trial wavelets were averaged within subjects and peak spectral wavelet values for each frequency band −600 to −200 ms prior to stimulus presentation were exported for further analysis.

2.11. Statistical analysis

All analysis was conducted using RStudio Version 1.0.136 (RStudio, Inc.). Individual averages for (1) reaction time, (2) error rates, (3) post error slowing, (4) ERN/CRN amplitude, (5) N2 amplitudes, (6) spectral power and (7) Phase-locking factor (PLF) were entered in a Linear Mixed Effects Model (LME). Thus, possible factors were *condition* (GHB vs. Placebo), *GHB_plasma* (GHB plasma concentration), and furthermore *correctness* for PM analysis and *congruency* for CM analysis.

3. Results

3.1. Behavioral data

Statistical analysis of behavioral data (F.1A-C) revealed a significant main effect of *GHB_plasma* ($p<0.01$) and *congruency* ($p<0.001$) on reaction times. Moreover, post-hoc testing revealed that GHB prolonged reaction times only for congruent ($p<0.05$) and not for incongruent trials ($p>0.05$). Neither error rates ($p>0.05$) nor post-error slowing ($p>0.05$) were affected by the drug (Fig. 1).

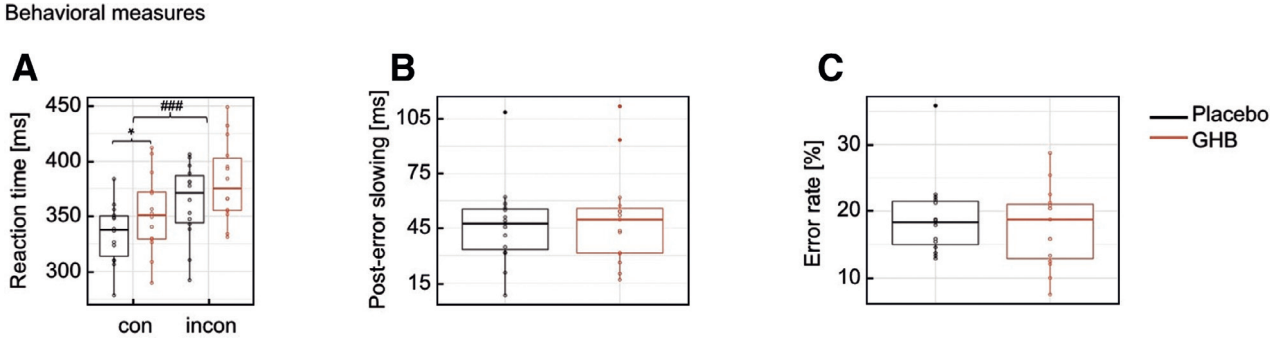


Fig. 1 Means and standard error of means of behavioral parameter. (A) represents reaction times, depicted for congruent (con) and incongruent (inc) trials, (B) post-error slowing and (C) error rates. * represents significant *GHB_plasma* effect: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. # represents significant *congruency* effect: # $p < 0.05$, ## $p < 0.01$, ### $p < 0.001$.

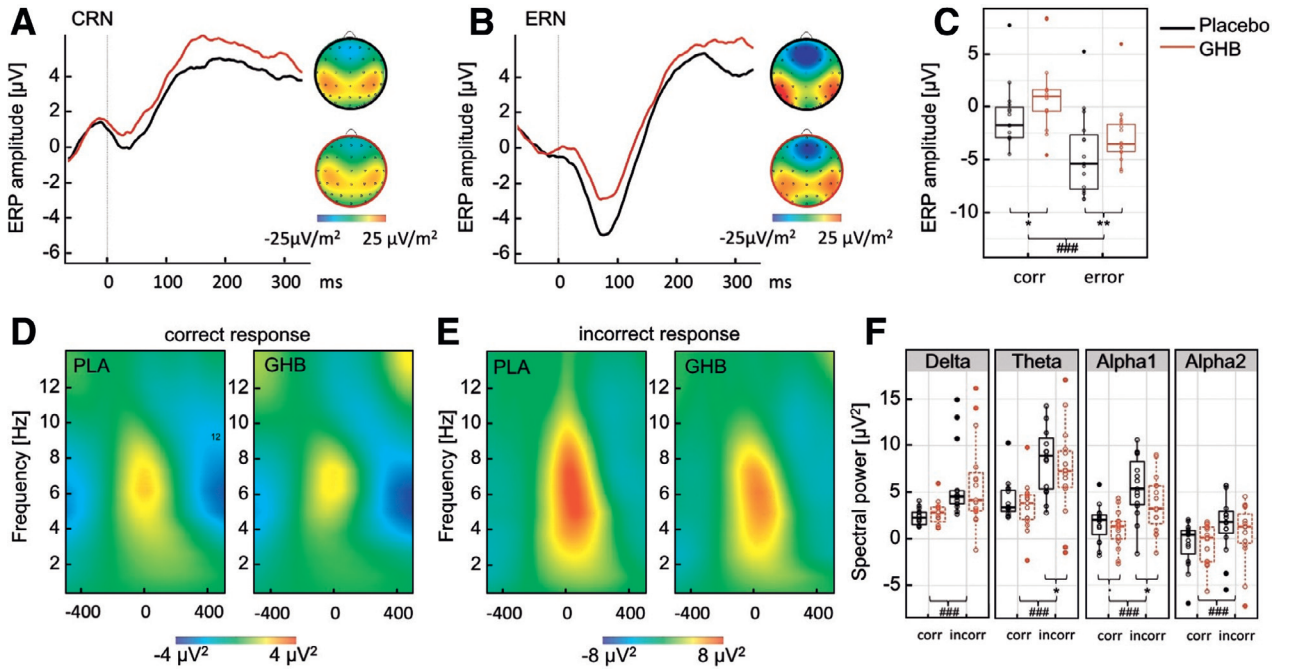


Fig. 2 (A) CRN and (B) ERN with topographical maps thereof, depicted for the placebo (black) and GHB (red) condition. (C) Means and standard error of means of CRN and ERN amplitudes. (D) Correct and (E) incorrect response-locked spectral analysis for the placebo (PLA) and the GHB (GHB) condition. (F) Means and standard error of means of correct and incorrect response-locked spectral powers for delta, theta, alpha1 and alpha2 range. * represents significant *GHB_plasma* effect: · p< 0.1, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. # represents significant *correctness* effect: # $p < 0.05$, ## $p < 0.01$, ### $p < 0.001$. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

3.2. Response-locked potentials

Statistical analysis of response-locked potentials (F.2A-C) revealed a significant decreasing effect of *GHB_plasma* ($p<0.05$) on ERN ($p<0.01$) and CRN ($p<0.05$) amplitudes. Post-hoc testing revealed a decreasing effect of *GHB_plasma* on CRN ($p<0.05$) and ERN ($p<0.01$) amplitudes. Furthermore, there was a significant *correctness* effect ($p<0.001$), indicated by higher amplitude for incorrect compared to correct trials.

3.3. Response-locked oscillations

Statistical analysis of response-locked spectral power values (F.2F) revealed a significant main *GHB_plasma* ($p<0.05$) and *correctness* ($p<0.001$) effect on response-locked spectral power. Post-hoc testing revealed a significant *correctness* effect on all investigated frequency ranges (delta ($p<0.001$), theta ($p<0.001$), alpha1 ($p<0.001$), alpha2 ($p<0.001$)). Furthermore, we found a significant *GHB_plasma* effect on theta ($p<0.05$) and alpha1 ($p<0.05$) power for incorrect trials, and a trend-level decrease for correct trials in the alpha1 range ($p = 0.09891$)(Fig. 2).

3.4. Stimulus-locked potentials

Statistical analysis of stimulus-locked potentials (F.3A-C) revealed a significant *GHB_plasma* effect ($p<0.01$) and no *congruency* effect on N2 amplitudes ($p>0.05$). Furthermore, we found a significant increasing effect of *GHB_plasma* on N2-inc amplitudes ($p<0.05$), whereas, N2-con amplitudes were increased on a trend level ($p = 0.07043$).

3.5. Stimulus-locked oscillations

Statistical analysis of spectral power values (F.3D-F) revealed a significant main *GHB-plasma* ($p<0.05$) and *congruency* ($p<0.05$) effect on stimulus-locked spectral power. Post-hoc testing revealed a significant increasing effect of *GHB_plasma* on delta power for congruent trials ($p<0.05$) and a significant effect on alpha1 ($p<0.05$) power and a trend level decreasing effect on the theta ($p = 0.08793$) for grouped congruent and incongruent trials. Moreover, there was a significant congruency effect on theta power ($p<0.05$)(Fig. 3).

3.6. Response-locked phase-locking

Statistical analysis revealed a main *GHB_plasma* ($p<0.05$), but no *correctness* ($p>0.05$) effect on PLF (F.4A). Post-hoc testing revealed a significant decreasing effect of *GHB_plasma* on PLF in the delta ($p<0.001$) and alpha2 ($p<0.05$) frequency ranges, but only for incorrect trials.

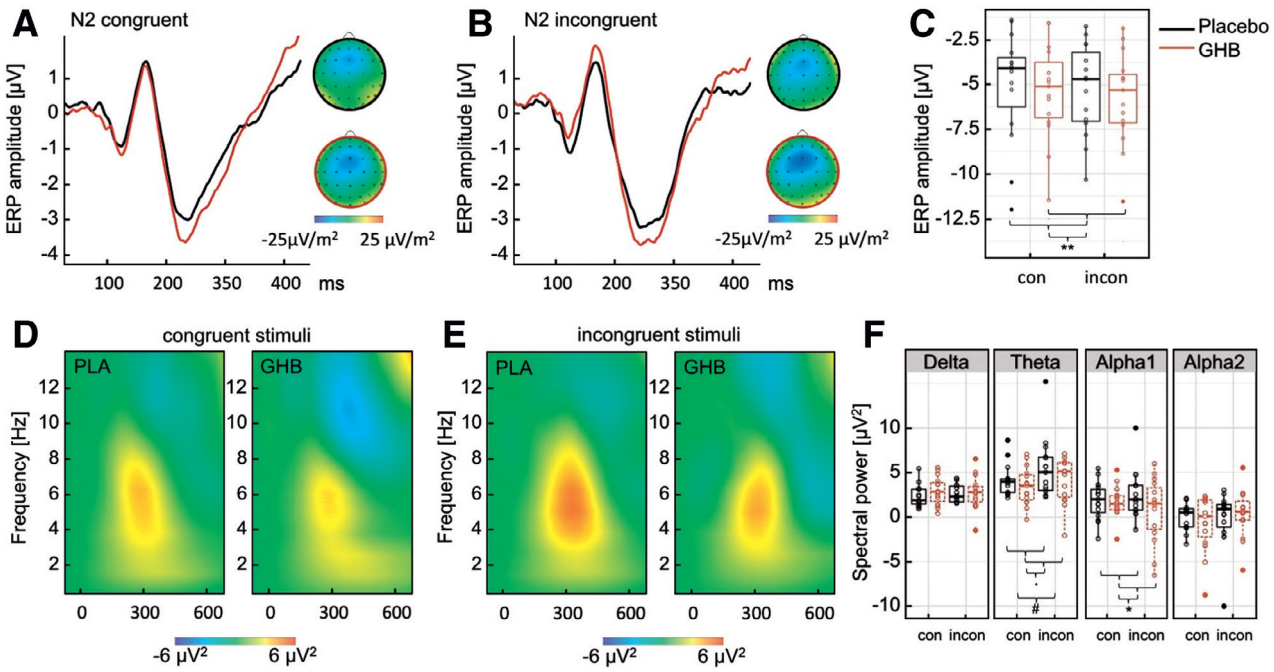


Fig. 3 (A) N2-con and (B) N2-inc with topographical maps thereof, depicted for the placebo (black) and GHB (red) condition. (C) Means and standard error of means of N2-con and N2-inc amplitudes. (D) Congruent and (E) incongruent stimulus-locked spectra for the placebo and the GHB condition. (F) Means and standard error of means of congruent and incongruent stimulus-locked spectral powers for the delta, theta, alpha1 and alpha2 range. * represents significant GHB_plasma effect: · p< 0.1, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. # represents significant *congruency* effect: # $p < 0.05$, ## $p < 0.01$, ### $p < 0.001$. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

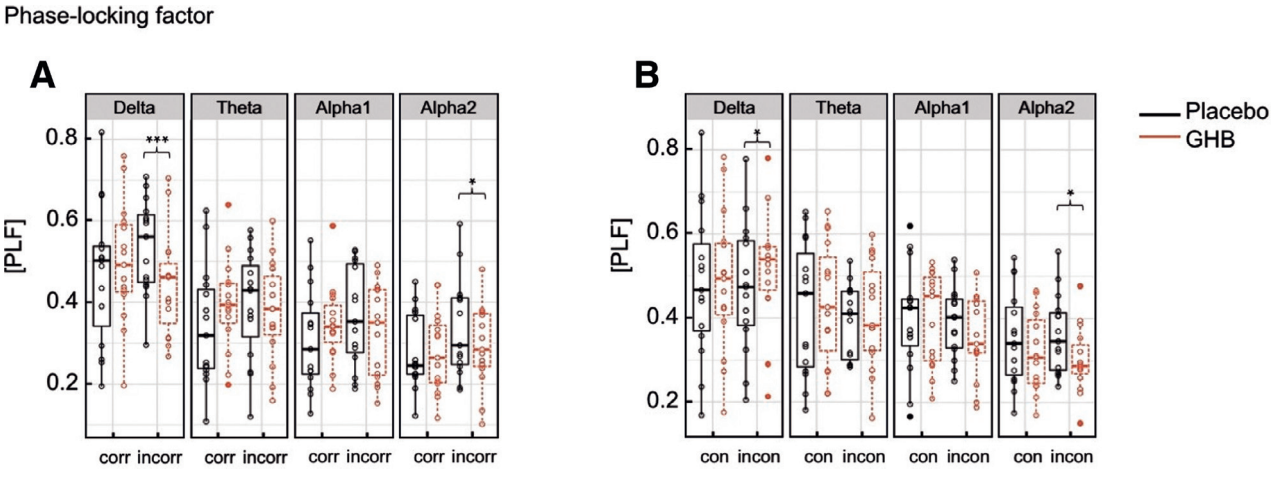


Fig. 4 Means and standard error of means of (A) response-locked trials, depicted for correct (corr) and incorrect (incorr) and (B) stimulus-locked trials, depicted for congruent (con) and incongruent (inc) trials. PLFs are shown separately for the delta, theta, alpha1 and alpha2 range. * represents significant a *GHB_plasma* effect: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

3.7. Stimulus-locked phase-locking

Statistical analysis revealed a main GHB_plasma ($p<0.05$), but no *congruency* ($p>0.05$) effect on PLF (F.4B). Post-hoc testing revealed a significant increasing effect of *GHB_plasma* on PLF in the delta range ($p<0.05$) for incongruent trials and a decreasing effect on the alpha2 range ($p<0.05$) for incongruent trials(Fig. 4).

3.8. Pre-stimulus activity

Statistical analysis of pre-stimulus time-frequency analysis (F.5A-C) revealed a significant main *GHB_plasma* effect on spectral power values. Post-hoc testing revealed a significant increasing effect of *GHB_plasma* on all frequencies (delta ($p<0.001$), theta ($p<0.001$), alpha1 ($p<0.01$) and alpha2 ($p<0.01$))(Fig. 5).

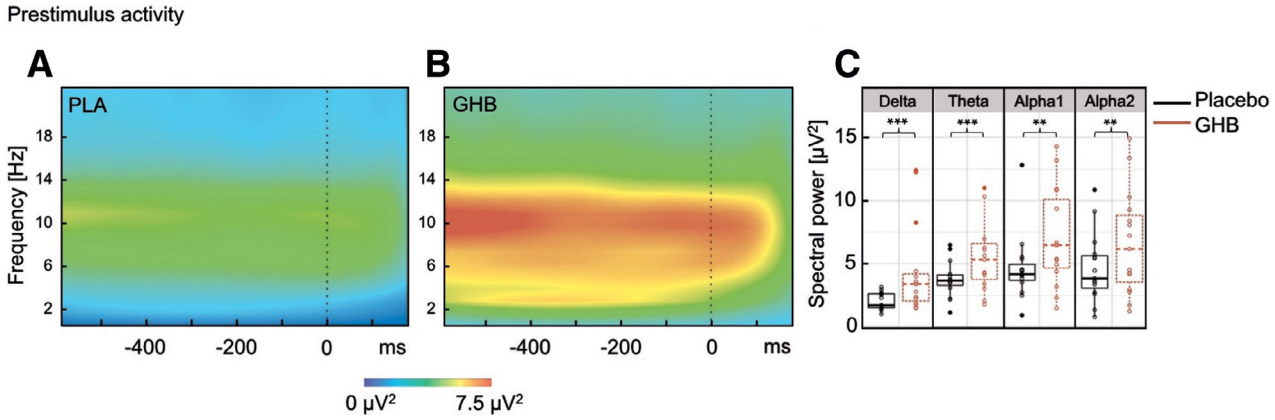


Fig. 5 Wavelet analysis of the prestimulus activity depicted for the placebo (A) and GHB condition (B). (C) Means and standard error of means of prestimulus spectral powers for the delta, theta, alpha1 and alpha2 range. * represents a significant *GHB_plasma* effect: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

4. Discussion

The current study revealed a significant effect of the $GABA_BR$ agonist GHB on the neurophysiological correlates of PM and CM. GHB decreased the ERN and associated frontomedial oscillations in the theta/alpha1 range. Similarly, GHB reduced neural oscillations in the theta/alpha1 range associated with the N2 component, but intriguingly increased the N2 amplitude itself. Behavioral analysis revealed prolonged reaction times and unaffected error rates or post-error slowing under GHB. These effects were accompanied by mixed subjective effects of sedation, stimulation and euphoria as published previously (Bosch et al., 2015).

Our data suggest a disrupting effect of GHB on PM as reflected by the reduced ERN magnitude. As reported in previous studies, the ERN component most likely derives from an amplitude increase and a phase-resetting of ongoing delta and theta oscillation after error commission (Trujillo and Allen, 2007; Yordanova et al., 2004). Consistently, GHB also reduced spectral power in the theta/alpha1 range, as well as phase-locking in the delta range during error commission. As the blunting effect of GHB on these correlates was more pronounced for incorrect then correct responses, it seems likely that GHB particularly impairs the ability to detect the commission of errors and not PM in general. Furthermore, we found enhanced spectral power over all examined frequencies (1–12 Hz) after error commission, compared to correct trials. These findings further underpin the sensitivity of these frontomedial neural oscillators to erroneous responses (Yordanova et al., 2004). Interestingly, we found no differences in phase-locking between correct and incorrect responses, suggesting that the power of these oscillations is more decisive for error detection than phase-resetting, at least in the data at hand. Based on these findings we conclude that GHB disrupts PM by diminishing the ability to elevate phasic neural oscillations in response to an error, characterized by decreased power in the theta/alpha1 range and a reduced phase-locking of delta oscillations. These oscillatory effects most likely underlie the GHB-induced reduction in the ERN, as previous studies have revealed a close relationship between those oscillations and the ERN (Trujillo and Allen, 2007; Yordanova et al., 2004). Several studies found the ACC to be the core neural structure involved in the generation of these neural rhythms (e.g., Gehring and Willoughby, 2004). As assumed by the reinforcement learning theory, error commission produces a neural encoded error signal, which is transmitted to the ACC via a phasic decline in the tonic activity of mesencephalic dopaminergic neurons (Holroyd et al., 2002). Importantly, GHB has been shown repeatedly to substantially affect both the ACC and dopaminergic transmission (e.g. Bosch et al., 2017; Cruz et al., 2004). In the present study, GHB induced a tonic power increase in pre-stimulus frontomedial oscillations over all examined frequencies (1–12 Hz). Moreover, in a previously published electrical source localization analysis, we found an increase in resting-state alpha power in the ACC under GHB compared to placebo (Rotz et al., 2017). According to the work of Jensen and Mazaheri (2010) pre-stimulus alpha activity provides inhibition, therewith reducing the processing capabilities of a given area, an effect that has been shown to be mainly mediated by GABAergic interneurons. Consequently, GHB might reduce the ERN and associated oscillations by increasing the tone of the inhibitory alpha rhythm within the ACC

The mechanisms underlying GHB's effects on the waking EEG and ERP components, has not been investigated in detail so far. Anyhow, two possible pharmacological mechanisms seem particularly likely to account for the observed changes in the investigated ERPs and neural oscillations in this study. First, GHB might directly hyperpolarize neurons within the ACC by activating pre- and postsynaptic $GABA_BR$. The activation of presynaptic $GABA_BR$ suppresses the release of numerous excitatory neurotransmitters, thus reducing the occurrence of excitatory postsynaptic potentials (Andresen et al., 2011). Additionally, the postsynaptic activation of $GABA_BR$ directly hyperpolarizes the membrane by triggering the opening of G-protein-coupled inwardly-rectifying potassium channels (Cruz et al., 2004). Secondly, GHB might indirectly modulate the activity of the ACC by its strong downstream effects on several neurotransmitter systems, including the noradrenergic, serotonergic, cholinergic, and dopaminergic system (Andresen et al., 2011).

Given the established relationship between dopaminergic firing and the generation of the ERN, a modulation of the dopaminergic system by GHB seems to provide the most plausible explanation for the observed effects on PM in this study (Cruz et al., 2004; Holroyd et al., 2002). According to that, GHB may not disrupt PM due to its effects on the ACC, but by modulating the transmission of prediction errors by the MCDS. It is not yet clear, whether GHB enhances (Cruz et al., 2004) or decreases (Brancucci et al., 2004) dopaminergic output in terminal regions, but converging evidence indicates a dose-dependent, bi-directional modulation of mesolimbic dopamine release, with lower doses having a disinhibiting effect on dopaminergic neurons in the ventral tegmental area (VTA) and higher doses directly inhibiting dopaminergic neurons (Labouèbe et al., 2007). Considering the euphorogenic and stimulating effects of GHB observed in our subjects, it seems likely that the dose range used can be considered low enough to disinhibit dopaminergic transmission rather than inhibiting it. Consequently, we suggest that the resulting increase in tonic mesencephalic dopaminergic transmission could counter the ability to decrease dopaminergic signaling in response to errors, leading to a deteriorated generation of prediction errors and thus a reduced disinhibition of the ACC. Further studies employing a simultaneous administration of GHB and dopamine receptor antagonists may prove this assumption.

In summary, our results of disrupted PM under GHB complement the findings of previous studies on the inhibiting effect of $GABA_AR$ agonists, such as benzodiazepines and ethanol, on the ERN (Bruijn et al., 2004; Holroyd and Yeung, 2003; Riba et al., 2005; Ridderinkhof et al., 2002), demonstrating that $GABA_BR$ agonism also has a suppressing effect on ERN-generating networks, despite its stimulant effects.

We further explored the impact of GHB on neurophysiological correlates of CM. Against expectations, N2 amplitudes were found to be significantly higher in the GHB condition compared to the placebo condition, indicating enhanced conflict detection under GHB. Interestingly, GHB also reduced – but to a lesser extent – spectral power in the theta/alpha1 range, similarly to the reduction observed for PM, implying an equally inhibiting effect of $GABA_BR$ agonism on frontomedial oscillations, both during error commission and response conflict. This diverging effect on the N2 and associated spectral power might indicate that the N2 does not equally interrelate with frontomedial neural oscillations in the theta/alpha1 band, contrary to observations for the ERN.

Moreover, we found no significant congruency effect on N2 amplitudes, prima facie implying a similar response conflict load for congruent and incongruent trials. Nevertheless, time-frequency analysis revealed significantly higher spectral power (1–12 Hz) locked to incongruent than to congruent stimuli, demonstrating the sensitivity of these oscillations to conflict load (Yeung and Nieuwenhuis, 2009). Again, we observed a dissociation of the N2 component and corresponding neural oscillations, here in regard to their susceptibility to response conflict, providing further evidence supporting the view that the N2 does not equally rely on these oscillations, compared to the ERN. Based on our results, it seems likely that the neurophysiological relationship between the phase-locking and power of neural oscillations on the one hand, and evoked potentials on the other hand, might not be as straightforward across different ERP components as originally assumed.

Interestingly, we found an increased phase-locking in the delta range, which is opposed to the reduction seen during error commission. Besides its involvement during error detection (Yordanova et al., 2004), delta band activity has also been associated with target detection (Schurmann et al., 2001). From this point of view, such a delta increase might be indicative of an increased salience of the target stimuli. This view is supported by our recent neuroimaging studies, where GHB was found to activate the salience network (SN), a network involved in the detection of relevant internal and external stimuli to manage adaptive behavior (Bosch et al., 2018). The SN is anchored in the anterior insula and the dorsal ACC as well as in subcortical structures such as the ventral striatum and nucleus accumbens and the VTA (Menon, 2011, 2015; Menon and Uddin, 2010).

Taking the response conflict theory into account, similar drug effects on both PM and CM would be expected, as this theory suggests that the same neural ERP-generating mechanisms underlie the ERN and the N2 (Botvinick et al., 2001). However, our data revealed that GHB differently affects PM and CM at the electrophysiological level. Thereby, these results support the view of previous neuroimaging studies investigating PM and CM, where spatially distinct substructures within the medio-frontal cortex were found to be responsible either for PM or CM (Ullsperger and Von Cramon, 2001). Previous studies have revealed dissociative drug effects on the ERN and the N2 but, to our knowledge, GHB is the only drug reported so far to elicit opposite effects on the ERN and the N2. This divergence might reflect or underpin the different cognitive functions of the ERN and the N2. One prominent theory states that, while the ERN stems from the processing of implicit target stimulus information, the N2 rather deals explicitly with the processing of external stimulus information (Yeung and Cohen, 2006). This view is consistent with our above suggestion that GHB's increasing effect on the activity within the SN could account for an increase in the experienced salience of external stimuli, resulting in increased N2 amplitudes. Regarding the ERN, it seems likely that GHB – with its positive effects on mood – decreases the affective valence of negative internal information, resulting in a blunted ERN (Bosch et al., 2015). Conclusively, our results indicate that GHB has a distinctly different effect on CM than that of the $GABA_AR$ agonistic benzodiazepines or ethanol (Riba et al., 2005; Ridderinkhof et al., 2002).

The present study bears a number of limitations: our sample size was moderate and limited to male subjects. However, we initially investigated 20 individuals, but because of data quality control reasons we had to exclude 5 participants. Since PM and CM were assessed between 70 and 90 min after GHB ingestion, our findings may not reflect peak drug effects. Nevertheless, subjective drug effects were still present in the time window of data assessment, indicating that our findings still reflect $GABA_BR$ effects. Finally, in our discussion we attribute the effects mainly to the $GABA_BR$, although GHB also has agonistic properties at the GHB receptor. However, it has been shown that the behavioral effects of exogeneously administered GHB are mainly mediated by $GABA_B$ and not by GHB receptors (Carter et al., 2009).

5. Conclusion

The present study reveals a dissociating effect of the $GABA_B$-/GHB-R agonist GHB on the neurophysiological correlates of PM and CM, reflected in decreased PM and inverse effects on CM. Reduced PM most likely derives from a disrupted transmission of prediction errors to the ACC, caused by a tonic increase of mesencephalic dopaminergic signaling. Elevated CM, conversely, may stem from GHB's ability to increase the visual salience of external stimuli. These effects resemble those observed for ethanol and benzodiazepines, with a distinct difference regarding an enhancing effect of GHB on the N2. Therefore, GHB is the first drug reported so far to have diverging effects on the neurophysiological correlates of PM and CM, underlined by its unique neuropsychopharmacological signature.

Role of funding source

Funding for this study was provided by grants from the Swiss National Science Foundation (SNSF; Grant No. PP00P1-123516/1 and PP00P1-146326/1), the Swiss Neuromatrix Foundation (No. ER2-2016), Switzerland, and the Heffter Research Institute (No. 4-190416), The funding sources had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Contributors

Oliver G. Bosch designed the study and wrote the protocol. Dario Dornbierer managed the analyses and wrote the first manuscript. Erich Studerus undertook the statistical analysis. Jürg Gertsch and Maria Gachet conducted performed the quantification of drug plasma concentrations. All authors contributed to and have approved the final manuscript.

Conflict of interest

All authors report no biomedical financial interests or potential conflicts of interest. Boris B. Quednow was supported by grants from the Swiss National Science Foundation (SNSF; Grant No. PP00P1-123516/1 and PP00P1-146326/1). Franz X. Vollenweider and Michael Kometer were supported by grants from the Swiss Neuromatrix Foundation (No. ER2-2016), Switzerland, and the Heffter Research Institute (No. 4-190416), USA. Dario Dornbierer had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Acknowledgments

We would like to thank Sara Romer for her helpful assistance in data collection and in participant recruitment. Moreover, we want to thank David Cole for his valuable comments on the manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.euroneuro.2019.02.004.

References

Abanades, S., Farré, M., Segura, M., Pichini, S., Barral, D., Pacifici, R., et al., 2006. Gamma-hydroxybutyrate (GHB) in humans: pharmacodynamics and pharmacokinetics. Ann. N. Y. Acad. Sci. 1074, 559–576.

Andresen, H., Aydin, B.E., Mueller, A., Iwersen-Bergmann, S., 2011. An overview of gamma-hydroxybutyric acid: pharmacodynamics, pharmacokinetics, toxic effects, addiction, analytical methods, and interpretation of results. Drug Test Anal. 3, 560–568.

Borgen, L.A., Okerholm, R.A., Lai, A., Scharf, M.B., 2004. The Pharmacokinetics of Sodium Oxybate Oral Solution following Acute and Chronic Administration to Narcoleptic Patients. J. Clin. Pharmacol. 44, 253–257.

Bosch, O.G., Eisenegger, C., Gertsch, J., Rotz, R.Von, Dornbierer, D., Salomé Gachet, M., et al., 2015. Gamma-hydroxybutyrate enhances mood and prosocial behavior without affecting plasma oxytocin and testosterone. Psychoneuroendocrinology 62, 1–10.

Bosch, O.G., Esposito, F., Dornbierer, D., Havranek, M.M., von Rotz, R., Kometer, M., Staempfli, P., Quednow, B.B., Seifritz, E., 2018. Gamma-hydroxybutyrate increases brain resting-state functional connectivity of the salience network and dorsal nexus in humans. Neuroimage 173, 448–459. https://doi.org/10.1016/j.neuroimage.2018.03.011.

Bosch, O.G., Quednow, B.B., Seifritz, E., Wetter, T.C., 2012. Reconsidering GHB: orphan drug or new model antidepressant. J. Psychopharmacol. 26, 618–628.

Bosch, O.G., Esposito, F., Havranek, M.M., Dornbierer, D., von Rotz, R., Staempfli, P., Quednow, B.B., Seifritz, E., 2017. Gamma-Hydroxybutyrate Increases Resting-State Limbic Perfusion and Body and Emotion Awareness in Humans. Neuropsychopharmacology 42 (11), 2141–2151.

Botvinick, M.M., Braver, T.S., Barch, D.M., Carter, C.S., Cohen, J.D., 2001. Conflict monitoring and cognitive control. Psychol. Rev. 108, 624–652.

Brancucci, A., Berretta, N., Mercuri, N.B., Francesconi, W., 2004. Gamma-hydroxybutyrate and ethanol depress spontaneous excitatory postsynaptic currents in dopaminergic neurons of the substantianigra. Brain Res. 997, 62–66.

Bruijn, E.R.A.De, Hulstijn, W., Verkes, R.J., Ruigt, G.S.F., Sabbe, B.G.C., 2004. Drug-induced stimulation and suppression of action monitoring in healthy volunteers. Psychopharmacology 177, 151–160 (Berl).

Bruijn E.R.A. De, Sabbe B.G.C., Hulstijn W., Ruigt G.S.F., Verkes R.J. (2006). Effects of antipsychotic and antidepressant drugs on action monitoring in healthy volunteers. doi:10.1016/j.brainr.

Carter L.P., Koek W., France C.P. Behavioral Analyses of GHB: Receptor Mechanisms. 2009 doi:10.1016/j.pharmthera.2008.10.003.

Cavanagh, J.F., Cohen, M.X., Allen, J.J.B., 2009. Prelude to and resolution of an error: eeg phase synchrony reveals cognitive control dynamics during action monitoring. J. Neurosci. 29, 98–105.

Cruz, H.G., Ivanova, T., Lunn, M.-L., Stoffel, M., Slesinger, P.A., Lüscher, C., 2004. Bi-directional effects of GABAB receptor agonists on the mesolimbic dopamine system. Nat. Neurosci. 7, 153–159.

Devinsky, O., Morrell, M.J., Vogt, B.A., 1995. Contributions of anterior cingulate cortex to behaviour. Brain 118 (Pt 1), 279–306.

Eriksen, B.A., Eriksen, C.W., 1974. Effects of noise letters upon the identification of a target letter in a nonsearch task. Percept. Psychophys. 16, 143–149.
Falkenstein, M., Hoormann, J., Christ, S., Hohnsbein, J., 2000. ERP components on reaction errors and their functional significance: a tutorial. Biol. Psychol. 51, 87–107.
Franken, I.H.A., Strien, J.W.Van, Kuijpers, I., 2010. Evidence for a deficit in the salience attribution to errors in smokers. Drug Alcohol Depend. 106, 181–185.
Gehring, W.J., Coles, M.G., Meyer, D.E., Donchin, E., 1995. A brain potential manifestation of error-related processing. Electroencephalogr. Clin. Neurophysiol. Suppl. 44, 261–272.
Gehring, W.J., Willoughby, A.R., 2004. Are all medial frontal negativities created equal? Toward a richer empirical basis for theories of action monitoring. Errors, Conflicts and the Brain 14-20 (2004) (2001).
Holroyd, C.B., Coles, M.G.H., Program, N., 2002. The Neural Basis of Human Error Processing: Reinforcement Learning, Dopamine, and the Error-Related Negativity. Psychol Rev 109 (4), 679–709.
Holroyd, C.B., Nieuwenhuis, S., Yeung, N., Nystrom, L., Mars, R.B., Coles, M.G.H., et al., 2004. Dorsal anterior cingulate cortex shows fMRI response to internal and external error signals. Nat. Neurosci. 7, 497–498.
Holroyd, C.B., Yeung, N., 2003. Alcohol and error processing. Trends Neurosci. 26 (8), 402–404 2003 Aug.
Jensen, O., Mazaheri, A., 2010. Shaping functional architecture by oscillatory alpha activity: gating by inhibition. Front. Hum. Neurosci. 4, 186.
Labouèbe, G., Lomazzi, M., Cruz, H.G., Creton, C., Luján, R., Li, M., Yanagawa, Y., Obata, K., Watanabe, M., Wickman, K., Boyer, S.B., Slesinger, P.A., Lüscher, C., 2007. RGS2 modulates coupling between GABAB receptors and GIRK channels in dopamine neurons of the ventral tegmental area. Nat. Neurosci. 10, 1559–1568.
Lachaux, J.P., Rodriguez, E., Martinerie, J., Varela, F.J., 1999. Measuring phase synchrony in brain signals. Hum. Brain Mapp. 8, 194–208.
Liechti, M.E., Quednow, B.B., Liakoni, E., Dornbierer, D., Rotz, R.Von, Gachet, M.S., et al., 2016. Pharmacokinetics and pharmacodynamics of γ-hydroxybutyrate in healthy subjects. Br. J. Clin. Pharmacol. 81, 980–988.
Luu, P., Tucker, D.M., Makeig, S., 2004. Frontal midline theta and the error-related negativity: neurophysiological mechanisms of action regulation. Clin. Neurophysiol. 115, 1821–1835.
MacDonald, A.W., 2000. Dissociating the role of the dorsolateral prefrontal and anterior cingulate cortex in cognitive control. Science (80-) 288, 1835–1838.
Mamelak, M., 2007. Alzheimer' s disease, oxidative stress and gammahydroxybutyrate. Neurobiol. Aging 28, 1340–1360.
Menon, V., 2015. Salience Network. Brain Mapping: An Encyclopedic Reference, pp. 597–611.
Menon, V., 2011. Large-scale brain networks and psychopathology: A unifying triple network model. Trends Cogn Sci. 15 (10), 483–506 2011 Oct.
Menon, V., Uddin, L.Q., 2010. Saliency, switching, attention and control: a network model of insula function. Brain Struct. Funct. 214, 655–667.
Meyer, M.R., Weber, A.A., Maurer, H.H., 2011. A validated GC–MS procedure for fast, simple, and cost-effective quantification of glycols and GHB in human plasma and their identification in urine and plasma developed for emergency toxicology. Anal. Bioanal. Chem. 400, 411–414.
Munneke, G.-J., Nap, T.S., Schippers, E.E., Cohen, M.X., Cohen, M., 2015. A statistical comparison of EEG time- and time–frequency domain representations of error processing. Brain Res. 1618, 222–230.
Nissbrandt, H., Engberg, G., 1996. GABA B-receptor antagonist, CGP 35348, antagonises y-hydroxybutyrate-and baclofen-induced alterations in locomotor activity and forebrain dopamine levels in mice. J. Neural Transm. 103, 1255–1263.
Ondo, W.G., Perkins, T., Swick, T., Hull, K.L., Jimenez, J.E., Garris, T.S., et al., 2008. Sodium oxybate for excessive daytime sleepiness in parkinson disease. Arch. Neurol. 65, 1337–1340.
Palatini, P., Tedeschi, L., Frison, G., Padrini, R., Zordan, R., Orlando, R., et al., 1993. Dose-dependent absorption and elimination of gamma-hydroxybutyric acid in healthy volunteers. Eur. J. Clin. Pharmacol. 45, 353–356.
Riba, J., Rodríguez-Fornells, A., Münte, T.F., Barbanoj, M.J., 2005. A neurophysiological study of the detrimental effects of alprazolam on human action monitoring. Cognit. Brain Res. 25, 554–565.
Ridderinkhof, K.R., Vlugt, Y.De, Bramlage, A., Spaan, M., Elton, M., Snel, J., et al., 2002. Alcohol consumption impairs detection of performance errors in mediofrontal cortex. at. http://science.sciencemag.org/content/sci/298/5601/2209.full.pdf.
Rotz R. Von, Kometer M., Dornbierer D., Gertsch J., Salomé Gachet M., Vollenweider F.X., et al. 2017 Neuronal Oscillations and Synchronicity Associated with Gamma-Hydroxybutyrate During Resting-State in Healthy Male Volunteers. doi:10.1007/s00213-017-4603-z.
Schultz, W., Dayan, P., Montague, P.R., 1997. A neural substrate of prediction and reward. Science (80-) 275, 1593–1599.
Schurmann, M., Baar-Eroglu, C., Kolev, V., Baar, E., 2001. Delta responses and cognitive processing: single-trial evaluations of human visual P300. Int. J. Psychophysiol. 39 (2-3), 229–239.
Shima, K., 1998. Role for cingulate motor area cells in voluntary movement selection based on reward. Science (80-) 282, 1335–1338.
Spronk, D., 2011. Acute effects of delta-9-tetrahydrocannabinol on performance monitoring in healthy volunteers. Front. Behav. Neurosci. 5 (59).
Spronk, D.B., Dumont, G.J.H., Verkes, R.J., Bruijn, E.R.A.De, 2014. The acute effects of MDMA and ethanol administration on electrophysiological correlates of performance monitoring in healthy volunteers. Psychopharmacology 231, 2877–2888 (Berl).
Ullsperger, M., 2006. Performance monitoring in neurological and psychiatric patients. Int. J. Psychophysiol. 59, 59–69.
Ullsperger, M., Von Cramon, D.Y., 2001. Subprocesses of performance monitoring: A dissociation of error processing and response competition revealed by event-related fMRI and ERPs. Neuroimage 14, 1387–1401.
Veen, V.Van, Carter, C.S., 2002. The anterior cingulate as a conflict monitor: FMRI and ERP studies. Physiol. Behav. 77, 477–482.
Yeung, N., Botvinick, M.M., Cohen, J.D., 2004. The neural basis of error detection: conflict monitoring and the error-related negativity. Psychol. Rev. 111, 931–959.
Yeung, N., Cohen, J.D., 2006. The Impact of Cognitive Deficits on Conflict Monitoring. Psychol Sci. 17 (2), 164–171.
Yeung, N., Nieuwenhuis, S., 2009. Dissociating response conflict and error likelihood in anterior cingulate cortex. J Neurosci. 29 (46), 14506–14510.
Yordanova J., Falkenstein M., Hohnsbein J., Kolev V. (2004). Parallel Systems of Error Processing in the Brain. doi:10.1016/j.neuroimage.2004.01.040.