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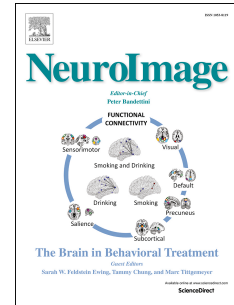
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The impact of GABAergic drugs on TMS-induced brain oscillations in human motor cortex

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1 **The impact of GABAergic drugs on TMS-induced brain oscillations in**
2 **human motor cortex**

3
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26

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34

35 *Highlights*

- 36 • The response to TMS of M1 is composed of evoked and induced oscillatory
37 activity
- 38 • TMS induced early α -/ β -synchronization and late α -/ β -desynchronization in M1
- 39 • GABAergic vs. GABAergic drugs had opposite effects on early α -
40 synchronization
- 41 • GABAergic and GABAergic drugs enhanced the late β -desynchronization

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48 **Abstract**

49 Brain responses to transcranial magnetic stimulation (TMS) as measured with
50 electroencephalography (EEG) have so far been assessed either by TMS-evoked EEG
51 potentials (TEPs), mostly reflecting phase-locked neuronal activity, or time-frequency-
52 representations (TFRs), reflecting oscillatory power arising from a mixture of both
53 evoked (i.e., phase-locked) and induced (i.e., non-phase-locked) responses. Single-
54 pulse TMS of the human primary motor cortex induces a specific pattern of oscillatory
55 changes, characterized by an early (30-200 ms after TMS) synchronization in the α - and
56 β -bands over the stimulated sensorimotor cortex and adjacent lateral frontal cortex,
57 followed by a late (200-400 ms) α - and β -desynchronization over the stimulated and
58 contralateral sensorimotor cortex. As GABAergic inhibition plays an important role in
59 shaping oscillatory brain activity, we sought here to understand if GABAergic inhibition
60 contributes to these TMS-induced oscillations. We tested single oral doses of
61 alprazolam, diazepam, zolpidem (positive modulators of the GABAA receptor), and
62 baclofen (specific GABAB receptor agonist). Diazepam and zolpidem enhanced, and
63 alprazolam tended to enhance while baclofen decreased the early α -synchronization.
64 Alprazolam and baclofen enhanced the early β -synchronization. Baclofen enhanced the
65 late α -desynchronization, and alprazolam, diazepam and baclofen enhanced the late β -
66 desynchronization. The observed GABAergic drug effects on TMS-induced α - and
67 β -band oscillations were not explained by drug-induced changes on corticospinal
68 excitability, muscle response size, or resting-state EEG power. Our results provide first
69 insights into the pharmacological profile of TMS-induced oscillatory responses of motor
70 cortex.

71

72 **1. Introduction**

73 The combination of transcranial magnetic stimulation and electroencephalography
74 (TMS-EEG) is a powerful approach to assess aspects of cortical excitation and
75 inhibition (Chellappa et al., 2016; Chung et al., 2015; Ilmoniemi and Kicic, 2010;
76 Ziemann, 2011). TMS-evoked EEG potentials (TEPs) represent the averaged time-
77 locked brain response to single-pulse TMS in the time domain, which likely involves
78 both excitatory and inhibitory neuronal processes (Rogasch and Fitzgerald, 2013). So
79 far, the most direct evidence for the role of inhibition in the generation of TEPs comes
80 from pharmacological studies that assessed the impact of central nervous system
81 (CNS) active drugs that modulate GABAergic neurotransmission (Darmani et al., 2016;
82 Premoli et al., 2014a; Premoli et al., 2014b). However, pharmacological TMS studies
83 have so far only considered the impact of TMS in the time domain, while also the
84 frequency domain provides relevant and complementary information about the brain
85 response to TMS (Herring et al., 2015; Rosanova et al., 2009).

86 Calculating the time-frequency representation (TFR) of the oscillatory EEG
87 response to TMS allows to simultaneously assess power levels in a variety of
88 frequencies in a time resolved manner. Importantly, oscillatory responses to TMS can
89 either be evoked (i.e. phase-locked) or induced (i.e. non-phase-locked) by the
90 stimulation, and each single trial can reflect a combination of both (i.e., *mixed* response)
91 (Herrmann et al., 2014; Pellicciari et al., 2017). Evoked responses may either result
92 from an additive neuronal response elicited by the stimulation or a phase-reset of
93 ongoing (*spontaneous*) oscillations (David et al., 2006). Evoked oscillations can be
94 calculated on the average of single-trials (i.e., TEP), as most of the non-phase-locked

95 activity is cancelled out by averaging in the time domain. In contrast, induced responses
96 result from the stimulus-related modulation of the amplitude but not the phase of an
97 ongoing oscillation, and they are generally estimated by means of event-related
98 synchronization and desynchronization (Pfurtscheller and Aranibar, 1977). Induced
99 oscillations are detected when TFRs are estimated on the single-trial level and
100 averaged subsequently, e.g. when calculating the so-called *event-related spectral*
101 *perturbation* (ERSP) index (Makeig, 1993). However, ERSP provides a mixed response
102 as this procedure is equally sensitive for induced and evoked oscillations and cannot
103 discriminate the two oscillatory response types (Herrmann et al., 2014; Pellicciari et al.,
104 2017). Previous TMS-EEG studies have either focused on TMS-evoked responses
105 (Bonato et al., 2006; Farzan et al., 2013; Garcia et al., 2011; Herring et al., 2015; Paus
106 et al., 2001) or on mixed responses (Ferrarelli et al., 2008; Ferrarelli et al., 2012;
107 Johnson et al., 2012; Rosanova et al., 2009). For TMS of the hand area of the primary
108 motor cortex ($M1_{\text{HAND}}$), mixed oscillatory responses in the α - and β -band have been
109 reported to transiently emerge in proximity of the stimulated site (Brignani et al., 2008;
110 Fuggetta et al., 2005; Paus et al., 2001; Veniero et al., 2011). However, a systematic
111 study of TMS-induced oscillations and their underlying neuronal mechanisms is still
112 lacking.

113 To further explore TMS-related oscillations as novel indicators of cortical
114 processes we sought to disentangle TMS-induced from the contribution of TMS-evoked
115 oscillations and analyze their GABAergic pharmacological profile. For this purpose, we
116 reanalyzed the data from two previously published experiments (Premoli et al., 2014a),
117 in which the respective roles of different α -subunit-containing GABAARs (Experiment 1)

118 and GABABRs (Experiment 2) was investigated, as they underlie different physiological
119 (Mohler et al., 2002) and pathological (Cossette et al., 2002) functions. In Experiment 1,
120 we investigated the effects of *alprazolam*, a classical benzodiazepine and positive
121 modulator of α 1-, α 2-, α 3- and α 5-containing GABA type A receptors (GABAAR), and
122 *zolpidem*, a short-acting non-benzodiazepine hypnotic drug, which mainly binds to the
123 α 1-containing GABAAR. In Experiment 2, we tested the effects of *diazepam*, another
124 classical benzodiazepine binding to α 1-, α 2-, α 3- and α 5-containing GABAARs, and
125 *baclofen*, a specific GABAB receptor (GABABR) agonist.

126 Understanding the neuropharmacological basis of TMS-induced oscillations is of
127 fundamental importance as this knowledge may lead to new markers of excitatory and
128 inhibitory processes in the human brain, which could be used for detecting abnormal
129 excitability in brain disorders.

130

131 **2. Methods and Materials**

132 *2.1 Subjects*

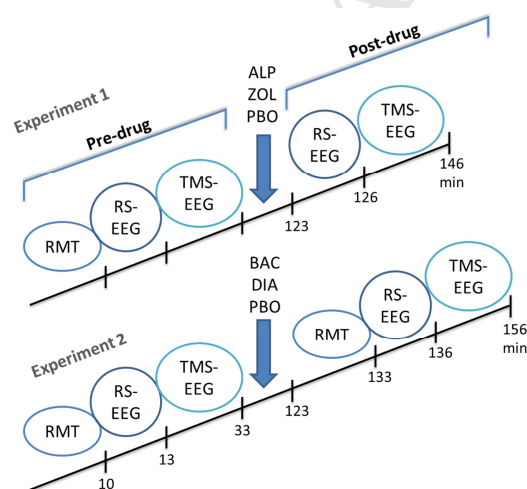
133 Twenty-two (Experiment 1, mean age: 25.0 ± 2.5 years, range: 21–32 years) and 19
134 male healthy subjects (Experiment 2, mean age: 26.4 ± 3.5 years; range: 22–32 years)
135 gave written informed consent before enrolment in this study. Here, the data presented
136 are from 16 and 15 subjects, respectively for Experiment 1 and 2, as several subjects
137 had to be excluded due to data quality issues (see below). The TMS-evoked EEG
138 potential (TEP) analyses of this sample have already been published (Premoli et al.,

139 2014a) and is outside the scope of this paper. Female participants were not recruited
140 because of menstrual cycle-related effects on cortical excitability, which can be a
141 potential confound in TMS studies (Smith et al., 1999). Subjects were tested for right-
142 handedness following the Edinburgh Handedness Inventory (laterality score $\geq 75\%$)
143 (Oldfield, 1971). All participants were screened for contraindications to TMS during a
144 physical and neurological examination (Rossi et al., 2011). Exclusion criteria
145 encompassed the presence of a history of neurological or psychiatric disease, use of
146 CNS active drugs, abuse of any drugs (including nicotine and alcohol) as well as
147 contraindications to the study medications. Experiments were approved by the Federal
148 Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und
149 Medizinprodukte), and by the local Ethics Committees of the Medical Faculty of Goethe-
150 University Frankfurt (Experiment 1) and the Medical Faculty of Eberhard-Karls-
151 University Tübingen (Experiment 2).

152 *2.2 Experimental design*

153 We performed two double-blind, randomized, crossover design studies to investigate
154 the impact of GABA_AR (Experiment 1) and GABA_BR (Experiment 2) mediated inhibitory
155 neurotransmission on TMS-induced oscillations. In Experiment 1 we tested the acute
156 effects of a single oral dose of alprazolam (1 mg, Alprazolam ratiopharm, ratiopharm),
157 zolpidem (10 mg, Zolpidem-ratiopharm, ratiopharm), or placebo (P-Tabletten
158 Lichtenstein). In Experiment 2 we tested a single oral dose of baclofen (50 mg Lioresal,
159 Novartis Pharma), diazepam (20 mg Diazepam-ratiopharm, ratiopharm), or placebo (P-
160 Tabletten Lichtenstein).

161 In both studies, subjects participated in three experimental sessions, randomized
 162 in order and separated by one week to avoid drug carryover effects. Both resting state
 163 EEG (3 min with eyes open) and TMS-EEG measurements were performed
 164 immediately before and 90 min after drug intake (**Figure 1**). In Experiment 1 only 13
 165 subjects underwent resting state EEG measurements. Drug dosages and post-drug
 166 measurement time were chosen according to the pharmacokinetic properties of the
 167 study drugs (Greenblatt and Wright, 1993; Salva and Costa, 1995; Shader et al., 1984),
 168 as well as to our previous TMS-electromyography (TMS-EMG) studies that have
 169 demonstrated significant modulation of motor cortical excitability (Ilic et al., 2002;
 170 McDonnell et al., 2006; Müller-Dahlhaus et al., 2008).



171
 172 **Figure 1. Timeline of experiments:** Resting Motor Threshold (RMT), 3 min of resting state EEG (RS-
 173 EEG) and TMS-EEG measurements were performed before (pre-drug) and 90 minutes after (post-drug)
 174 the intake of alprazolam (ALP), zolpidem (ZOL) or placebo (PBO) in Experiment 1, and baclofen (BAC),
 175 diazepam (DIA) and PBO in Experiment 2. RMT was not registered post-drug in Experiment 1.

176 2.3 TMS

177 A figure-of-eight coil (external diameter of each wing, 90 mm) connected to a Magstim
 178 200² magnetic stimulator (The Magstim Company Ltd., Whitland, UK) with a

179 monophasic current flow was used to deliver single-pulse TMS to the left M1_{HAND}. We
180 targeted the representation of the right *abductor pollicis brevis* muscle (APB), which was
181 determined as the site where TMS at a slightly suprathreshold intensity consistently
182 produced the largest motor evoked potentials (MEPs) (Rossini et al., 2015). MEP
183 recordings were obtained from surface EMG, using Ag-AgCl cup electrodes in a belly-
184 tendon montage. The EMG raw signal was amplified and bandpass filtered (20 Hz to 2
185 kHz; D360 amplifier, Digitimer) and digitized at an A/D rate of 10 kHz (CED Micro 1401;
186 Cambridge Electronic Design). The coil was placed tangential to the scalp with the
187 handle pointing backwards and 45° away from the mid line, inducing a posterolateral to
188 anteromedial current in the brain. This is the optimal orientation to transsynaptically
189 activate the corticospinal system via horizontal corticocortical connections (Di Lazzaro
190 et al., 2008). Resting motor threshold (RMT) was determined to nearest 1% of
191 maximum stimulator output, following the relative frequency method (Rossini et al.,
192 2015), that is the minimum intensity necessary to elicit an MEP of $\geq 50 \mu\text{V}$ in peak-to-
193 peak amplitude in at least 5 of 10 subsequent trials. A number of 150 TMS pulses
194 (Experiment 1) and 125 TMS pulses (Experiment 2) each were applied over the left M1
195 APB hotspot at an intensity of 100% RMT. In Experiment 1, RMT was tested pre-drug
196 only, and stimulation intensity was kept constant throughout all measurements, whereas
197 in Experiment 2, RMT was tested pre- and post-drug to assess possible drug-induced
198 changes in RMT (**Figure 1**) and re-adjust stimulation intensity to keep it constant at
199 relative to 100% RMT. Per definition, this stimulation intensity elicited MEPs $\geq 50 \mu\text{V}$ in
200 approximately half of the trials. Only for Experiment 2, EMG was co-registered also
201 during the TMS-EEG measurements. The position of the APB hotspot was marked with

202 a felt tip pen on the EEG cap to ensure constant coil placement throughout an
203 experimental session. Further, coil position and orientation relative to the marked
204 position were carefully monitored by the experimenter throughout stimulation and
205 corrected if necessary (i.e., if the participant moved). Importantly, any lack of precision
206 (relative to the use of a neuronavigation system) would have resulted only in increased
207 unsystematic error variance (and potentially false negatives), but the double-blind
208 design ensured that no systematic bias (and thus no false positives) could be
209 introduced.

210 *2.4 High-density EEG recordings during TMS*

211 A 64-channel electrode cap (BrainCap-Fast'n Easy 64Ch, Brain Products) connected to
212 TMS-compatible EEG amplifiers (BrainAmp DC, BrainProducts) was used to record
213 brain oscillations, hardware-filtered between 0.016 and 1000 Hz and digitized with a 5
214 kHz sampling rate. Vertical electrooculogram was recorded with 2 additional electrodes
215 to measure eye movements and blinks. Impedances of all electrodes were kept $< 5 \text{ k}\Omega$.
216 During TMS-EEG recordings, subjects were seated on a comfortable reclining chair and
217 asked to stay awake with eyes open. Masking white noise was played through
218 earphones to avoid contamination of the EEG signal by auditory potentials evoked by
219 the click of the discharging TMS coil (Casarotto et al., 2010; Massimini et al., 2005). The
220 noise intensity was adjusted individually in each experimental session, until the
221 participant reported not being able anymore to hear the TMS-click. While residual input
222 via bone conduction cannot be completely excluded, based on their topography our
223 results cannot be explained by auditory evoked potentials. During EEG co-registration,
224 we applied 2 blocks of 125 TMS pulses each pre- and post-drug over the left M1_{HAND}

225 APB hotspot. The inter-stimulus interval between TMS pulses was on average 5 s with
226 a random inter-trial interval variation of 25% to reduce trial anticipation.

227 *2.5 TMS-EEG data analysis*

228 This study is based on data from our two previously published experiments with an
229 original dataset of 22 (Experiment 1) and 19 (Experiment 2) subjects (Premoli et al.,
230 2014a). In this work, data from 2 subjects in Experiment 1 and 4 subjects in Experiment
231 2 had to be excluded from final analysis because of excessive artifact contamination of
232 the EEG traces. In addition, in Experiment 1, data from other 5 subjects had to be
233 excluded as they were particularly affected by Magstim 200² capacitors recharge
234 artifact. Note that analyses, including artifact removal, trial rejection, and subject
235 exclusion were performed completely blind towards experimental condition.

236 TMS-EEG data were analyzed by using MATLAB® (Mathworks Ltd, USA, R2012b) (The
237 Mathworks Inc.), EEGLAB (Delorme and Makeig, 2004) and FieldTrip toolboxes
238 (Oostenveld et al., 2011). After visual inspection, trials affected by prominent artifacts
239 (i.e. eye and muscle movement) were removed, and bad channels were deleted and
240 spatially interpolated. On average, 80 trials were retained for analysis per data set. A
241 linear interpolation was applied between -2 and 6 ms relative to the TMS pulse to
242 remove the initial TMS artifact caused by the step-response of the amplifier. In
243 Experiment 2 an additional linear interpolation (between -102 and -94 ms) was used to
244 remove a TMS-recharge artifact at -100ms. This technical artifact was related to the
245 effectively omitted conditioning pulse (i.e. with intensity of 0 % MSO) from the paired-
246 pulse TMS trials that was part of the same protocol (Premoli et al., 2014b). Data were

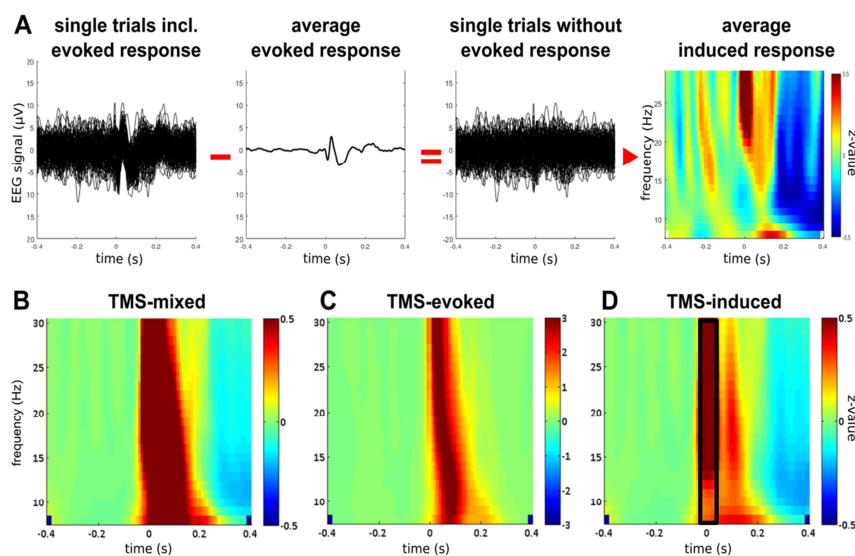
247 then linearly detrended, band-pass (1-45 Hz) and band-stop filtered (49-51 Hz),
248 segmented (-600 to 600 ms), down-sampled to 625 Hz, and referenced to the common
249 average of all electrodes. Independent Component analysis (ICA) was then applied to
250 remove remaining TMS-related artifacts (i.e., the cranial muscle response, the
251 recharging of capacitors, and related exponential decay artifacts (Herring et al., 2015;
252 Korhonen et al., 2011; Rogasch et al., 2016)), as well as further muscle and ocular
253 activity. Artifact components were removed if their spatio-temporal profile indicated the
254 activation of temporal muscles by a characteristic sinusoidal waveform peaking around
255 5 and 15 ms post-TMS (with opposite sign) over frontotemporal sites close to the
256 temporal muscle (Mutanen et al., 2013). Due to excessive artifact contamination, data
257 from six and four subjects had to be excluded from Experiment 1 and 2, resulting in 16
258 and 15 subjects, respectively. Note that analyses, including artifact removal, trial
259 rejection, and subject exclusion were performed completely blind towards experimental
260 condition.

261 Time-frequency representations (TFRs) of TMS-related oscillatory power
262 changes were calculated, separately for each pre- and post-drug condition, by means of
263 a Hanning taper windowed FFT with frequency-dependent window length (width: 3.5
264 cycles per time window, time steps: 10 ms, frequency steps: 1 Hz from 8 to 30 Hz)
265 (Delorme and Makeig, 2004) (**Figure 2B**). We divided neuronal response components
266 into those *evoked* (i.e. phase-locked) vs. *induced* (i.e. non-phase-locked) by TMS
267 (**Figure 2A**, (Cohen and Donner, 2013; Donner and Siegel, 2011; Herrmann et al.,
268 2014; Pellicciari et al., 2017)). The TFR of the *induced* response was then isolated by
269 subtracting the individual time-domain average from each trial before calculating the

270 TFRs of the single trials (as done in Cohen and Donner, 2013, but note that we used a
271 sliding window FFT instead of complex Morlet wavelets to calculate the TFRs; **Figure**
272 **2D)** instead of subtracting the average TFR of the evoked response from the average
273 TFR of the total response (as suggested in Herrmann et al., 2014; Pellicciari et al.,
274 2017). The former approach was preferred since we performed single-trial normalization
275 by z-transforming the TFR of each trial for each frequency, which the latter approach
276 would not allow. The z-transformation was based on the respective mean and standard
277 deviation derived from the full trial length. This was followed by an absolute baseline
278 correction for each trial by subtracting the average of the -400 to -200 ms period (this
279 artifact-free baseline window was chosen because the presence of a technical artifact at
280 -100ms did not allow a later window; see above) for each frequency to ensure z-values
281 represent a change from pre-TMS baseline. Subsequently, TFRs were averaged across
282 trials per experimental condition. This procedure resulted in an *event related spectral*
283 *perturbation (ERSP)* measure that is robustly normalized based on the single trial level
284 (Grandchamp and Delorme, 2011), however, with the contribution of the TMS-evoked
285 response removed at the single-trial level. Finally, TFRs were cropped to the time of
286 interest (-400 to 400 ms), removing time-frequency bins at the trial edges for which no
287 values could be computed. Values were averaged across frequency bins to calculate
288 the power within the α (8-12 Hz) and β (13-30 Hz) frequency bands, which represent the
289 dominating oscillations of the sensorimotor cortex (Engel and Fries, 2010; Jensen et al.,
290 2005; Neuper et al., 2005). While this approach for disentangling TMS-induced from
291 TMS-evoked oscillations is naturally imperfect (slight trial-by-trial variations in the
292 latency and amplitude of the TEP waveform are not captured and result in small

293 subtraction errors, which may be misinterpreted as induced power) it is to the best of
 294 our knowledge currently the best method available. In this particular study, the specific
 295 pattern of early synchronization and late desynchronization is not observed in
 296 TMS-evoked responses and is thus highly unlikely to reflect mere residuals of evoked
 297 activity (**Figure 2**).

298
 299



300

301 **Figure 2. Disentangling TMS-induced and TMS-evoked oscillations.** (A) Illustration of the method used
 302 to disentangle induced from evoked oscillatory responses for a single TMS-EEG session of a
 303 representative subject. The average time-locked evoked response is subtracted from every single trial
 304 before calculating the TFR, thus capturing the non-phase-locked (i.e. induced) oscillatory responses only
 305 (see Methods for details). (B) Time-frequency representation (TFR) of the *mixed* TMS-related power
 306 change, shown for conceptual reasons only (obtained by calculating TFRs on the single-trial level *without*
 307 previous removal of the evoked response). (C) TMS-evoked oscillations, shown for conceptual reasons
 308 only (obtained by calculating the TFR of the individual average TEP, i.e. after averaging the time-locked
 309 signal across trials in the time domain). (D) TMS-induced oscillations (obtained by calculating the TFR at
 310 single-trial level *after* removal of the evoked component, see Methods section for details). Results are
 311 shown for electrode C3 (approximately overlying the stimulated left M1_{HAND}) and correspond to the
 312 grand-average across subjects and across the three pre-drug conditions of Experiment 1. The black box
 313 in proximity of 0 highlights the residual of the TMS artifacts and corresponds to the time window which
 314 was not included in the analysis. Note that the common, symmetrical color scaling for all subpanels
 315 facilitates visibility of the late desynchronization but causes a saturation for synchronization values

316 leading to an apparent fusion (particularly for mixed responses in B) of the broadband power increase
317 during the residual TMS-related artifact (approx. -30 to 30 ms) and the subsequent oscillatory
318 synchronization in alpha and beta bands (approx. 30- 200 ms; TOI1). Also note the clear demarcation
319 line with z-values close to zero between these two areas for the TMS-induced oscillations (D) under
320 investigation.

321

322 *2.6 TMS-EMG data analysis*

323 For Experiment 2, EMG had been co-registered during TMS-EEG measurements and
324 MEP peak-to-peak amplitudes were evaluated for each trial. MEP amplitudes were
325 calculated as difference between the maximum and minimum of the EMG signal as
326 extracted from an individualized search window to account for differences in MEP
327 latency. The individual search window was defined based on the average TMS-locked
328 EMG waveform (but always within the limits of 0.015 to 0.045 s post-TMS). MEP data
329 was only available for both pre- and post-drug measurements for 12 subjects (baclofen)
330 and 13 subjects (diazepam and placebo). Average MEP amplitudes were compared
331 between pre- and post-drug measurements using paired-sample t-tests. Single-trial
332 MEP amplitudes were further used to split the above described analysis of TMS-
333 induced oscillatory power into subthreshold (< 0.05 mV) and suprathreshold (≥ 0.05 mV)
334 trials.

335 *2.7 Resting state EEG data analysis*

336 GABAergic drugs, such as diazepam (Jensen et al., 2005; Saletu et al., 1987),
337 alprazolam (Kaplan et al., 1998), and zolpidem (de Haas et al., 2010) are known to also
338 affect spontaneous oscillations at rest. However, to the best of our knowledge the effect
339 of baclofen has not yet been tested with quantitative EEG in awake human subjects. To

340 investigate the relationship between drug-induced changes of TMS-induced and
341 spontaneous oscillations, 3 min segments of eyes open resting state EEG data were
342 analyzed as well. Data were initially divided into non-overlapping 2 s time-windows. A
343 Morlet-wavelet convolution (width of 5 cycles, in time steps of 10 ms and frequency
344 steps of 1 Hz from 8 to 45 Hz) was used to analyze the power spectra of the resting
345 state EEG signal before and after drug intake in the α (8-12 Hz) and β (13-30 Hz)
346 frequency bands. We performed a correlational analysis to explore a possible relation of
347 drug-induced changes in TMS-induced and spontaneous resting state EEG oscillations.
348 To pursue this, we extracted the power values for each spectral band, for each subject,
349 before and after drug administration in those channels that showed a drug-induced
350 change in both TMS-induced and spontaneous power (see Results). Those channels
351 were selected to test whether changes in spontaneous oscillations may affect changes
352 in TMS-induced oscillations. Spearman correlation analyses were run between the
353 TMS-induced power change (power post-drug minus power pre-drug) and the resting
354 state EEG power modulation (power post-drug minus power pre-drug) in the different
355 drug conditions.

356 *2.8 Statistics*

357 Significant differences in TMS-induced α -band (8-12 Hz) and β -band (13-30 Hz) power
358 changes from baseline (pre-TMS) were assessed using non-parametric permutation
359 tests based on one-sample t-statistics (Maris and Oostenveld, 2007) comparing the
360 z-normalized TFRs against zero, as the pre-TMS baseline is zero on average by
361 definition (due to the above described baseline subtraction after full trial
362 z-normalization). The analysis was performed in two fixed time windows of interest

363 (TOIs), an early (30-200 ms; TOI1) and a late (200-400 ms; TOI2) window. TOIs were
364 chosen on the basis of the grand average of the pooled pre-drug measurements to track
365 power changes over time, and TOIs were kept identical for each statistical comparison
366 (**Figure 2D**) (Grent-'t-Jong et al., 2016). Note that TOI1 is close to spurious power
367 increases due to residual TMS-artifacts (approx. -30 to 30 ms), but that (i) a clear
368 demarcation line can be seen between the two areas for the TMS-induced oscillations
369 under investigation (cf. Figure 2D, Figure 3, and Figure 5), and that (ii) no systematic
370 confounds can arise from any residual TMS-related artifacts (as they are independent of
371 the pharmacological interventions).

372 To analyze drug modulation on TMS-induced α - and β -bands oscillatory power, multiple
373 non-parametric permutation tests based on dependent-sample t-statistics (Maris and
374 Oostenveld, 2007) were run between the different conditions (post- vs. pre-drug),
375 separately for each drug condition and TOIs. To correct for multiple comparisons due to
376 the large number of electrodes and time points within TOIs, we additionally conducted
377 cluster based permutation tests (Maris and Oostenveld, 2007) as implemented in
378 FieldTrip (<http://fieldtrip.fcdonders.nl>). Thus, a non-parametric permutation test (Monte-
379 Carlo method based on paired t-statistics) comparing the post-drug versus pre-drug
380 condition was performed for each electrode at each time bin within the two different
381 TOIs while averaging over the frequency bins of the spectral band of interest. Then,
382 t-values exceeding an *a priori* threshold of $p < 0.05$ were clustered based on adjacent
383 time bins and neighboring electrodes. Cluster-level statistics were calculated by taking
384 the sum of the t-values within each cluster. The statistical comparisons were performed
385 with respect to the maximum values of summed t-values. By means of a permutation

386 test (i.e., randomizing data across post-drug and pre-drug conditions and rerunning the
387 statistical test 1500 times), we obtained a reference distribution of the maximum of
388 summed cluster t-values to evaluate the statistic of the actual data. Clusters in the
389 original dataset were considered to be significant at $p < 0.05$ if $< 5\%$ of the permutations
390 used to construct the reference distribution yielded a maximum cluster-level statistic
391 larger than the cluster-level value observed in the original data.

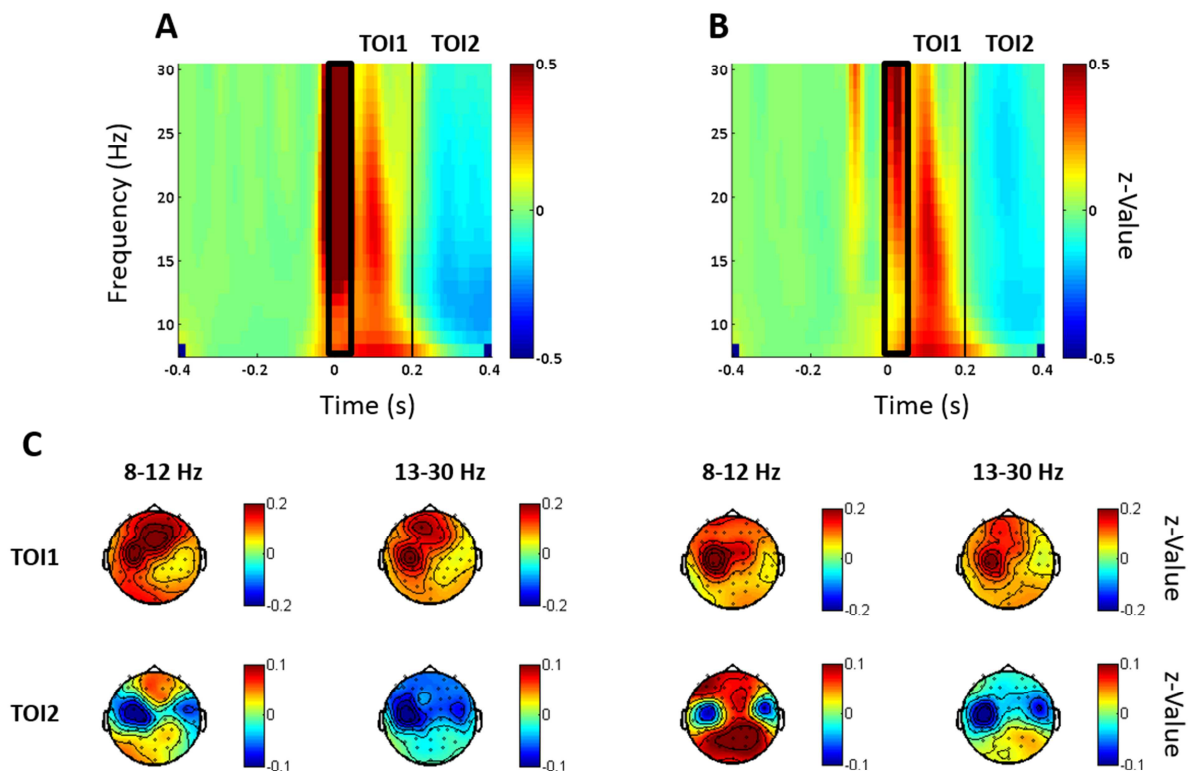
392 Finally, the cluster-based permutation approach was also used to evaluate drug-
393 induced power changes in spontaneous α - and β -band oscillations in the resting state
394 EEG (i.e., in the absence of TMS). Multiple dependent t-tests were run between the
395 different conditions (post- vs. pre-drug), separately for each drug condition.

396 **3. Results**

397 *3.1 Characterization of TMS-induced oscillations before drug intake*

398 Compared to pre-TMS baseline, time-frequency representation of TMS-induced
399 oscillations revealed a significant power increase (i.e. synchronization) in the β -band
400 (13-30 Hz) in TOI1 ($p < 0.001$, from 30 to 200 ms in both Experiment 1 and 2) and a
401 significant β -band power decrease (i.e. desynchronization) encompassing bilateral
402 sensorimotor cortices in TOI2 ($p < 0.05$, from 200 to 400 ms in both Experiments;
403 **Figure 3A-B**). For the α -band (8-12 Hz), only the early synchronization in TOI1 was
404 significant ($p = 0.001$ for both Experiments) but not the late desynchronization ($p > 0.05$;
405 **Figure 3A-B**); but there were significant increases in α -band power in TOI2 for frontal
406 and posterior clusters ($p = 0.003$ and $p = 0.03$, respectively). The topographic
407 distribution of induced power changes for α - and β -bands, shown in **Figure 3C**,

408 suggests maximal effects over the stimulated left M1 in both TOIs, with an additional
 409 homologue cluster in the contralateral right hemisphere (usually smaller and located
 410 slightly more anterior) for the α - and β -power desynchronization in TOI2. Topographical
 411 information is only based on sensor-level data, and should thus be interpreted with care.
 412



413

414 **Figure 3. Characterization of TMS-induced oscillations at pre-drug baseline.** Grand average of the
 415 time-frequency representation (TFR) of TMS-induced oscillations (averaged across subjects and the three
 416 pre-drug measurements) recorded at the C3 electrode as the best representation of the stimulated left
 417 M1_{HAND} in Experiment 1 (A) and Experiment 2 (B). TMS induced β -band (13-30 Hz) synchronization in
 418 TOI1 (30-200 ms) and β -desynchronization in TOI2 (200-400 ms). Topographical distribution of the
 419 average power in the respective frequency band at sensor level is shown in (C) for both TOI1 (top row)
 420 and TOI2 (bottom row) in each of the analyzed frequency bands. High-frequency noise at -100ms shown
 421 in panel B represents residual TMS-recharge artifact after interpolation due to the paired-pulse protocol
 422 (note that no actual TMS pulse was applied at -100 ms in the analyzed trials, see Methods section). The
 423 black boxes in proximity of 0 sec in A-B highlight the residual of the TMS artifacts and correspond to the
 424 time window which was not included in the analysis.

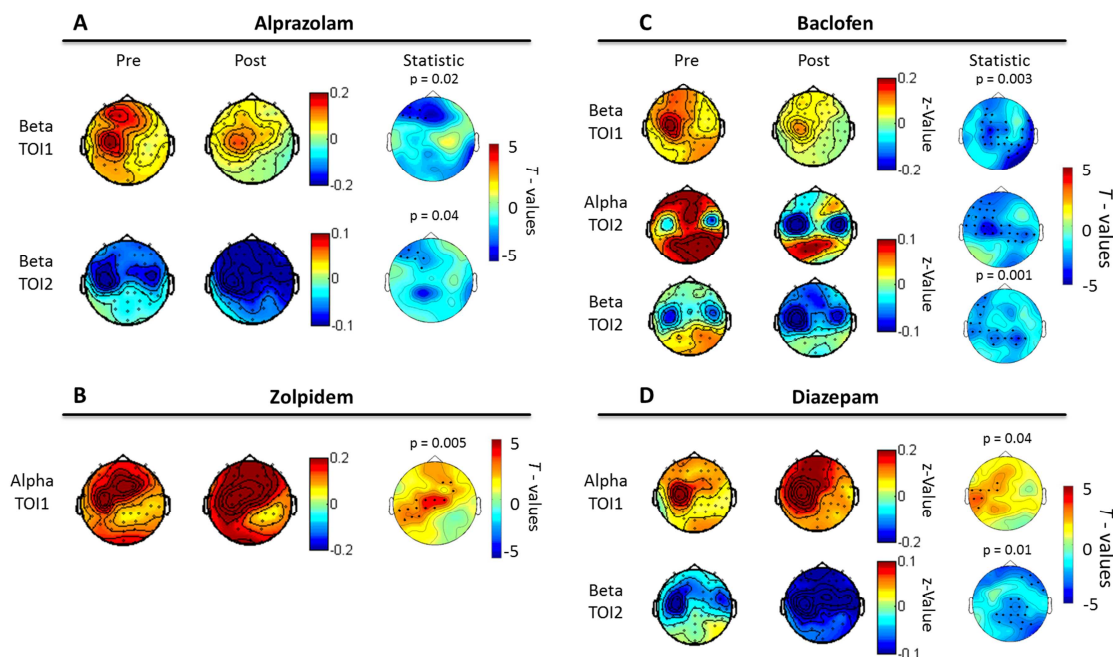
425 *3.2 Effects of GABAAR mediated inhibition on TMS-induced oscillations: Experiment 1*

426 Cluster-based permutation analyses revealed no differences in oscillatory power
427 between pre-drug conditions (all $p > 0.05$). Alprazolam resulted in a trend towards
428 increased α -band synchronization in TOI1 ($p = 0.08$), but significantly reduced β -band
429 synchronization in TOI1 ($p = 0.02$), and increased β -band desynchronization in TOI2
430 ($p = 0.04$; **Figure 4A**). Both effects appeared over left fronto-central electrodes.
431 Zolpidem increased the TMS-induced α -band synchronization in TOI1 over channels
432 close to the stimulated left M1_{HAND} ($p = 0.005$; **Figure 4B**). Placebo showed no effect in
433 any of the frequency bands or TOIs (all $p > 0.05$). The comparison of post-drug
434 conditions to placebo confirmed that zolpidem increased α -band synchronization in
435 TOI1 ($p = 0.01$), and that alprazolam decreased β -band synchronization in TOI1 ($p =$
436 0.002) and increased β -band desynchronization in TOI2 ($p = 0.03$).

437 *3.3 Effects of GABAAR and GABABR mediated inhibition on TMS-induced oscillations:*
438 *Experiment 2*

439 Cluster-based permutation analyses showed no differences in oscillatory power
440 between pre-drug conditions ($p > 0.05$). Baclofen significantly reduced TMS-induced
441 oscillations in the β -band in TOI1 in a widespread area including the stimulated left
442 sensorimotor cortex as well as left frontal and right parieto-occipital regions ($p = 0.003$).
443 This effect was followed during TOI2 by an increase of α - and β -band
444 desynchronization with a roughly comparable topography (both $p = 0.001$; **Figure 4C**).
445 Diazepam increased α -band synchronization in TOI1 at electrodes close the stimulated
446 sensorimotor cortex ($p = 0.04$), and increased β -band desynchronization in TOI2 mainly

447 in right frontal and centro-parietal sites ($p = 0.01$; **Figures 4D**). No significant
 448 modulation of TMS-induced oscillations was observed in the placebo condition in either
 449 TOI ($p > 0.05$). The comparison of post-drug conditions to placebo confirmed that
 450 baclofen decreased β -band synchronization in TOI1 ($p = 0.003$), and that diazepam
 451 increased β -band desynchronization in TOI2 ($p = 0.04$).



452
 453 **Figure 4. Topographies of significant drug-induced changes in TMS-induced oscillatory power.**
 454 Topographies of drug-induced changes in TMS-induced oscillatory power are shown for alprazolam (A)
 455 and zolpidem (B) from Experiment 1 and for baclofen (C) and diazepam (D) from Experiment 2,
 456 separately for α - (8-12 Hz) and β -band (13-30 Hz) power and for TOI1 (30-200 ms) and TOI2 (200-400
 457 ms). (A) Alprazolam decreased β -band synchronization in TOI1 and further increased β -band
 458 desynchronization in TOI2, both in left frontal regions. (B) Zolpidem only increased α -band
 459 synchronization in TOI1 in left centro-parietal and right frontal regions. (C) Baclofen decreased β -band
 460 synchronization in TOI1 and increased both α - and β -band desynchronization in TOI2. (D) Diazepam
 461 increased TMS-induced α -band synchronization in TOI1 in left central regions and increased β -band
 462 desynchronization in right frontal and medial centro-parietal regions. Significant electrodes ($p < 0.05$,
 463 cluster corrected) are denoted with crosses in the t-statistic maps.

464 *3.4 Effects of drugs on MEPs*

465 We aimed to ensure that the observed drug changes in TMS-induced oscillations
466 cannot be explained by concurrent pharmacological changes in either corticospinal
467 excitability or somatosensory re-afferent feedback due to the TMS-evoked muscle
468 twitch, a potential confounding factor (Fecchio et al., 2017; Petrichella et al., 2017).
469 Therefore, we analyzed the average amplitude of MEPs and the proportion of trials with
470 suprathreshold MEPs obtained during the TMS-EEG recordings of Experiment 2 (no
471 EMG data was co-registered during TEP measurements for Experiment 1). Since TMS
472 intensity for TEP recordings was set to 100% RMT, roughly 50% each of trials with
473 subthreshold and suprathreshold MEP were obtained (**Table 1**). RMT increased after
474 the intake of baclofen ($p = 0.028$) and diazepam ($p = 0.004$), but not after placebo ($p >$
475 0.2). After post-drug re-adjustment of stimulus intensity to 100% RMT, there were no
476 post- vs. pre-drug differences for average MEP amplitude or the proportion of
477 suprathreshold trials in any of the drug conditions (**Table 1**).

478 *3.5 Contribution of MEP-related afferent feedback to TMS-induced oscillatory power*

479 Since somatosensory stimulation alone can induce α - and β -desynchronization (Neuper
480 et al., 2005), and TMS-evoked muscle twitches in the contralateral hand muscles are
481 inevitably associated with somatosensory afferent feedback from muscle spindles
482 reentering the sensorimotor cortex, we tested for Experiment 2 (for which MEP data
483 was available) whether the observed TMS-induced α - and β -band desynchronization
484 can be explained by the presence or absence of suprathreshold MEPs > 0.05 mV

485 (Rossini et al., 2015). According to the stimulation intensity of 100% RMT, per definition
486 roughly half of the trials were supra- and subthreshold trials, respectively (**Table 1**).

487

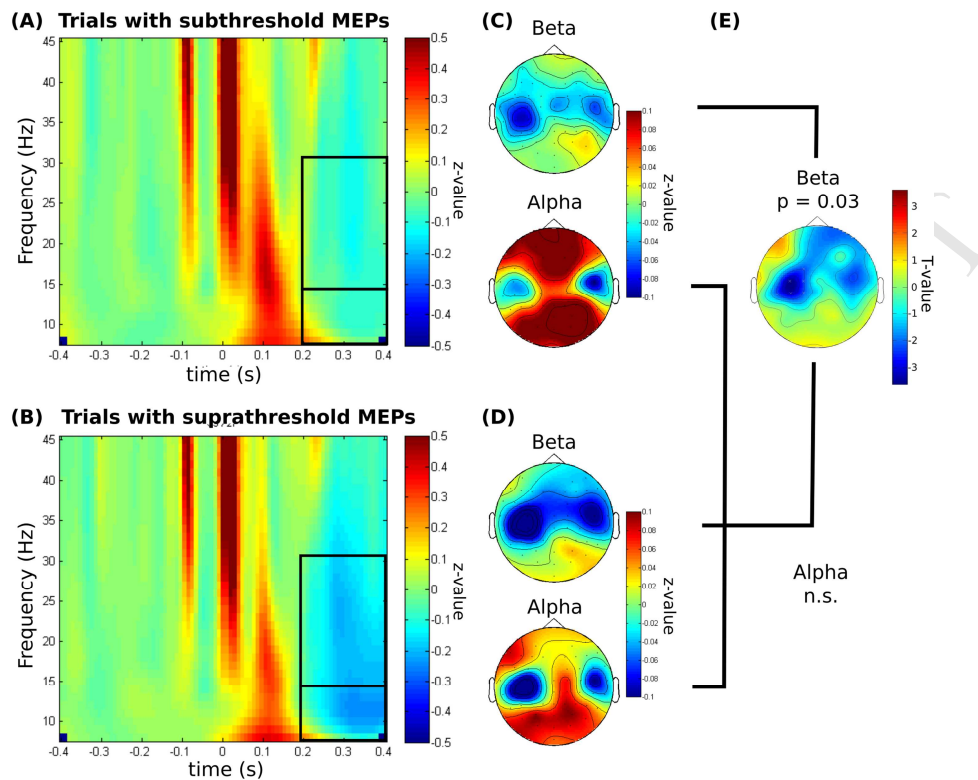
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488 **Table 1: RMT (% maximum stimulator output, %MSO), MEP amplitudes (mV) and proportion of**
 489 **suprathreshold MEPs (%) for pre- and post-drug conditions of Experiment 2.**

	pre-drug			post-drug			t-test (post-pre)		
	RMT %MSO	Amp (mV)	% supra	RMT %MSO	Amp (mV)	% supra	RMT	Amp	% supra
Baclofen	44.07	0.15	50.43	44.87	0.20	58.66	$t_{15} = 2.45$ $p = 0.028$	$t_{11} = 1.31$ $p = 0.22$	$t_{11} = 1.10$ $p = 0.29$
	\pm 4.37	\pm 0.1	\pm 18.16	\pm 4.79	\pm 0.12	\pm 16.28			
Diazepam	44.60	0.16	53.19	46.80	0.17	51.58	$t_{15} = 3.51$ $p = 0.004$	$t_{12} = 0.06$ $p = 0.95$	$t_{12} = -0.15$ $p = 0.88$
	\pm 5.04	\pm 0.11	\pm 23.09	\pm 5.71	\pm 0.11	\pm 20.64			
Placebo	44.80	0.18	56.62	45.20	0.23	56.65	$t_{15} = 1.19$ $p = 0.25$	$t_{12} = 1.91$ $p = 0.08$	$t_{12} = 0.18$ $p = 0.86$
	\pm 4.75	\pm 0.10	\pm 20.59	\pm 4.57	\pm 0.16	\pm 26.06			

490 Mean \pm SD as well as t-statistic and p-value are provided for post-pre comparisons per drug condition.
 491 Different degrees of freedom result from varying number of available datasets (N = 15 for RMT
 492 measurements; N = 12 (baclofen) and N = 13 (diazepam and placebo) for co-registered EMG (MEP and
 493 % supra) during TEP measurements.

494 We thus repeated the above described analyses of TMS-induced oscillations in the
 495 α - and β -bands during TOI1 and TOI2, separately for suprathreshold and subthreshold
 496 MEP trials, pooled over all pre-drug measurements of Experiment 2 (to gain sufficient
 497 trial numbers and thus statistical power). While no differences were observed in either
 498 frequency band for the early synchronization (TOI1) between suprathreshold and
 499 subthreshold MEPs (all $p > 0.05$), we found indeed stronger β -band desynchronization
 500 in TOI2 for trials with suprathreshold compared to subthreshold MEPs ($p = 0.03$),
 501 whereas a similar effect for α -band desynchronization remained non-significant ($p >$
 502 0.05) (**Figure 5**). Low trial numbers and thus reduced statistical power after trial splitting
 503 did not allow statistical post-pre cluster t-test comparisons divided by sub- and
 504 suprathreshold trials and drug condition.



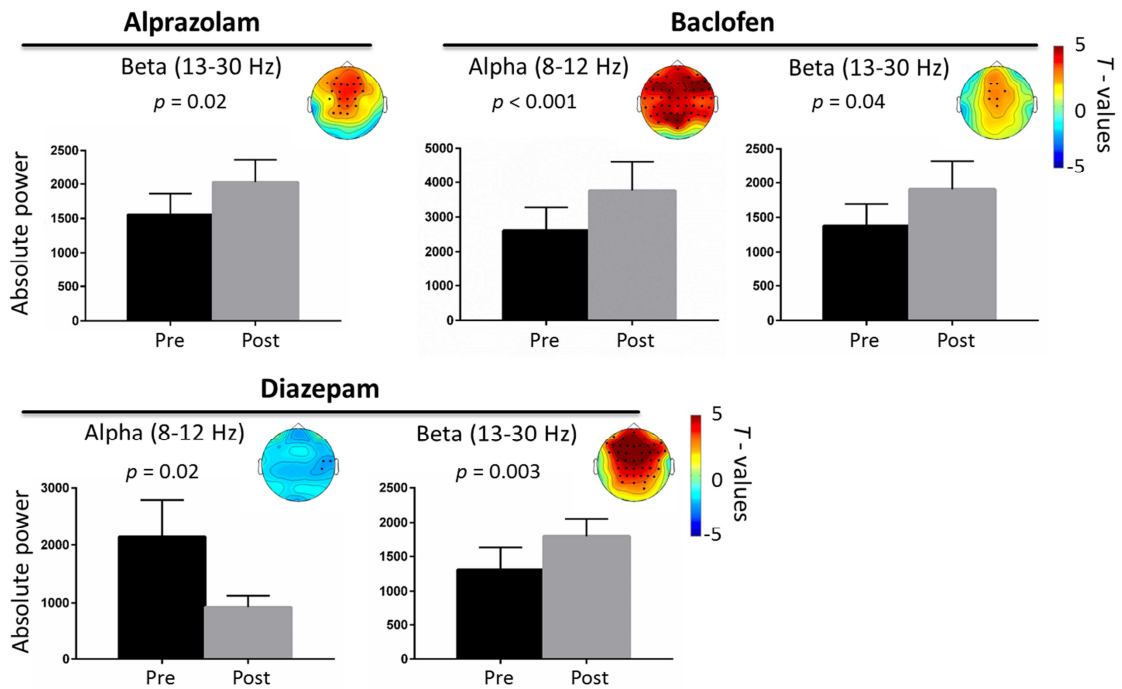
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506 **Figure 5. Comparison of TMS-induced α - and β -desynchronization for trials with supra- vs.**
 507 **subthreshold MEPs at pre-drug baseline.** TFRs suggest that late α - and β -desynchronization in TO12
 508 was smaller for (A) trials with subthreshold MEPs than for (B) trials with suprathreshold MEPs at electrode
 509 C3 (roughly overlying the left sensorimotor cortex). Topographical representations of TMS-induced α - and
 510 β -band power show that for both (C) sub- and (D) suprathreshold MEPs, desynchronization was confined
 511 to the stimulated left (and to a lesser degree contralateral right) sensorimotor cortex. (E) Direct
 512 comparison of supra vs. subthreshold MEP trials using cluster t-statistics, revealed significantly larger
 513 β -band desynchronization associated with supra- than subthreshold MEPs over the left sensorimotor
 514 cortex, whereas α -band desynchronization showed the same tendency but did not reach significance.
 515 Data were pooled over all pre-drug measures of Experiment 2 to gain sufficient statistical power despite
 516 trial splitting.

517 3.6 Effects of drugs on resting state EEG

518 We finally analyzed the impact of each drug on resting state spontaneous oscillatory
 519 activity without TMS events (i.e. resting state EEG). In Experiment 1, alprazolam
 520 increased spontaneous β -band power at fronto-central sites (n=13, p = 0.02; **Figure 6**)
 521 but had no significant effect on α -band power (p > 0.05), whereas no significant
 522 modulations could be observed for zolpidem and placebo (p > 0.05). The lack of effect

523 by zolpidem could be explained by the fact that we obtained resting state EEG in the
524 eyes open condition, and that its increasing effect on β -band power has disappeared
525 after 90 min (Patat et al., 1994). In Experiment 2, baclofen significantly enhanced
526 spontaneous α -band power at lateral frontal as well as medial parietal sites ($p < 0.001$),
527 and β -band power at medial frontal sites ($p = 0.04$); diazepam decreased α -band power
528 at a right lateral central cluster ($p = 0.02$) and increased β -band power at medial frontal
529 sites ($p = 0.003$; **Figure 6**), whereas placebo did not induce any significant changes ($p >$
530 0.05). Importantly, the above described drug effects on TMS-induced oscillatory power
531 are unlikely to be explained by ceiling effects resulting from drug-induced changes of
532 spontaneous brain oscillations. While their topographies partially overlap (both
533 comprising medial and lateral frontal as well as medial parietal sites), and increases in
534 spontaneous EEG power are matched by decreases in TMS-induced synchronization or
535 increases in desynchronization (cf. **Figure 5** to **Figure 4**), there was no significant
536 correlation between the drug-induced changes in spontaneous α - or β -band resting
537 state EEG oscillatory power and the respective drug effects on TMS-induced
538 oscillations (all $p > 0.3$).



539

540 **Figure 6. Effects of drugs on resting state EEG (eyes open):** Bar charts represent absolute EEG
 541 power (mean \pm SEM) pre (black) and post (grey) drug intake. Each plot shows the grand average across
 542 all subjects and the significant channels, which are indicated by black dots in the t-statistic maps. Red
 543 represents as increase of power, whereas blue depicts a decrease. For further details, see Material and
 544 Methods.

545

546 4. Discussion

547 We disentangled for the first time the mixed activity that is usually captured by TMS-
 548 related spectral perturbation measures to investigate the specific contribution of induced
 549 oscillatory power after removal of the evoked responses (**Figure 2**), the importance of
 550 which has recently been highlighted by Pellicciari et al. (2017). TMS induced a specific
 551 pattern of oscillatory power in the α - and β -bands, characterized by an early
 552 synchronization over the stimulated sensorimotor and adjacent frontal cortex and a
 553 subsequent profound desynchronization over the stimulated and contralateral
 554 sensorimotor cortex (**Figure 3**). Pharmacological manipulation (**Figure 4**) suggested

555 that GABAAR mediated inhibition contributes to the early α -band synchronization (30-
556 200 ms after the TMS pulse) in the stimulated sensorimotor cortex, as it was increased
557 exclusively by GABAAR positive modulators (i.e., diazepam and zolpidem, and a trend
558 towards increase by alprazolam). Furthermore, all drugs except zolpidem increased the
559 late β -band desynchronization (200-400 ms after the TMS pulse) over lateral frontal and
560 medial parietal sites, suggesting an involvement of both GABAergic and GABAergic
561 processes. Finally, baclofen increased the late α -band desynchronization over the
562 stimulated sensorimotor cortex and its contralateral homologue but also adjacent lateral
563 frontal regions, suggesting the specific contribution of late GABAergic mediated inhibition.
564 Importantly, while late α - and β -desynchronization were partially driven by
565 somatosensory re-afferent feedback from the evoked muscle twitch (**Figure 5**), the
566 observed pharmacological modulations of TMS-induced oscillatory activity cannot be
567 attributed to pharmacologically induced changes in corticospinal excitability (**Table 1**),
568 the amount of sensorimotor re-afferent feedback from the muscle twitch (**Figure 5**), or
569 changes in the resting state EEG power in the respective frequency bands (**Figure 6**).

570 *4.1 TMS-induced oscillations in the sensorimotor cortex*

571 We characterized the spatiotemporal profile of oscillations induced by single-pulse TMS
572 of left M1_{HAND}. In line with the idea of site-specific 'natural frequencies' (Ferrarelli et al.,
573 2012; Rosanova et al., 2009), EEG responses were dominated by specific dynamics in
574 the α - and β -bands, the prevalent oscillations of the sensorimotor system (Neuper et al.,
575 2005). TMS-induced oscillations showed an initial synchronization over the stimulated
576 sensorimotor and adjacent lateral frontal cortex, followed by a subsequent

577 desynchronization over the stimulated sensorimotor cortex as well as its contralateral
578 homologue (**Figure 3**). TMS-evoked responses in the α - and β -band have previously
579 been reported (Brignani et al., 2008; Fuggetta et al., 2005; Paus et al., 2001; Van Der
580 Werf and Paus, 2006; Van Der Werf et al., 2006; Veniero et al., 2011), but the non-
581 phase-locked modulation of α - and β -band oscillations has not been described yet.
582 What may be their underlying mechanisms? MEP-informed control analyses,
583 contrasting trials with suprathreshold vs. subthreshold MEPs (with identical stimulation
584 intensity), suggest that the late β -band desynchronization over the stimulated (and
585 contralateral) sensorimotor cortex was partially driven by muscle twitch-related
586 somatosensory re-afferent feedback associated with suprathreshold MEPs (**Figure 5**).
587 Indeed, both movement and sensory stimulation are well known to desynchronize
588 α - and β -band oscillations in the sensorimotor cortex (Neuper et al., 2006; Pfurtscheller,
589 2001). However, these results do not exclude the possibility that a third factor, for
590 example spontaneous fluctuations of corticospinal excitability, accounted for both the
591 amount of TMS-induced cortical desynchronization and the MEP amplitude. In that
592 case, the observed β -band desynchronization would be a direct consequence of the
593 cortical stimulation, accompanied by corresponding variations in MEP amplitude. To
594 eventually solve this question, one would need to block sensory afference independent
595 of corticospinal excitability or stimulation intensity, e.g., by transient ischemic forearm
596 deafferentation (Ziemann et al., 1998).

597 Moreover, the early synchronization of the stimulated sensorimotor cortex does
598 not seem to be dependent on the TMS-evoked muscle twitch, as it did not differ
599 between sub- and suprathreshold MEPs (**Figure 5A-B**), and may thus rather reflect the

600 direct transcranial excitation of the oscillation-generating circuits in the motor network.
601 Commonly, β -band synchronization is observed during the so called 'rebound' phase,
602 which follows about 200-600 ms after an initial stimulus- or movement-induced
603 desynchronization and is usually not observed for the α -band (Neuper et al., 2006). In
604 line with our findings, this pattern is typically located in bilateral sensorimotor cortex,
605 with the β -band rebound specifically peaking in M1 contralateral to the movement
606 (Jurkiewicz et al., 2006; Neuper et al., 2006). However, the TMS-induced
607 synchronization preceded the desynchronization and thus cannot be attributed to a
608 rebound phenomenon.

609 Previous TMS-EEG work has described a topographically wide-spread net
610 increase in the α - and β -band oscillatory EEG power within 530 ms after the TMS pulse,
611 scaling with stimulation intensity (Fuggetta et al., 2005). However, early and late
612 intervals were not distinguished, and induced oscillations were not analyzed separately
613 from evoked responses. Therefore, evoked components may have considerably
614 influenced these findings. Our results are in line with the oscillatory pattern observed in
615 the local field potential of the subthalamic nucleus (STN) following TMS of the ipsilateral
616 (and even contralateral) M1, as recorded via intracranial electrodes for deep brain
617 stimulation in patients with Parkinson's disease (Doyle Gaynor et al., 2008). Importantly,
618 TMS at both suprathreshold and subthreshold intensities caused an initial β -band
619 synchronization before 200 ms and a subsequent prolonged desynchronization (200 to
620 600 ms) of STN β -band oscillations, again suggesting that β -band desynchronization is
621 not entirely driven by sensory feedback. But also in that study, the induced and evoked
622 oscillations were not disentangled, and no concurrent scalp EEG was recorded, leaving

623 the origin of the oscillatory change unresolved. Interestingly, no effect on α -band power
624 was observed in the STN, in line with the idea that TMS-induced α - and β -band
625 oscillations engage separate, though partially overlapping, circuits. While it has been
626 suggested that rolandic α - and β -band oscillations emerge from somatosensory and
627 motor networks, respectively (Salmelin and Hari, 1994), α -band oscillations have also
628 been recorded from layer III of the rat M1, whereas β -band oscillations dominated in
629 layer V (Ronnqvist et al., 2013). In summary, the observed TMS-induced
630 synchronization-desynchronization dynamic of α - and particularly β -band oscillations
631 over sensorimotor cortices is likely to be a direct consequence of the transcranial
632 activation of α - and β -oscillation generating cortico-cortical and cortico-subcortical
633 circuits, while re-afferent feedback from the muscles may further enforce cortical
634 desynchronization.

635 *4.2 Pharmacological modulation of TMS-induced oscillations*

636 Inhibitory GABAergic neurotransmission is critical for synchronization of neural activity
637 and generation of network oscillations (Wang, 2010). For instance, both α - and β -band
638 oscillations have been linked to inhibitory function, i.e. the suppression of perceptual
639 input processing via 'pulsed inhibition' (Jensen and Mazaheri, 2010; Klimesch et al.,
640 2007; Mathewson, 2011) and the control of motor output during response inhibition
641 (Picazio et al., 2014; Zhang et al., 2008). Further, the period of decreased motor cortical
642 excitability following electrical median nerve stimulation (Chen et al., 1999) may be
643 related to the stimulation-induced β -band rebound. Accordingly, GABAergic drugs also
644 modulated TMS-induced oscillatory power synchronization at early (30-200 ms) and
645 desynchronization at late (200-400) post-TMS intervals, for both the α - and β -bands

646 **(Figure 4)**. The rather complementary effects of GABAAR and GABABR mediated
647 inhibition suggest that TMS-induced early synchronization and late desynchronization
648 may be dominated by different inhibitory mechanisms. Both broad and α -1 subunit
649 specific GABAergic drive enhanced the early α -band synchronization. In contrast, the
650 late β -band desynchronization was under the influence of subunit-unspecific GABAAR
651 and GABABR activity, whilst late α -band desynchronization was exclusively driven by
652 GABABR neurotransmission. It is important to highlight that the two benzodiazepines
653 diazepam and alprazolam showed highly similar effect patterns, but not identical with
654 respect to their statistical significance. Two main points have to be considered that may
655 have contributed independently to these slight differences: (i) the two drugs were
656 administered in two separate experiments to independent subject samples, rendering
657 direct between-study comparisons difficult; (ii) the two drugs are highly similar but not
658 identical, and slight differences in the pharmacokinetics may have had an impact. For
659 instance, diazepam is more likely than alprazolam to cause drowsiness, but alprazolam
660 is reported to have more severe withdrawal effects on discontinuation. Finally,
661 alprazolam has a shorter half-life compared to diazepam.

662 How does the observed GABAergic modulation of TMS-induced oscillatory power
663 relate to the GABAergic impact on spontaneous α - and β -band oscillations at rest and
664 during movement-related modulation? At rest, GABAAR positive modulators
665 consistently increase β -band power (in rolandic and frontal regions), whereas they often
666 reduce α -band power (usually reported for parieto-occipital and not specifically for
667 rolandic cortex). These opposing effects have been demonstrated for all drugs tested in
668 this study, namely diazepam (Jensen et al., 2005; Saletu et al., 1987), alprazolam

669 (Kaplan et al., 1998; Saletu et al., 1994), and zolpidem (de Haas et al., 2010). For
670 diazepam, we could replicate the power increase and decrease for β - and α -bands,
671 respectively, and we also observed β -band power increase for alprazolam, but contrary
672 to our expectations, no effects for zolpidem (**Figure 6**). The effect of the GABABR
673 agonist baclofen on the resting state EEG had not been investigated before in humans.
674 We showed a strong and topographically widespread drug-induced increase in both
675 spontaneous α - and β -band power (**Figure 6**), to some extent similar to an increase in
676 β - (but not α -) band power shown in DBA/2J mice (Marrosu et al., 2006).

677 Conversely, during and directly after movement, GABAergic inhibition appears to
678 enhance *movement related β -band desynchronization* (MRBD) but reduce subsequent
679 *post-movement β -band rebound* (PMBR). While bulk GABA concentration in M1_{HAND}, as
680 measured by magnetic resonance spectroscopy (MRS), shows a positive relationship
681 with individual PMBR (Gaetz et al., 2011), pharmacological manipulation of its
682 synaptically active portion revealed the opposite. Tiagabine, a GABA reuptake inhibitor
683 and thus receptor unspecific, increased spontaneous β -band power at rest, but
684 enhanced MRBD and reduced PMBR (Muthukumaraswamy et al., 2013), whereas
685 diazepam also enhanced MRBD, but did not affect PMBR (Hall et al., 2011). The
686 authors suggested that MRBD is GABAAR dependent, whereas PMBR may be
687 GABABR dependent. Thus, TMS-induced β -band oscillations seem to be more similar
688 to movement-related than resting β -band oscillations, as both GABAA- and GABABergic
689 inhibition enhanced late β -band desynchronization, and GABABR mediated inhibition
690 also enhanced late α -band desynchronization, while GABAergic effects on spontaneous
691 and TMS-induced oscillations did not correlate. It remains unclear why the

692 pharmacological enhancement of GABAergic inhibition synchronizes spontaneous but
693 desynchronizes movement-related and TMS-induced β - (and α -) oscillations. However,
694 our results suggest that GABAergic inhibition plays a different role in the resting and
695 activated motor cortex.

696 Importantly, the observed GABAergic effects on TMS-induced oscillations cannot
697 be explained merely by TMS-evoked muscle twitches or the associated re-afferent
698 somatosensory feedback. Firstly, drug-induced changes in TMS-induced oscillations
699 mainly occurred over medial and lateral frontal as well as medial parietal sites, for which
700 no somatosensory feedback-related activation was observed (**Figure 4** vs. **Figure 5**).
701 Secondly, diazepam and baclofen did alter TMS-induced α - and β -band oscillatory
702 power in Experiment 2, although TMS-evoked muscle responses, and thus
703 somatosensory afferent feedback, were unchanged, because stimulation intensity was
704 kept constant at 100% RMT (**Table 1**).

705 The question of whether or not to re-adjust stimulation intensity after a
706 pharmacological intervention based on a certain excitability estimate (here the RMT) is
707 difficult to answer, and there are advantages and disadvantages of both options. In fact,
708 this dilemma holds true for any kind of intervention that modulates the excitability of
709 certain neuron populations in the target region while using a network response (such as
710 TMS-evoked or -induced EEG responses) as a readout. In the case of the motor cortex,
711 readjustment of stimulation intensity to compensate for drug-induced RMT changes
712 ensures comparable excitation of the corticospinal system and thus keeps TMS-evoked
713 muscle responses and related sensory feedback constant. However, there are two
714 important unknowns. Firstly, it is unclear the excitability change of which specific neuron

715 population gave rise to the RMT change in the first place (corticospinal motor neurons in
716 layer IV, connected pyramidal neurons in layer II-III, interneurons, or even spinal motor
717 neurons). And secondly, it is unknown which specific neuron populations (and even
718 which brain regions) give rise to the TMS-evoked/-induced EEG response. Thus, if RMT
719 reflects the excitability of cortical motor neurons, adjustment will ensure that those
720 neurons will be effectively excited to the same degree before and after drug intake, and
721 a changed EEG response is attributable to changed excitability of other connected
722 regions or changed functional connectivity within the same network. Conversely, no
723 adjustment would result in different excitation and consequently different output levels of
724 the cortical motor neurons, ranging from no output at all (if stimulation became
725 subthreshold) to a strong enhancement of the output to connected regions, limiting the
726 interpretability of changed network responses. However, different stimulation intensities
727 may also affect different neuron populations, and for other co-stimulated neuron
728 populations, unaffected by the RMT change but involved in the network response,
729 adjustment would result in different levels of effective excitation and thus different EEG
730 responses (Casarotto et al., 2010). Thus, re-adjustment to RMT can be both a necessity
731 and a potential confound when investigating changes in TMS-evoked/induced
732 oscillatory activity after drug intake (or any other intervention). While on the expense of
733 consistency and direct comparability between the two experiments, we were also
734 fortunate having employed both approaches in Experiment 1 and 2, respectively, using
735 drugs with highly comparable GABAergic effects (i.e., alprazolam and diazepam) and
736 finding largely comparable effects for both (**Figures 4A, D**). Future studies, should thus
737 evaluate post-drug (or generally post-interventional) measures with both adjusted and

738 unadjusted intensities to overcome these limitations. For target sites outside M1 (lacking
739 an index such as RMT, maybe requiring electric field estimates), it is an even larger
740 challenge to disentangle excitability changes of the transcranially stimulated neurons
741 from that of transsynaptically stimulated ones within the connected network.

742 *4.3 Conclusion*

743 We aimed at disentangling TMS-induced (non-phase-locked) oscillatory activity
744 following M1_{HAND} stimulation from TMS-evoked (phase-locked) responses. Results
745 revealed a specific and dynamic TMS-induced synchronization-desynchronization
746 pattern in the α - and β -bands, mainly over the stimulated and contralateral sensorimotor
747 cortices that is complementary to TMS-evoked EEG potentials and resting-state EEG.
748 The early α -synchronization was increased by the GABAergic drugs and decreased by
749 the GABAergic drug, the late α -desynchronization was increased by the GABAergic
750 drug, and the late β - desynchronization was increased by GABAergic and
751 GABAergic drugs. These findings are relevant for future investigations of GABA-
752 related alterations in functional brain connectivity, e.g., in brain network disorders such
753 as schizophrenia or epilepsy, as functional connectivity generally employs frequency
754 information as a code.

755

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763 **References**

- 764 Bonato, C., Miniussi, C., Rossini, P.M., 2006. Transcranial magnetic stimulation and cortical evoked
765 potentials: a TMS/EEG co-registration study. *Clin Neurophysiol* 117, 1699-1707.
- 766 Brignani, D., Manganotti, P., Rossini, P.M., Miniussi, C., 2008. Modulation of cortical oscillatory activity
767 during transcranial magnetic stimulation. *Hum Brain Mapp* 29, 603-612.
- 768 Casarotto, S., Romero Lauro, L.J., Bellina, V., Casali, A.G., Rosanova, M., Pigorini, A., Defendi, S.,
769 Mariotti, M., Massimini, M., 2010. EEG responses to TMS are sensitive to changes in the perturbation
770 parameters and repeatable over time. *PLoS One* 5, e10281.
- 771 Chellappa, S.L., Gaggioni, G., Ly, J.Q., Papachilleos, S., Borsu, C., Brzozowski, A., Rosanova, M.,
772 Sarasso, S., Luxen, A., Middleton, B., Archer, S.N., Dijk, D.J., Massimini, M., Maquet, P., Phillips, C.,
773 Moran, R.J., Vandewalle, G., 2016. Circadian dynamics in measures of cortical excitation and inhibition
774 balance. *Sci Rep* 6, 33661.
- 775 Chen, R., Corwell, B., Hallett, M., 1999. Modulation of motor cortex excitability by median nerve and digit
776 stimulation. *Exp Brain Res* 129, 77-86.
- 777 Chung, S.W., Rogasch, N.C., Hoy, K.E., Fitzgerald, P.B., 2015. Measuring Brain Stimulation Induced
778 Changes in Cortical Properties Using TMS-EEG. *Brain Stimul*.
- 779 Cohen, M.X., Donner, T.H., 2013. Midfrontal conflict-related theta-band power reflects neural oscillations
780 that predict behavior. *J Neurophysiol* 110, 2752-2763.
- 781 Cossette, P., Liu, L., Brisebois, K., Dong, H., Lortie, A., Vanasse, M., Saint-Hilaire, J.M., Carmant, L.,
782 Verner, A., Lu, W.Y., Wang, Y.T., Rouleau, G.A., 2002. Mutation of GABRA1 in an autosomal dominant
783 form of juvenile myoclonic epilepsy. *Nat Genet* 31, 184-189.
- 784 Darmani, G., Zipser, C.M., Bohmer, G.M., Deschet, K., Muller-Dahlhaus, F., Belardinelli, P., Schwab, M.,
785 Ziemann, U., 2016. Effects of the Selective alpha5-GABAAR Antagonist S44819 on Excitability in the
786 Human Brain: A TMS-EMG and TMS-EEG Phase I Study. *J Neurosci* 36, 12312-12320.
- 787 David, O., Kilner, J.M., Friston, K.J., 2006. Mechanisms of evoked and induced responses in MEG/EEG.
788 *Neuroimage* 31, 1580-1591.
- 789 de Haas, S.L., Schoemaker, R.C., van Gerven, J.M., Hoever, P., Cohen, A.F., Dingemans, J., 2010.
790 Pharmacokinetics, pharmacodynamics and the pharmacokinetic/ pharmacodynamic relationship of
791 zolpidem in healthy subjects. *J Psychopharmacol* 24, 1619-1629.
- 792 Delorme, A., Makeig, S., 2004. EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics
793 including independent component analysis. *J Neurosci Methods* 134, 9-21.
- 794 Di Lazzaro, V., Ziemann, U., Lemon, R.N., 2008. State of the art: Physiology of transcranial motor cortex
795 stimulation. *Brain Stimul* 1, 345-362.
- 796 Donner, T.H., Siegel, M., 2011. A framework for local cortical oscillation patterns. *Tr. Cog. Sci.* 15, 191-199.
- 797 Doyle Gaynor, L., Kühn, A., Dileone, M., Litvak, V., Eusebio, A., Pogosyan, A., Androulidakis, A., Tisch, S.,
798 Limousin, P., Insola, A., 2008. Suppression of beta oscillations in the subthalamic nucleus following cortical
799 stimulation in humans. *Eur. J. Neurosci.* 28, 1686-1695.
- 800 Engel, A.K., Fries, P., 2010. Beta-band oscillations--signalling the status quo? *Curr Opin Neurobiol* 20, 156-
801 165.
- 802 Farzan, F., Barr, M.S., Hoppenbrouwers, S.S., Fitzgerald, P.B., Chen, R., Pascual-Leone, A., Daskalakis,
803 Z.J., 2013. The EEG correlates of the TMS-induced EMG silent period in humans. *Neuroimage* 83C, 120-
804 134.
- 805 Fecchio, M., Pigorini, A., Comanducci, A., Sarasso, S., Casarotto, S., Premoli, I., Mazza, A., Derchi, C.-C.,
806 Russo, S., Resta, F., Ferrarelli, F., Mariotti, M., Ziemann, U., Massimini, M., Rosanova, M., 2017. The
807 Spectral Features Of EEG Responses To Transcranial Magnetic Stimulation Of The Primary Motor Cortex
808 Depend On The Amplitude Of The Motor Evoked Potentials. *bioRxiv*.

- 809 Ferrarelli, F., Massimini, M., Peterson, M.J., Riedner, B.A., Lazar, M., Murphy, M.J., Huber, R., Rosanova,
810 M., Alexander, A.L., Kalin, N., Tononi, G., 2008. Reduced Evoked Gamma Oscillations in the Frontal
811 Cortex in Schizophrenia Patients: A TMS/EEG Study. *Am J Psychiatry*.
- 812 Ferrarelli, F., Sarasso, S., Guller, Y., Riedner, B.A., Peterson, M.J., Bellesi, M., Massimini, M., Postle, B.R.,
813 Tononi, G., 2012. Reduced Natural Oscillatory Frequency of Frontal Thalamocortical Circuits in
814 Schizophrenia. *Arch Gen Psychiatry*.
- 815 Fuggetta, G., Fiaschi, A., Manganotti, P., 2005. Modulation of cortical oscillatory activities induced by
816 varying single-pulse transcranial magnetic stimulation intensity over the left primary motor area: a
817 combined EEG and TMS study. *Neuroimage* 27, 896-908.
- 818 Gaetz, W., Edgar, J.C., Wang, D.J., Roberts, T.P., 2011. Relating MEG measured motor cortical
819 oscillations to resting gamma-aminobutyric acid (GABA) concentration. *Neuroimage* 55, 616-621.
- 820 Garcia, J.O., Grossman, E.D., Srinivasan, R., 2011. Evoked potentials in large-scale cortical networks
821 elicited by TMS of the visual cortex. *J Neurophysiol* 106, 1734-1746.
- 822 Grandchamp, R., Delorme, A., 2011. Single-trial normalization for event-related spectral decomposition
823 reduces sensitivity to noisy trials. *Front Psychol* 2, 236.
- 824 Greenblatt, D.J., Wright, C.E., 1993. Clinical pharmacokinetics of alprazolam. Therapeutic implications. *Clin*
825 *Pharmacokinet* 24, 453-471.
- 826 Grent-'t-Jong, T., Rivolta, D., Sauer, A., Grube, M., Singer, W., Wibral, M., Uhlhaas, P.J., 2016. MEG-
827 measured visually induced gamma-band oscillations in chronic schizophrenia: Evidence for impaired
828 generation of rhythmic activity in ventral stream regions. *Schizophr Res* 176, 177-185.
- 829 Hall, S.D., Stanford, I.M., Yamawaki, N., McAllister, C.J., Ronnqvist, K.C., Woodhall, G.L., Furlong, P.L.,
830 2011. The role of GABAergic modulation in motor function related neuronal network activity. *Neuroimage*
831 56, 1506-1510.
- 832 Herring, J.D., Thut, G., Jensen, O., Bergmann, T.O., 2015. Attention Modulates TMS-Locked Alpha
833 Oscillations in the Visual Cortex. *J Neurosci* 35, 14435-14447.
- 834 Herrmann, C.S., Rach, S., Voskuhl, J., Struber, D., 2014. Time-frequency analysis of event-related
835 potentials: a brief tutorial. *Brain Topogr* 27, 438-450.
- 836 Ilic, T.V., Meintzschel, F., Cleff, U., Ruge, D., Kessler, K.R., Ziemann, U., 2002. Short-interval paired-pulse
837 inhibition and facilitation of human motor cortex: the dimension of stimulus intensity. *J Physiol* 545, 153-
838 167.
- 839 Ilmoniemi, R.J., Kicic, D., 2010. Methodology for combined TMS and EEG. *Brain Topogr* 22, 233-248.
- 840 Jensen, O., Goel, P., Kopell, N., Pohja, M., Hari, R., Ermentrout, B., 2005. On the human sensorimotor-
841 cortex beta rhythm: sources and modeling. *Neuroimage* 26, 347-355.
- 842 Jensen, O., Mazaheri, A., 2010. Shaping functional architecture by oscillatory alpha activity: gating by
843 inhibition. *Front. Hum. Neurosci.* 4, 186.
- 844 Johnson, J.S., Kundu, B., Casali, A.G., Postle, B.R., 2012. Task-dependent changes in cortical excitability
845 and effective connectivity: A combined TMS-EEG study. *J Neurophysiol*.
- 846 Jurkiewicz, M.T., Gaetz, W.C., Bostan, A.C., Cheyne, D., 2006. Post-movement beta rebound is generated
847 in motor cortex: evidence from neuromagnetic recordings. *Neuroimage* 32, 1281-1289.
- 848 Kaplan, G.B., Greenblatt, D.J., Ehrenberg, B.L., Goddard, J.E., Harmatz, J.S., Shader, R.I., 1998. Single-
849 dose pharmacokinetics and pharmacodynamics of alprazolam in elderly and young subjects. *J Clin*
850 *Pharmacol* 38, 14-21.
- 851 Klimesch, W., Sauseng, P., Hanslmayr, S., 2007. EEG alpha oscillations: the inhibition-timing hypothesis.
852 *Brain Res. Rev.* 53, 63-88.
- 853 Korhonen, R.J., Hernandez-Pavon, J.C., Metsomaa, J., Maki, H., Ilmoniemi, R.J., Sarvas, J., 2011.
854 Removal of large muscle artifacts from transcranial magnetic stimulation-evoked EEG by independent
855 component analysis. *Med Biol Eng Comput* 49, 397-407.

- 856 Makeig, S., 1993. Auditory event-related dynamics of the EEG spectrum and effects of exposure to tones.
857 *Electroencephalogr Clin Neurophysiol* 86, 283-293.
- 858 Maris, E., Oostenveld, R., 2007. Nonparametric statistical testing of EEG- and MEG-data. *J Neurosci*
859 *Methods* 164, 177-190.
- 860 Marrosu, F., Santoni, F., Fa, M., Puligheddu, M., Barberini, L., Genugu, F., Frau, R., Manunta, M., Mereu,
861 G., 2006. Beta and gamma range EEG power-spectrum correlation with spiking discharges in DBA/2J mice
862 absence model: role of GABA receptors. *Epilepsia* 47, 489-494.
- 863 Massimini, M., Ferrarelli, F., Huber, R., Esser, S.K., Singh, H., Tononi, G., 2005. Breakdown of cortical
864 effective connectivity during sleep. *Science* 309, 2228-2232.
- 865 Mathewson, K.E., 2011. Pulsed out of awareness: EEG alpha oscillations represent a pulsed inhibition of
866 ongoing cortical processing. University of Illinois at Urbana-Champaign.
- 867 McDonnell, M.N., Orekhov, Y., Ziemann, U., 2006. The role of GABA(B) receptors in intracortical inhibition
868 in the human motor cortex. *Exp Brain Res* 173, 86-93.
- 869 Mohler, H., Fritschy, J.M., Rudolph, U., 2002. A new benzodiazepine pharmacology. *J Pharmacol Exp Ther*
870 300, 2-8.
- 871 Müller-Dahlhaus, J.F.M., Liu, Y., Ziemann, U., 2008. Inhibitory circuits and the nature of their interactions in
872 the human motor cortex a pharmacological TMS study. *J Physiol* 586, 495-514.
- 873 Mutanen, T., Maki, H., Ilmoniemi, R.J., 2013. The effect of stimulus parameters on TMS-EEG muscle
874 artifacts. *Brain Stimul* 6, 371-376.
- 875 Muthukumaraswamy, S.D., Myers, J.F., Wilson, S.J., Nutt, D.J., Lingford-Hughes, A., Singh, K.D.,
876 Hamandi, K., 2013. The effects of elevated endogenous GABA levels on movement-related network
877 oscillations. *Neuroimage* 66, 36-41.
- 878 Neuper, C., Grabner, R.H., Fink, A., Neubauer, A.C., 2005. Long-term stability and consistency of EEG
879 event-related (de-)synchronization across different cognitive tasks. *Clin Neurophysiol* 116, 1681-1694.
- 880 Neuper, C., Wörtz, M., Pfurtscheller, G., 2006. ERD/ERS patterns reflecting sensorimotor activation and
881 deactivation. *Prog. Brain Res.* 159, 211-222.
- 882 Oldfield, R.C., 1971. The assessment and analysis of handedness: the Edinburgh inventory.
883 *Neuropsychologia* 9, 97-113.
- 884 Oostenveld, R., Fries, P., Maris, E., Schoffelen, J.M., 2011. FieldTrip: Open source software for advanced
885 analysis of MEG, EEG, and invasive electrophysiological data. *Comput Intell Neurosci* 2011, 156869.
- 886 Patat, A., Trocherie, S., Thebault, J.J., Rosenzweig, P., Dubruc, C., Bianchetti, G., Court, L.A., Morselli,
887 P.L., 1994. EEG profile of intravenous zolpidem in healthy volunteers. *Psychopharmacology (Berl)* 114,
888 138-146.
- 889 Paus, T., Sipila, P.K., Strafella, A.P., 2001. Synchronization of neuronal activity in the human primary motor
890 cortex by transcranial magnetic stimulation: an EEG study. *J Neurophysiol* 86, 1983-1990.
- 891 Pellicciari, M.C., Veniero, D., Miniussi, C., 2017. Characterizing the Cortical Oscillatory Response to TMS
892 Pulse. *Front Cell Neurosci*.
- 893 Petrichella, S., Johnson, N., He, B., 2017. The influence of corticospinal activity on TMS-evoked activity
894 and connectivity in healthy subjects: A TMS-EEG study. *PLoS One* 12, e0174879.
- 895 Pfurtscheller, G., 2001. Functional brain imaging based on ERD/ERS. *Vision Res.* 41, 1257-1260.
- 896 Pfurtscheller, G., Aranibar, A., 1977. Event-related cortical desynchronization detected by power
897 measurements of scalp EEG. *Electroencephalogr Clin Neurophysiol* 42, 817-826.
- 898 Picazio, S., Veniero, D., Ponzio, V., Caltagirone, C., Gross, J., Thut, G., Koch, G., 2014. Prefrontal control
899 over motor cortex cycles at beta frequency during movement inhibition. *Curr. Biol.* 24, 2940-2945.
- 900 Premoli, I., Castellanos, N., Rivolta, D., Belardinelli, P., Bajo, R., Zipser, C., Espenhahn, S., Heidegger, T.,
901 Müller-Dahlhaus, F., Ziemann, U., 2014a. TMS-EEG Signatures of GABAergic Neurotransmission in the
902 Human Cortex. *J Neurosci* 34, 5603-5612.

- 903 Premoli, I., Rivolta, D., Espenhahn, S., Castellanos, N., Belardinelli, P., Ziemann, U., Muller-Dahlhaus, F.,
904 2014b. Characterization of GABAB-receptor mediated neurotransmission in the human cortex by paired-
905 pulse TMS-EEG. *Neuroimage* 103, 152-162.
- 906 Rogasch, N.C., Fitzgerald, P.B., 2013. Assessing cortical network properties using TMS-EEG. *Hum Brain*
907 *Mapp* 34, 1652-1669.
- 908 Rogasch, N.C., Sullivan, C., Thomson, R.H., Rose, N.S., Bailey, N.W., Fitzgerald, P.B., Farzan, F.,
909 Hernandez-Pavon, J.C., 2016. Analysing concurrent transcranial magnetic stimulation and
910 electroencephalographic data: a review and introduction to the open-source TESA software. *Neuroimage*.
911 Ronnqvist, K.C., McAllister, C.J., Woodhall, G.L., Stanford, I.M., Hall, S.D., 2013. A multimodal perspective
912 on the composition of cortical oscillations. *Front Hum Neurosci* 7, 132.
- 913 Rosanova, M., Casali, A., Bellina, V., Resta, F., Mariotti, M., Massimini, M., 2009. Natural frequencies of
914 human corticothalamic circuits. *J Neurosci* 29, 7679-7685.
- 915 Rossi, S., Hallett, M., Rossini, P.M., Pascual-Leone, A., 2011. Screening questionnaire before TMS: an
916 update. *Clin Neurophysiol* 122, 1686.
- 917 Rossini, P.M., Burke, D., Chen, R., Cohen, L.G., Daskalakis, Z., Di Iorio, R., Di Lazzaro, V., Ferreri, F.,
918 Fitzgerald, P.B., George, M.S., Hallett, M., Lefaucheur, J.P., Langguth, B., Matsumoto, H., Miniussi, C.,
919 Nitsche, M.A., Pascual-Leone, A., Paulus, W., Rossi, S., Rothwell, J.C., Siebner, H.R., Ugawa, Y., Walsh,
920 V., Ziemann, U., 2015. Non-invasive electrical and magnetic stimulation of the brain, spinal cord, roots and
921 peripheral nerves: Basic principles and procedures for routine clinical and research application. An updated
922 report from an I.F.C.N. Committee. *Clin Neurophysiol* 126, 1071-1107.
- 923 Saletu, B., Grunberger, J., Cepko, H., 1987. Pharmacology-EEG and psychometric studies with a novel
924 selective benzodiazepine agonist/antagonist Ro 23-0364. *Int J Clin Pharmacol Ther Toxicol* 25, 421-437.
- 925 Saletu, B., Grunberger, J., Linzmayer, L., Semlitsch, H.V., Anderer, P., Chwatal, K., 1994. Pharmacokinetic
926 and -dynamic studies with a new anxiolytic, suriclone, utilizing EEG mapping and psychometry. *Br J Clin*
927 *Pharmacol* 37, 145-156.
- 928 Salmelin, R., Hari, R., 1994. Spatiotemporal characteristics of sensorimotor neuromagnetic rhythms related
929 to thumb movement. *Neuroscience* 60, 537-550.
- 930 Salva, P., Costa, J., 1995. Clinical pharmacokinetics and pharmacodynamics of zolpidem. Therapeutic
931 implications. *Clin Pharmacokinet* 29, 142-153.
- 932 Shader, R.I., Pary, R.J., Harmatz, J.S., Allison, S., Locniskar, A., Greenblatt, D.J., 1984. Plasma
933 concentrations and clinical effects after single oral doses of prazepam, clorazepate, and diazepam. *J Clin*
934 *Psychiatry* 45, 411-413.
- 935 Smith, M.J., Keel, J.C., Greenberg, B.D., Adams, L.F., Schmidt, P.J., Rubinow, D.A., Wassermann, E.M.,
936 1999. Menstrual cycle effects on cortical excitability. *Neurology* 53, 2069-2072.
- 937 Van Der Werf, Y.D., Paus, T., 2006. The neural response to transcranial magnetic stimulation of the human
938 motor cortex. I. Intracortical and cortico-cortical contributions. *Exp Brain Res* 175, 231-245.
- 939 Van Der Werf, Y.D., Sadikot, A.F., Strafella, A.P., Paus, T., 2006. The neural response to transcranial
940 magnetic stimulation of the human motor cortex. II. Thalamocortical contributions. *Exp Brain Res* 175, 246-
941 255.
- 942 Veniero, D., Brignani, D., Thut, G., Miniussi, C., 2011. Alpha-generation as basic response-signature to
943 transcranial magnetic stimulation (TMS) targeting the human resting motor cortex: a TMS/EEG co-
944 registration study. *Psychophysiology* 48, 1381-1389.
- 945 Wang, X.J., 2010. Neurophysiological and computational principles of cortical rhythms in cognition. *Physiol*
946 *Rev* 90, 1195-1268.
- 947 Zhang, Y., Chen, Y., Bressler, S.L., Ding, M., 2008. Response preparation and inhibition: the role of the
948 cortical sensorimotor beta rhythm. *Neuroscience* 156, 238-246.

- 949 Ziemann, U., 2011. Transcranial Magnetic Stimulation at the Interface with Other Techniques: A Powerful
950 Tool for Studying the Human Cortex. *Neuroscientist*.
- 951 Ziemann, U., Corwell, B., Cohen, L.G., 1998. Modulation of plasticity in human motor cortex after forearm
952 ischemic nerve block. *J Neurosci* 18, 1115-1123.

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