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Neural excitation/inhibition imbalance and the treatment of severe depression

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Neural excitation/inhibition imbalance and the treatment of severe depression

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45 **Abstract**

46 An influential hypothesis holds that depression is related to a neural excitation/inhibition
47 imbalance, but its role in the treatment of depression remains unclear. Here, we show that
48 unmedicated patients with severe depression demonstrated reduced inhibition of brain-
49 wide resting-state networks relative to healthy controls. Patients using antidepressants
50 showed inhibition that was higher than unmedicated patients and comparable to controls,
51 but they still suffered from severe depression. Subsequent treatment with
52 electroconvulsive therapy (ECT) reduced depressive symptoms, but its effectiveness did
53 not depend on changes in network inhibition. Concomitant pharmacotherapy increased the
54 effectiveness of ECT, but only when the strength of neural inhibition before ECT was
55 within the normal range and not when inhibition was excessive. These findings suggest
56 that reversing the excitation/inhibition imbalance may not be sufficient nor necessary for
57 the effective treatment of severe depression, and that brain-state informed
58 pharmacotherapy management may enhance the effectiveness of ECT.

59 Main

60 With more than 250 million people affected, depression is one of the leading causes of
61 disability worldwide¹. Patients suffer weeks to sometimes years of low mood, anhedonia,
62 sleep problems, weight loss, and — in more severe cases — suicidality, motor retardation
63 and psychotic features. Although 70% of patients show a positive response to (extensive)
64 treatments with pharmacotherapy and psychotherapy², approximately half of them
65 eventually relapse and experience one or more recurrent episodes in their lifetime^{2,3}.
66 Patients suffering from severe depressive episodes that are not responsive to initial
67 treatments may benefit from electroconvulsive therapy (ECT). With a remission rate of 48-
68 65%, ECT is currently the most effective treatment for pharmacotherapy-resistant
69 depression⁴. Nevertheless, it is clear that for a substantial group of depressed patients an
70 effective treatment is still lacking. Enhancing our understanding on the neural mechanisms
71 of depression and its treatments is indispensable to improve treatment effectiveness and
72 to develop novel treatments.

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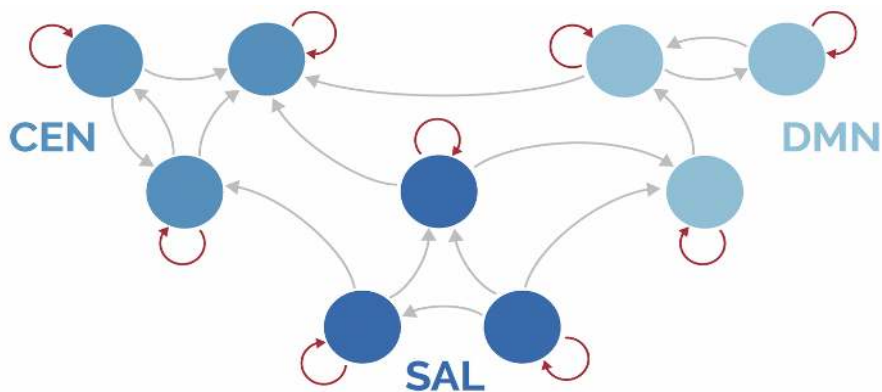
74 Healthy functioning of cortical brain circuits depends on processes that promote
75 homeostasis throughout the network, which is regulated by excitatory and inhibitory
76 neurotransmission⁵. One of the proposed neural mechanisms of depression states that
77 symptoms are caused by deficits in inhibitory neurotransmission, resulting in an
78 excitation/inhibition imbalance⁶⁻⁹. In line with this hypothesis, deficits in the principal
79 inhibitory neurotransmitter γ -aminobutyric acid (GABA) seem to cause depression-like
80 behavior in animal models^{10,11}. Furthermore, GABA concentrations are reduced in
81 depressed patients but not in remitted patients¹². Accordingly, this hypothesis also predicts
82 that reversing the excitation/inhibition imbalance in depressed patients will lead to a
83 reduction of depressive symptoms^{7,9,10}. Indeed, even though classical antidepressants

84 primarily target other neurotransmitters, these agents seem to stimulate GABA-ergic
85 neurotransmission as well^{6,7,9,13,14}. Furthermore, benzodiazepines (i.e., a GABA_A receptor
86 agonist) provide early antidepressant effects when combined with antidepressants¹⁵. Thus,
87 this hypothesis poses that the neural excitation/inhibition imbalance takes a central
88 position in the pathophysiology of depression and its treatment.

89
90 Similar to pharmacotherapy, the effectiveness of ECT may also depend on mechanisms
91 that are closely related to the neural excitation/inhibition balance¹⁶. ECT uses a brief
92 electrical stimulus to the cranium in order to elicit seizure activity which propagates
93 throughout the brain¹⁷. For a beneficial treatment response, the administered stimulus
94 should significantly exceed the individuals' seizure threshold¹⁸, thereby providing strong
95 excitation of the brain. Furthermore, ECT effectiveness depends on the generalization of
96 the induced seizure¹⁹, which is accomplished through the opposing forces of excitatory
97 seizure activity and inhibitory restraints²⁰. Also, ECT effectiveness is associated with the
98 strength of the post-ictal suppression of induced seizure activity²¹. This phenomenon is
99 marked by strong inhibitory processes terminating the excitatory seizure dynamics. Thus,
100 the working mechanisms of ECT seem to be tightly linked to the excitation/inhibition
101 balance, indicating that disturbances in this balance may influence ECT effectiveness.

102
103 In order to investigate the excitation/inhibition balance in depression and its relation to
104 treatment effects, we used data from a large multicenter international consortium that
105 included patients with severe depression who were treated with pharmacotherapy and
106 subsequent ECT. We used spectral dynamic causal modeling (spDCM) of resting-state
107 functional magnetic resonance imaging (RS-fMRI) data²². spDCM is able to accurately
108 estimate extrinsic (i.e., between-region) and intrinsic (i.e., regional self-inhibition) effective
109 connectivity (Figure 1)²²⁻²⁴. Well-tuned regional self-inhibition allows for sustained activity

110 in the cortex while maintaining a balance between excitation and inhibition throughout the
111 network. The strength of intrinsic self-inhibition can thus be interpreted as a proxy for the
112 regional excitation/inhibition balance²⁵. Recently, a study using magnetoencephalography
113 showed that DCM can quantify the increase in tonic inhibition by a GABA reuptake
114 inhibitor²⁶. Here, we use spDCM to study the effects of pharmacotherapy and ECT on
115 extrinsic and intrinsic effective connectivity in severely depressed patients. We provide
116 evidence indicating that reversing the neural excitation/inhibition imbalance is, in and of
117 itself, not sufficient nor necessary for an antidepressant response in patients suffering from
118 severe depression. Our findings also suggest that concomitant pharmacotherapy
119 increases the effectiveness of ECT if the strength of inhibition remains within a healthy
120 range, but not when the degree of inhibition is excessive.



128 **Figure 1 Schematic representation of a directed cortical network.** The nodes (blue circles) represent
129 cortical regions of brain networks that interact through effective connections (gray arrows). The self-
130 connections (red arrows) regulating the strength of regional inhibition. Optimal strength of self-connections
131 allows for sustained activity in the cortex while maintaining a balance between excitation and inhibition
132 throughout the cortical network. The selected networks in this study are the central executive network (CEN),
133 salience network (SAL), and default mode network (DMN).

134 Results

135 Reversal of the excitation/inhibition imbalance is not sufficient for pharmacotherapy 136 effectiveness in severe depression

137 Data were obtained from the Global ECT-MRI Research Collaboration (GEMRIC)
138 database²⁷. Participants from seven sites across Europe and North America were divided
139 into four groups: healthy controls (n = 59), unipolar depressed patients without current use
140 of antidepressants or benzodiazepines (patients might use other types of medication, but
141 for convenience were labeled as ‘unmedicated group’; n = 60), unipolar depressed
142 patients using antidepressants (n = 56), and unipolar depressed patients using
143 benzodiazepines (n = 63). The latter two groups included patients using both types of
144 medication (n = 24), this considerable overlap was accounted for in the analysis (see SI
145 Methods). Demographic and clinical characteristics of each group are reported in Table 1.

146

				Overlap = 24	
	Statistic	HC (n = 59)	NM (n = 60)	AD (n = 56)	BZ (n = 63)
Age ^{a,c,d,e,f}	Mean (+- 1SD)	48.1 (15.1)	48.7 (16.1)	63.1 (11.5)	54.9 (14.3)
Sex	Count (%)	26 (44.1)	25 (41.7)	19 (33.9)	29 (46)
HAM-D ^e	Mean (+- 1SD)	NA	23.8 (6.1)	25.2 (6.6)	27.6 (7.1)
Antipsychotics use ^{d,e}	Count (%)	NA	4 (6.7)	29 (51.8)	25 (39.7)
Lithium carbonate use	Count (%)	NA	1 (1.7)	4 (7.1)	2 (3.2)
Recurrent depression	Count (%)	NA	56 (93.3)	53 (94.6)	59 (93.7)
Psychotic features ^{d,e}	Count (%)	NA	8 (13.3)	17 (30.4)	10 (15.9)

147

148 **Table 1 Overview of demographic and clinical information.** Mean (\pm SD) and count (%) statistics of
149 variables for each specific group. Analyses on group differences were performed using student’s t-test or X²-
150 test, where appropriate. HC = healthy controls; AD = patients using antidepressants; BZ = patients using
151 benzodiazepines; NM = patients without current AD or BZ medication use; HAM-D = Hamilton Rating Scale
152 for depression; ^a P_{HC vs AD} < 0.1; ^b P_{HC vs NM} < 0.1; ^c P_{HC vs BZ} < 0.1; ^d P_{NM vs AD} < 0.1; ^e P_{NM vs BZ} < 0.1; ^f P_{AD vs BZ} < 0.1.

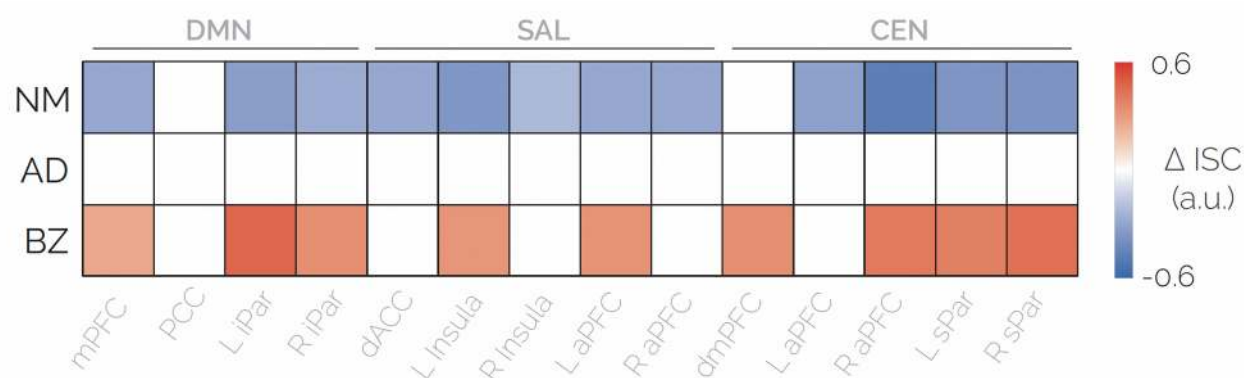
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154 We investigated whether these groups differed in effective connectivity using RS-fMRI and
155 spDCM (see SI Methods)²². On the individual level, spDCM modeled causal interactions
156 between neuronal populations located in the regions of interest (ROIs). A forward model
157 generated simulated RS-fMRI timeseries based on these neural models. The cross-
158 spectra of these simulated timeseries were compared to cross-spectra of observed RS-
159 fMRI timeseries. Specifically, Bayesian statistical methods identified neural connectivity
160 parameters that maximized model accuracy (the similarity of the simulated and observed
161 cross-spectra), while minimizing complexity (the effective number of parameters). Using
162 parametric empirical Bayes, the connectivity parameters were then taken to the group
163 level and modeled using a general linear model (GLM; for model designs, see SI Methods
164 and SI Figures). Thereby, spDCM enabled inference on effective (i.e., directed)
165 connectivity between brain regions (Figure 1). Additionally, it allowed inference on the
166 strength of regional inhibitory self-connections, which could be interpreted as local
167 regulation of the excitation/inhibition ratio in order to maintain balance throughout the
168 network (Figure 1)²⁵. Fourteen ROIs were selected, located at the core of the default mode
169 network (DMN), salience network (SN) and central executive network (CEN; see SI Figure
170 1). These networks are implicated in the pathophysiology of depression²⁸. The analyses
171 yielded no evidence for effects in between-region connectivity, so we focused on the
172 effects in self-connections below. By comparing the evidence for the full connectivity GLM
173 against specific reduced GLMs (SI Methods), we examined effects in inhibitory self-
174 connections of individual ROIs. Also, we examined effects at the network-level, which
175 tested if effects on self-inhibition were present in none of the networks (i.e., evidence for
176 absence of an effect), in a specific network, or widespread across networks (see SI Figure
177 3 and SI Methods). The degree of evidence was expressed as the probability of an effect
178 in a (combination of) connection(s) given the data (i.e., the posterior probability, written as

179 $p(m|Y)$). Evidence was considered strong if the posterior probability was 95% or higher
180 (i.e., $p(m|Y) > 0.95$).

181

182 Because multiple GLM designs could be used to examine cross-sectional group
183 differences, we tested the two most convenient designs and selected the one which
184 maximized model evidence (SI Figure 2). The winning model design consisted of separate
185 regressors for each patient group, while healthy controls were modeled as the reference
186 group (i.e., intercept). The results of the selected model showed that self-inhibition was
187 reduced across networks in unmedicated patients compared to healthy controls ($p(m_4|Y) =$
188 1.0). Patients using benzodiazepines showed an opposite pattern of increased self-
189 inhibition across networks compared to healthy controls ($p(m_4|Y) = 1.0$). Using Bayesian
190 statistics allowed us to establish the evidence for a null finding. In this case, the results
191 suggest that self-inhibition in patients using antidepressants was comparable to healthy
192 controls, but the level of evidence was not conclusive ($p(m_0|Y) = 0.53$). The analyses for
193 effects on individual nodes were in line with the above (Figure 2). These findings were
194 mostly robust against adjustments for potential confounding variables (i.e., age, sex,
195 depression severity, presence of recurrent depression, presence of psychotic depression,
196 use of lithium carbonate, use of antipsychotics, and site variables; SI Figure 4). The only
197 substantial difference in the adjusted analyses appeared in patients using
198 benzodiazepines, showing increased self-inhibition exclusively in specific network nodes
199 rather than a widespread increase across networks.



200 **Figure 2 Group differences in region-specific inhibitory self-connections.** Results of the analysis using
 201 automatic search over reduced models to obtain probabilities for specific connectivity parameters. Colored
 202 squares indicate very strong evidence ($p(Y|m) > 0.99$) for increased (red) or reduced (blue) self-inhibition
 203 between the specified patient group and healthy controls. Δ ISC = difference in inhibitory self-connection
 204 strength; AD = patients using antidepressants; BZ = patients using benzodiazepines NM= patients not using
 205 AD or BZ. DMN = default mode network; SAL = salience network; CEN = central executive network. L= left;
 206 R = right; mPFC = medial prefrontal cortex; PCC = posterior cingulate cortex; iPar = inferior parietal cortex;
 207 dACC = dorsal anterior cingulate cortex; aPFC = anterior prefrontal cortex; dmPFC = dorsomedial prefrontal
 208 cortex; sPar = superior parietal cortex.

209
210

211 We used post-hoc pairwise comparisons to test for differences between patient groups (SI
 212 Methods and SI Figure 5). Compared to unmedicated patients, patients using
 213 antidepressants and/or benzodiazepines showed increased inhibitory self-connection
 214 strengths in all nodes across networks ($p(m_4|Y) = 1.0$ for both groups). Compared to
 215 patients using antidepressants, benzodiazepines users showed increased inhibitory self-
 216 connections in specific nodes (particularly in the CEN; SI Figure 5). The analyses were
 217 adjusted for the same covariates as in the group comparison model described above and
 218 adjusted for the number of post-hoc comparisons.

219

220 In sum, these results yielded that, compared to unmedicated patients, antidepressants
221 users showed a higher degree of self-inhibition which was more similar to healthy controls.
222 Importantly, even though inhibitory deviations (from healthy controls) seemed to be
223 normalized in patients using antidepressants, all patient groups still suffered from severe
224 depressive symptoms (Table 1).

225
226 Next, an analysis was conducted on associations between inhibitory self-connections and
227 depression severity in the distinct patient groups, as measured by the Hamilton
228 Depression Rating Scale (HAM-D²⁹). The results showed that more severe depression was
229 associated with reduced self-inhibition across networks in unmedicated patients ($p(m_4|Y) =$
230 1.0 ; SI Figure 6). Except from a few individual nodes, no clear associations between
231 depression severity and inhibitory self-connections were found in patients using
232 antidepressants and/or benzodiazepines ($p(m_0|Y) = 0.51$ and $p(m_0|Y) = 0.43$, respectively).
233 The results were robust against adjustments for potential confounders (i.e., age, sex,
234 presence of recurrent depression, presence of psychotic depression, use of lithium
235 carbonate, use of antipsychotics, and site variables; SI Figure 6).

236 237 **Pharmacotherapy-related effects of excitation/inhibition imbalance on ECT** 238 **effectiveness**

239 Next, we examined whether excitation/inhibition imbalance at baseline was associated
240 with ECT effectiveness. We first extracted the inhibitory self-connection parameters of all
241 ROIs and identified the first principal component as a summary measure for regional self-
242 inhibition of cortical networks throughout the brain. Using multiple regression models, we
243 associated this summary measure to ECT effectiveness (i.e., the change in HAM-D scores
244 from before to after ECT). The analysis was adjusted for baseline HAM-D scores and other

245 known predictors of ECT effectiveness (i.e., presence of psychotic features, age, number
246 of ECT-sessions with bilateral electrode positioning, and site variables; see SI Methods).
247 The results showed a quadratic association between inhibitory self-connection and HAM-D
248 change in the total sample ($F(1,143) = 16.2, p < 0.001$, Cohen's $f^2 = 0.11$; Figure 3a).
249 Further analyses in the subgroups revealed that the quadratic relation was explained by
250 medication related differences. Whereas no linear association was found in currently
251 unmedicated patients ($F(1,52) = 0.72, p = 0.40$), patients using concomitant
252 benzodiazepines and/or antidepressants showed a negative linear association between
253 inhibitory strength and HAM-D change ($F(1,47) = 11.58, p = 0.001$ for antidepressants
254 users; $F(1,56) = 11.50, p = 0.001$ for benzodiazepines users; see Figures 3b and 3c). The
255 associations between neural inhibitory strength and ECT effectiveness in patients using
256 pharmacotherapy showed a medium effect size (Cohen's $f^2 = 0.21$ for benzodiazepines
257 users; Cohen's $f^2 = 0.25$ for antidepressants users), indicating that excessive inhibitory
258 strength might be an important predictor of ECT non-response. Since the regression
259 models were adjusted for potential confounders, the degree of variation in ECT
260 effectiveness explained by inhibition seemed to be independent from other known
261 predictors.

262

263 For the analysis of clinical data, we used a multiple regression model to examine the
264 association between relevant predictors — including antidepressants and benzodiazepines
265 use — and ECT effectiveness (see SI Methods). In line with previous research³⁰, the
266 analyses revealed that the use of antidepressants enhanced ECT effectiveness ($F(1,158)$
267 $= 7.32, p = 0.008$, Cohen's $f^2 = 0.05$). Therefore, our findings regarding the negative
268 effects of inhibitory strength on ECT effectiveness mediated by antidepressants use
269 seemed counterintuitive. Further analyses showed that the use of medication enhanced

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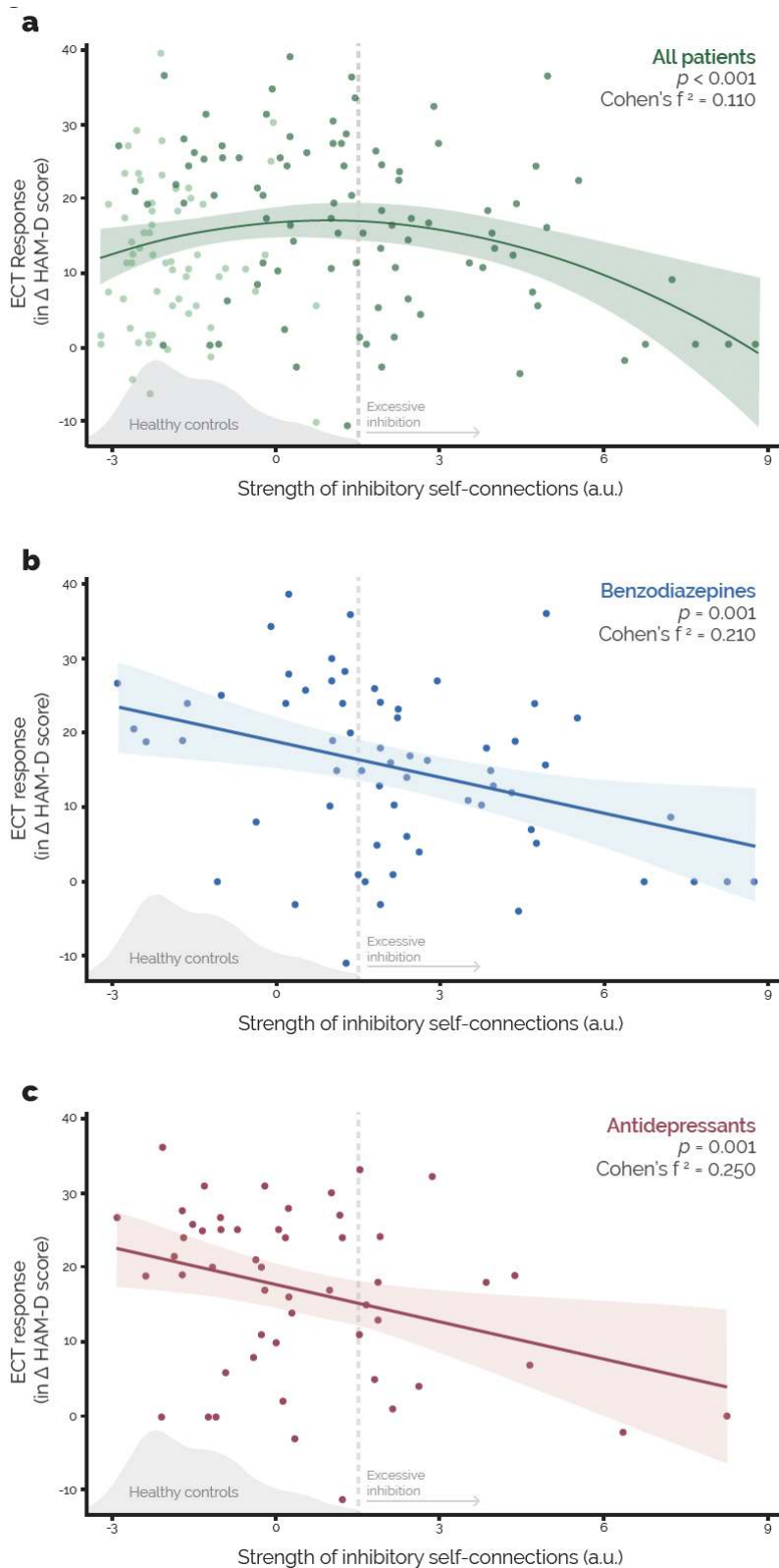


Figure 3 Associations between

baseline inhibitory self-connection strength and ECT effectiveness

Regression plots on the association between the first principal component of inhibitory self-connections (arbitrary units) and the antidepressant effectiveness of ECT (change in HAM-D score before and after the ECT-course).

The figure shows the regression plot for all patients (a), including both

unmedicated patients (lighter green)

and medicated patients (darker green).

Additionally, separate regression plots

are shown for patients using

benzodiazepines (b) and patients using

antidepressant (c). For each regression

analysis, p-values and effect sizes for

the displayed association are included

adjusted for covariates. A medium

effect size is indicated by $0.15 \leq f^2$

≥ 0.35 . In each plot, a density plot is

included to show the distribution of self-

inhibition in healthy controls. The

strength of patient's self-inhibition that

appeared beyond the range of healthy

controls is identified as excessive.

300 ECT effectiveness as long as the inhibitory strength was within the range of healthy
301 controls (Figure 3b and 3c). This appeared true for both patients using antidepressants
302 (mean Δ HAMD = 18.2 ± 11.1 SD; $t(75) = 3.02$, $p = 0.003$) and benzodiazepines (mean
303 Δ HAMD = 19.6 ± 12.5 SD; $t(37) = 2.83$, $p = 0.007$), compared to unmedicated patients
304 (mean Δ HAMD = 11.6 ± 10.0 SD). However, excessive inhibition (defined as an inhibitory
305 strength beyond the range of healthy controls) was present in 27.8% of antidepressants
306 users and 60.3% of benzodiazepines users. None of the unmedicated patients showed
307 excessive inhibition. Regarding the change in HAMD-scores, patients that showed
308 excessive inhibition while using antidepressants (mean Δ HAMD = 12.5 ± 9.7 SD; $t(22) =$
309 0.30 , $p = 0.765$) and/or benzodiazepines (mean Δ HAMD = 12.3 ± 9.6 SD; $t(81) = 0.33$, $p =$
310 0.738) did not differ from patients without concomitant medication use. This indicated that
311 the positive effects of concomitant pharmacotherapy on ECT effectiveness were nullified if
312 the degree of self-inhibition was excessive.

313

314 **Influence of ECT on excitation/inhibition balance and associations with clinical** 315 **effectiveness**

316 We used a longitudinal design to examine changes in excitation/inhibition ratios after the
317 ECT-course, compared to baseline, and its associations with antidepressive effectiveness.
318 We used a multisession resting-state spDCM analysis in a subsample of participants for
319 whom longitudinal data were available ($n_{\text{total}} = 113$; $n_{\text{patient}} = 89$; $n_{\text{HC}} = 24$). Patients were
320 scanned before and after the ECT-course. Healthy controls were also scanned twice,
321 approximately four weeks apart. First, a model was run to test for effects of ECT on
322 inhibitory self-connections in patients compared to longitudinal effects in controls. This
323 model also tested for associations between change in inhibitory self-connections and
324 treatment effectiveness (i.e., change in HAM-D; SI Figure 7). The analysis yielded weak

325 evidence suggesting that longitudinal effects of ECT in patients did not differ from
326 longitudinal effects in healthy controls ($p(m_0|Y) = 0.67$). The model did yield conclusive
327 evidence showing that ECT effectiveness was not associated with changes in inhibitory
328 self-connections in any of the networks ($p(m_0|Y) = 0.99$). These results were robust against
329 adjustments for potential confounding variables (i.e., age, sex, baseline depression
330 severity, presence of recurrent depression, presence of psychotic depression, lithium
331 carbonate use, antipsychotic use, number of ECT-sessions, and site variables). Also,
332 analysis on ECT response (i.e., a binary variable indicating >50% reduction of HAM-D
333 scores after ECT) yielded very similar results (SI Figure 8). Because the patient groups
334 (defined by medication use) showed different baseline inhibitory self-connection strengths,
335 we tested whether longitudinal effects differed between groups. The results showed that
336 ECT effectiveness was not associated with changes in inhibitory self-connections in any of
337 the patient groups ($p(m_0|Y) = 1.0$ for each group; SI Figure 9).

338

339 **Discussion**

340 In this study, we investigated the role of the excitation/inhibition imbalance in the treatment
341 of severe depression. The cross-sectional results revealed that unmedicated patients
342 showed reduced inhibition compared to healthy controls. Also, more severe depression
343 was associated with reduced self-inhibition in this group. Patients using antidepressants
344 and/or benzodiazepines showed increased inhibition compared to unmedicated patients.
345 The degree of inhibition in patients using antidepressants seemed comparable to healthy
346 controls, whereas patients using benzodiazepines showed increased inhibition compared
347 to controls. In these medicated patients, the degree of inhibition was not associated with
348 depression severity. In line with previous findings¹²⁻¹⁴, these findings suggest that
349 pharmacotherapy reverses the reduced inhibition that is associated with depression.

350 However, patients in this study all suffered from perpetuating severe depressive
351 symptoms, indicating that the reversal of the excitation/inhibition imbalance in patients
352 using pharmacotherapy, in and of itself, did not result in a persistent antidepressive effect.
353 Additionally, the subsequent ECT effectiveness was not associated with changes in the
354 strength of self-inhibition. Finally, we report that many patients using pharmacotherapy
355 showed a degree of inhibition beyond the range of healthy controls. If the degree of
356 inhibition was within the healthy range, concomitant antidepressants and/or
357 benzodiazepines use was associated with increased ECT effectiveness. Remarkably, the
358 presence of pre-treatment excessive neural inhibition nullified these positive effects of
359 concomitant pharmacotherapy on the outcome of ECT.

360

361 An influential hypothesis poses that deficits in neural excitation/inhibition balance
362 represent a fundamental aspect of depression and that reversing these deficits may be an
363 important property to the antidepressive effect of existing treatments⁶⁻⁹. In line with this
364 hypothesis, unmedicated severely depressed patients showed reduced inhibitory self-
365 connections compared to healthy controls. But contrary to this hypothesis, our results
366 suggest that reversal of inhibitory deficits by using antidepressants and/or
367 benzodiazepines is, in and of itself, not a sufficient condition for an antidepressive
368 treatment effect in patients with severe depression. This indicates that either the
369 effectiveness of pharmacotherapy in severe depression did not depend on reversing the
370 inhibitory deficits, or that additional conditions were needed for an antidepressant
371 response (i.e., the absence/presence of other biological, psychological, or social
372 phenotypes). One of such additional conditions could be that an increase in inhibition
373 should be accompanied by an increase in excitation for an antidepressant effect³¹. Also,
374 changes in self-inhibition were not associated with the effectiveness of subsequent ECT,

375 indicating that reversal of the excitation/inhibition balance neither was a necessary
376 condition for the effective treatment of severe depression. Based on these findings, the
377 previously stated hypothesis might be partially altered. Although the excitation/inhibition
378 imbalance still seemed a key aspect of the neural etiology of severe depression, its
379 reversal by treatment might not be a sufficient nor a necessary condition for an
380 antidepressive effect.

381

382 Recent studies showed antidepressant effects of a positive allosteric modulator of GABA_A
383 receptors in post-partum depression³² and major depressive disorder³³. In contrast to our
384 findings, these findings suggest that reversing the inhibitory deficit would be a sufficient
385 condition for an antidepressant effect in severe depression. However, the results of these
386 trials may reflect antidepressant effects that are not maintained at the longer-term. The
387 antidepressive effectiveness in the trial on major depressive disorder vanished within six
388 weeks after initiating the pharmacotherapy³⁴, and the trial on post-partum depression used
389 a follow-up period of only four weeks. Such short-term antidepressant effects are also
390 observed in the treatment of depressed patients with benzodiazepines, a well-known
391 GABA_A modulator¹⁵. In our study, data on the duration of current pharmacotherapy use
392 was not available. However, severely depressed patients indicated for ECT are typically
393 characterized by long-term pharmacotherapy use (i.e., at least multiple months, but most
394 likely years). Therefore, our findings probably reflect the clinical and neural state of
395 patients in a later phase of pharmacotherapy, as opposed to the early phase studied in the
396 mentioned studies^{32,33}. We therefore hypothesize that, even though reversing the
397 excitation/inhibition imbalance might induce short-term antidepressant effects, it might not
398 be sufficient for a long-term clinical response.

399

400 Our findings on the effects of pharmacotherapy on the excitation/inhibition balance might
401 be specific to more severe and treatment-resistant subtypes of depression and its
402 treatments. Preliminary evidence suggests that severe depression seems to differ from
403 milder subtypes of depression with respect to GABA-ergic dynamics^{35,36}. For instance, a
404 transcranial magnetic stimulation (TMS) study indicated that GABA_B receptors seem to be
405 affected by all subtypes of depression, whereas changes in GABA_A receptors might be
406 unique to treatment-resistant depression³⁷. Therefore, the pharmacotherapy-related effects
407 on the excitation/inhibition imbalance in our study might be established by changes in
408 specific GABA receptor types or subunits that were insufficient for achieving effectiveness
409 in these treatment-resistant patients, while changes in other receptor types or subunits
410 might. However, the lack of an association between ECT effectiveness and changes in
411 self-inhibition suggests that changes in GABA-ergic dynamics are not necessary for an
412 antidepressant response in severe depression. Also, in other subtypes of depression,
413 reversing the excitation/inhibition imbalance may be sufficient for an antidepressive
414 response. Therefore, further research is needed to test whether our findings generalize
415 across other subtypes of depression.

416

417 We also provide evidence suggesting that an optimized excitation/inhibition balance at
418 baseline is associated with increased ECT effectiveness, whereas too little or too much
419 inhibition can result in a lower antidepressive response. One possible explanation of this
420 effect is that excessive inhibition due to pharmacotherapy may reduce the propagation of
421 the induced seizure. For decades, it has been suggested that seizure propagation
422 between distant regions of the brain is pivotal for ECT effectiveness, including cortical–
423 thalamocortical interactions and direct cortical–cortical connections¹⁹. Consequently,
424 excessive inhibition might obstruct spreading of seizure activity to essential parts of the

425 patients' brain. In support of this, a study using TMS showed that baclofen, a GABA_B
426 receptor agonist, reduced interhemispheric signal propagation³⁸. Also, previous studies
427 showed that the strength of the post-ictal suppression is associated with ECT
428 effectiveness^{21,39}. Post-ictal suppression is an electroencephalographic phenomenon
429 characterized by an ictal slow-wave phase, associated with inhibitory restraints, after
430 which seizure activity is terminated. The interhemispheric coherence in ictal slow-wave
431 activity has been associated with greater ECT effectiveness^{21,40}, indicating that individual
432 differences in the seizure termination processes may explain the variation in treatment
433 effectiveness between patients. These termination processes may be suboptimal in
434 patients if the degree of self-inhibition is reduced. In light of the above, our findings denote
435 that an optimal excitation/inhibition balance at baseline increases the effectiveness of ECT
436 by allowing for a proper propagation and termination of the induced seizure.

437
438 ECT did not seem to affect the strength of neural inhibition in our patients, when compared
439 to changes in inhibition over time in healthy controls (although evidence was weak). Some
440 magnetic resonance spectroscopy (MRS) studies showed increase of inhibitory GABA
441 concentrations over the ECT-course, but adding healthy controls diminished these
442 significant findings⁴¹. Additionally, we provide strong evidence that ECT effectiveness did
443 not depend on changes in regional self-inhibition. This is compatible with previous null
444 findings in studies using frequentist statistics⁴¹. However, the classical statistics used in
445 these studies were not able to provide conclusive evidence on the absence of an
446 association between GABA concentrations and ECT effectiveness. Using a Bayesian
447 approach, we provide very strong evidence indicating that the effectiveness of ECT did not
448 depend on changes in the excitation/inhibition balance⁴².

449

450 In our study, use of pharmacotherapy influenced the relation between neural inhibition and
451 ECT effectiveness. In daily practice, combining ECT with antidepressants is regularly
452 attempted to further enhance effectiveness⁴³. Also, a recent meta-analysis of randomized
453 controlled trials showed that the use of antidepressants (i.e., as a dichotomous variable)
454 increased ECT effectiveness when considering the entire group of patients³⁰. However,
455 based on our findings, this statement may be nuanced by adding that the positive effects
456 of antidepressants can be nullified if the degree of inhibition (associated with
457 pharmacotherapy use) is excessive. The strength of neural inhibition in medicated patients
458 is probably due to a combination of pharmacotherapy dosage effects and variability in drug
459 metabolism between patients⁴⁴. Consequently, the administered dosage of concomitant
460 antidepressants and, in particular, benzodiazepines may affect the outcome of ECT. This
461 may also explain the contradictory results in the current literature, in which studies
462 reported positive, negative and absence of effects of concomitant benzodiazepines use on
463 ECT response⁴⁵. Additionally, higher dosages of concomitant used benzodiazepines (i.e.,
464 lorazepam) were associated with shorter seizure durations during ECT⁴⁶. To mitigate these
465 effects, the competitive benzodiazepine-antagonist flumazenil can be used. Although, it
466 was not known whether or which patients received flumazenil in our study, this could not
467 prevent that patients with excessive inhibition beforehand showed lower ECT
468 effectiveness. Thus, based on our findings we hypothesize that, while the use of
469 concomitant pharmacotherapy (as a dichotomous variable) may enhance ECT
470 effectiveness, higher dosages may result in a poorer clinical response. But, to provide
471 conclusive evidence on this hypothesis, randomized clinical trials have to be conducted, to
472 test dose-dependent (and preferably plasma-level controlled) effects of benzodiazepines
473 and antidepressants on ECT effectiveness. To the best of our knowledge, no such trials
474 have been reported in the literature yet.

475

476 Our findings may guide future research on treatments for severe depression. The findings
477 suggested that reversing the excitation/inhibition imbalance by pharmacotherapy might not
478 be sufficient in severe depression. This may inform the direction of drug development for
479 depression, especially regarding agents targeting GABA. Additionally, we identified
480 excessive inhibition as a potential novel biomarker of ECT ineffectiveness in patients using
481 benzodiazepines or antidepressants. In our study, the effect size of this biomarker was
482 comparable to the presence of psychotic features (data not shown), which is currently one
483 of the most powerful predictors of ECT outcome⁴⁷. Another advantage of this biomarker is
484 that it may be modifiable by adjusting the pharmacotherapy dosages in the individual ECT-
485 patient. Thereby, our findings suggest that pharmacotherapy management informed by the
486 excitation/inhibition ratio may prevent excessive inhibition and potentially enhance the
487 effectiveness of ECT. Alternatively, patients treated with ECT may simply benefit from
488 lower dosages of pharmacotherapy during the ECT-course. This may especially hold for
489 patients using benzodiazepines, which showed higher risks of excessive inhibition in this
490 study. However, replication neuroimaging and clinical studies are needed before
491 implementation of these findings in clinical guidelines.

492

493 Several limitations have to be taken into account when interpreting our findings. First, the
494 effects of pharmacotherapy on the excitation/inhibition balance were studied using cross-
495 sectional data and an observational design. These findings should be replicated in
496 longitudinal prospective studies to rule out potential selection bias and effects of
497 confounding variables not tested in the current study (e.g., comorbid psychiatric disorders,
498 level of anxiety, concomitant use of other medication). Also, data on the timing of
499 pharmacotherapy (dis)continuation was unavailable, which should be taken into account

500 by future studies. Additionally, effects of pretreatment with flumazenil could not be
501 evaluated. Furthermore, our study was observational and included severely depressed
502 patients that failed to respond to pharmacotherapy and were indicated for ECT. This is a
503 highly selected and severely ill population to test the general neural mechanisms of
504 pharmacotherapy. Therefore, our findings may not necessarily generalize to other
505 subtypes of depression. Moreover, we established neural inhibition/excitation on the level
506 of cortical networks, each node containing millions of neurons. This restrained our level of
507 inference and made conclusions on specific cellular processes impossible (e.g.,
508 neurotransmitter concentrations, effects on specific receptor types or subunits). Finally, no
509 (sufficient) data was available to test other effects of interest, such as dose-dependency of
510 pharmacotherapy effects. Future studies have to be conducted to overcome these
511 limitations.

512

513 In conclusion, our study provides novel evidence on the role of excitation/inhibition
514 imbalance in treatments for severe depression. We show that reversing the
515 excitation/inhibition imbalance may not be sufficient nor necessary for treatment
516 effectiveness using pharmacotherapy or ECT in severe depression. Furthermore, the
517 presence of excessive neural inhibition nullified the positive effects of concomitant
518 pharmacotherapy on the antidepressant effectiveness of ECT. These findings should be
519 replicated by future studies to assess generalizability to other samples and milder
520 subtypes of depression. Nonetheless, this work provides a modest but important step for
521 understanding the working mechanisms of treatments for severe depression and
522 enhancing their effectiveness.

523

524

525 **Methods**

526 **Participants and treatment**

527 Data were obtained from the Global ECT-MRI Research Collaboration (GEMRIC)²⁷. All
528 patients in this study were indicated for ECT and were treated according to internationally
529 accepted guidelines. The data used for this study were acquired at seven sites across
530 Europe and North America. Participants were divided into four groups: healthy controls (n
531 = 59), treatment-resistant patients without current use of antidepressants and
532 benzodiazepines (noAD/BZ; n = 60), treatment-resistant patients using antidepressants
533 (AD; n = 56), and treatment-resistant patients using benzodiazepines (BZ; n = 63). The
534 latter two groups showed considerable overlap (n = 24), which was accounted for in the
535 analyses. All patients had a clinical diagnosis of unipolar major depressive disorder,
536 classified according to the International Statistical Classification of Diseases and Related
537 Health Problems (ICD-10). Patients without current use of benzodiazepines and
538 antidepressants did receive at least one trial of pharmacotherapy before. Descriptive data
539 on demographics (age, sex) and clinical variables (depression severity, presence of
540 psychotic features, presence of recurrence) were available. Depression severity was
541 assessed using the Hamilton Depression Rating Scale (HAM-D) or Montgomery-Åsberg
542 Depression Rating Scale (MADRS), depending on the sites' preferences. Ratings of the
543 MADRS were converted to HAM-D scores, using the following formula⁴⁸:

$$544 \text{HAM-D} = -1.58 + 0.86 * \text{MADRS}.$$

545 Patients were excluded if (1) bipolar disorder was present⁴⁹, (2) BZ or AD use data were
546 incomplete, and (3) if neuroimaging data were unavailable or of insufficient quality.

547

548 The ADs that were examined in this study consisted of selective-serotonin reuptake
549 inhibitors (SSRIs), selective-noradrenaline reuptake inhibitors (SNRIs), tricyclic

550 antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs). In the group of
551 patients currently using AD, 34% used SSRIs, 36% used SNRIs, 27% used TCAs and 3%
552 used MAOIs. The specific type of BZ, and dosages for AD and BZ, were not available in
553 the database. Regarding used electrode placements, 126 patients received ECT with right
554 unilateral (RUL) and 62 patients with a bilateral (BL) electrode placement. The average
555 number of ECT-sessions per course was 12.4 ± 5.5 SD.

556

557 **fMRI acquisition, preprocessing, and quality control**

558 Structural and functional resting-state magnetic resonance imaging (MRI) data were
559 acquired at seven sites (for scanning parameters per site, see SI Table 4). The fMRI
560 preprocessing steps were identical for each participant. First, structural and
561 functional images were reoriented and brain extraction was performed using
562 Advanced Normalization Tools (ANTs v2.2.0). Images were coregistered using ANTs
563 and FMRI Software Library (FSL v5.0.10) using boundary-based registration. After
564 discarding the first two volumes for each fMRI series, FSL's MCFLIRT was used to
565 apply head movement correction by realigning the volumes to the middle volume
566 using six parameters for rigid body transformations. Functional images were spatially
567 smoothed using a Gaussian kernel with 5 mm full-width at half-maximum. For motion
568 correction, an ICA-based strategy for Automatic Removal of Motion Artifacts (ICA-
569 AROMA) was used. The noise components estimated by ICA-AROMA were used to
570 compute denoised cosines for high pass filtering ($f=0.009$). Furthermore, mean white
571 matter (WM) and cerebrospinal fluid (CSF) timeseries were computed as additional
572 nuisance variables. Temporal high-pass filtering was used to remove low-frequency
573 drifts (< 0.01 Hz) and images were registered to 4 mm isotropic voxel size. Both the
574 denoised cosines and WM/CSF nuisance variables were used to denoise the fMRI

575 data and perform high pass filtering in one single step⁵⁰ ANTs were used for
576 normalization of transformation matrices to MNI space using 2 mm standard
577 templates.

578 After the preprocessing, a quality control procedure was performed. First, participants that
579 showed a high degree of motion were identified using three criteria: (1) any
580 rotation/translation exceeding 4 mm/degrees, (2) the average framewise displacement
581 (FD) exceeding 0.3 mm, and (3) less than 4 minutes of RS-fMRI data unaffected by motion
582 (FD<0.25mm). If any of the criteria applied to a participant's RS-fMRI data, the participant
583 was excluded from the study. Then, the data were visually inspected to confirm high-
584 quality coregistration and normalization of the T1w and RS-fMRI scans. Finally, the EPI
585 signal-to-noise and field of view were assessed to identify potential signal dropout or other
586 artifacts. Again, participants with low quality preprocessed data were excluded from the
587 analysis. Finally, RS-fMRI of sufficient quality was available for a total of 214 participants
588 with respect to cross-sectional baseline data. Regarding longitudinal data, RS-fMRI data of
589 sufficient quality was available for 113 participants.

590

591 **First-level spDCM analysis**

592 Spectral dynamic causal modeling (spDCM) for RS-fMRI was used to estimate effective
593 connectivity parameters²². Analyses were conducted in Statistical Parametric Mapping
594 (SPM12, revision 7771) with DCM12.5 (revision 7497). spDCM used a generative forward
595 model with two components. The first one described how neuronal populations causally
596 interact. The second component mapped neuronal activity from the first model to observed
597 (crossspectra of) hemodynamic responses. Thereby, spDCM was able to estimate
598 directed connectivity between brain regions as well as regional self-connections. The

599 construct validity of spDCM has been shown by its ability to accurately recover effective
600 connectivity in simulated data^{22,23}, and specific effective connections corresponding to well-
601 documented neural pathways in rodents²⁴. The self-connections were assumed to be
602 inhibitory, which was in line with in vivo animal studies²⁵. By regulating the strength of
603 inhibition, the self-connections allowed for sustained activity in the cortex while maintaining
604 a balance between excitation and inhibition throughout the network. A recent
605 magnetoencephalography study using DCM showed that a GABA_A reuptake inhibitor
606 altered the strength of inhibitory (self-)connections in humans²⁶, indicating that the DCM
607 framework could be used to study the effect of therapeutic interventions on (self-)inhibition.
608

609 We used the following procedure. First, the RS-fMRI timeseries were extracted from
610 fourteen regions of interest (ROIs). These regions formed the core of three networks (i.e.,
611 default mode network (DMN), salience network (SAL) and central executive network
612 (CEN)) that are of central importance to depression²⁸ and psychopathology in general⁵¹.

613 Time series were extracted from a sphere with 5 mm radius centered around MNI
614 coordinates extracted from previous research (see SI Figure 1)⁵²single representative time
615 series was established by retaining the first component of a principal components analysis
616 across voxels in each sphere. For baseline analysis, a full spDCM was estimated for each
617 participant individually (i.e., all 196 connections in matrix A of the neural model, henceforth
618 the 'A-matrix', were turned on). Default settings were used for the individual-level spDCM
619 analyses and no experimental inputs were specified (i.e., all 196 connections in the 'B-
620 matrix' turned off). The expected values and covariances of the estimated parameters of
621 the 'A-matrix' were then taken to the group-level analysis.

622

623 For the longitudinal analysis, a multisession resting-state spDCM approach was used.
624 Only the longitudinal effect of ECT on inhibitory self-connections were estimated.
625 Therefore, a full ‘A-matrix’ was specified and an identity matrix was used as the ‘B-matrix’.
626 In this case, the ‘A-matrix’ provided the averaged connectivity over both sessions and the
627 ‘B-matrix’ modelled the change between sessions. Because we were interested in
628 changes associated with ECT, the estimated parameters of the ‘B-matrix’ were taken to
629 the group-level analysis.

630

631 **Parametric Empirical Bayes**

632 Group-level effects could be estimated using the Parametric Empirical Bayesian (PEB)
633 framework⁵³. A PEB general linear model (GLM) was able to infer effects at multiple levels
634 (e.g., group effects or between-session effects) by combining the expected values and
635 covariances from all individual-level spDCM parameters. Additionally, the PEB model was
636 able to finesse spDCM parameters at the individual level by using group-level posteriors
637 as empirical priors⁵⁴. PEB models were used for studying associations between baseline
638 self-inhibition and ECT effectiveness (see Analysis on baseline associations with ECT
639 effectiveness, below).

640

641 For each PEB model (see below for PEB model designs), effects on inhibitory self-
642 connections in individual nodes and effects on combinations of self-connections of multiple
643 nodes were examined. For effects on individual self-connections, Bayesian Model
644 Reduction (BMR) was used to automatically search over reduced models with certain
645 connectivity parameters ‘turned off’ (i.e., fixed at their prior mean of zero). In this method,
646 all possible reduced models were compared, and models with connectivity parameters that
647 did not contribute to model evidence were iteratively discarded. This process was

648 continued until removing parameters reduced the model evidence. Subsequently, a
649 Bayesian model average was calculated over the 256 models with the largest model
650 evidence in the final iteration (or over the remaining models, if less than 256 models
651 survived). Using this ‘pruning’ and averaging approach allowed inference on the posterior
652 probability of specific connectivity parameters. A threshold for posterior probabilities
653 indicating strong evidence was used for each second-level parameter ($p(m|Y) > 0.95$).

654

655 For the analysis on specific groups of connections, BMR was used to estimate the model
656 evidence for pre-specified reduced connectivity models. Subsequently, the model
657 evidence between the reduced models was compared to that of an empty model (i.e., all
658 parameters ‘turned off’) to determine which reduced model best fitted the observed data⁵⁴.
659 Five pre-specified reduced models were used, in which models included self-connections
660 in none of the networks, one of the networks (DMN, CEN or SAL), or all of the networks
661 (DMN, CEN and SAL; see SI Figure 3). Thereby, this procedure tested whether
662 associations between variables of interest (e.g., depression severity) and self-connections
663 parameters were absent, network-specific or widespread throughout brain networks.
664 Again, a threshold of a posterior probability indicating (at least) strong evidence in favor of
665 a model was used ($p(m|Y) > 0.95$).

666

667 **PEB model designs**

668 Multiple PEB GLMs were run to test for group differences in inhibitory self-connections at
669 baseline, associations with depression severity, and changes in inhibitory self-connections
670 before and after ECT.

671

672 First, an analysis on group differences between healthy controls and patient groups was
673 conducted. Group differences could be modeled using multiple GLM designs. We used a
674 model selection procedure by comparing the two most convenient designs with respect to
675 model evidence. A GLM in which all patient groups (unmedicated, AD, BZ) were modeled
676 with a separate binary regressor (and healthy controls as the intercept, i.e., reference
677 group) showed greatest model evidence, and was selected for the analysis on group
678 differences (see SI Figure 2 for the models and difference in model evidence). Additionally,
679 an identical model with extra regressors was run to test if the results of the initial model
680 were robust against effects of potential confounding variables. The added regressors
681 consisted of age, sex, baseline HAM-D score, presence of recurrent depression, presence
682 of psychotic depression, lithium carbonate use, antipsychotic use and site variables. The
683 age and sex variables were mean centered, such that the reference comparison group
684 (i.e., the intercept) represented healthy control subjects of a group average age, averaged
685 over males and females. Due to the collinearity constraint in a GLM design, not all sites
686 variables could be included as covariates (i.e., the sum of all site variables equals the
687 intercept). Therefore, site variables that added substantially to the model evidence were
688 selected as potential confounders. These variables were selected by comparing the model
689 evidence between the model with demographic and clinical covariates with an identical
690 model plus one of the site variables. If a site variable explained considerable variation in
691 the data, the model fit increased. However, adding a covariate also added extra complexity
692 to the model, which reduced model evidence. This procedure tested whether the increase
693 in the goodness-of-fit by adding the site variable outweighed the increase in complexity.
694 Site variables that increased model evidence were included as a potential confounder in
695 the GLM (SI Figure 3).

696

697 Because the model above did not allow direct comparisons between patient groups, post-
698 hoc pairwise comparisons between the AD, BZ and unmedicated patient groups were
699 conducted. For each comparison, a GLM was created that included patients of the
700 specified patient groups (see SI Figure 5 for model design). The same potential
701 confounding variables as in the model above were also included in the model. Additionally,
702 AD use was included in the comparison between patients using BZ and unmedicated
703 patients, and BZ use was included in the comparison between patients using AD and
704 unmedicated patients. The latter was done to account for the overlap between the AD and
705 BZ groups. For post-hoc analyses, a threshold that indicated strong evidence according to
706 Bayesian statistics was used, adjusted for multiple comparisons using Bonferroni ($p(m|Y)$
707 > 0.983).

708

709 Associations with depression severity were analyzed using a GLM that included patients
710 only (see SI Figure 6 for the model design). This model tested if there were effects of
711 depression severity on inhibitory self-connections in the complete group (i.e., main effect
712 of baseline HAM-D) or specific patient groups (i.e., patient group by baseline HAM-D
713 interactions). Aside from the unadjusted model, a model was run to test if the results were
714 robust against potential confounders. The same demographic and clinical covariates were
715 included as in the adjusted model for group comparison. Also, an identical procedure was
716 used to select relevant site variables (i.e., selecting site variables that increased model
717 evidence).

718

719 Finally, PEB models were used to test for longitudinal effects of ECT. Parameters of the
720 first-level longitudinal analyses were entered into group-level PEB models. The first GLM
721 tested for longitudinal effects in patients compared to healthy controls, and for associations

722 with ECT effectiveness (SI Figure 7). Again, we subsequently tested if the results were
723 robust against potential confounding variables. Based on previous studies^{47,55} and clinical
724 practice, the following demographic and clinical variables were included in the GLM as
725 potential confounders: age, sex, baseline HAM-D score, presence of recurrent depression,
726 presence of psychotic depression, lithium carbonate use, antipsychotic use, number of
727 ECT-sessions, and site variables. Site variables were selected using an identical
728 procedure as described in the analysis on group differences. Furthermore, an additional
729 model was run for effects of treatment response (i.e., a binary regressor indicating HAM-D
730 reduction greater than 50% compared to baseline), instead of the continuous measure for
731 ECT effectiveness used in the model above. Finally, because patient groups showed
732 different baseline strengths in inhibitory self-connections, we also tested for longitudinal
733 effects of ECT in the distinct patient groups (SI Figure 9 for the model design). The latter
734 model also tested if ECT effectiveness in distinct patient groups was associated with
735 changes in inhibitory self-connections.

736

737 **Analysis on baseline associations with ECT effectiveness**

738 For the clinical analysis, a multiple regression model was run to test the effect of clinical
739 variables on ECT effectiveness, which was defined as the change in HAM-D scores before
740 and after the ECT-course ($HAM-D_{PRE} - HAM-D_{POST}$; i.e., the dependent variable). The
741 included clinical variables were the use of BZ, the use of AD, baseline HAM-D scores,
742 presence of psychotic features, age, number of ECT-sessions with BL electrode
743 placement, and seven binary variables indicating site membership. These variables were
744 selected because those were identified as predictors of ECT effectiveness in previous
745 research⁴⁷ and in clinical practice.

746

747 In order to relate the excitation/inhibition ratio at baseline to ECT effectiveness, multiple
748 regression models were used in R⁵⁶. A different approach was used for this analysis
749 compared to the analyses described above (see PEB design models), because we aimed
750 to provide effect size measures that were comparable to the existing literature on ECT
751 outcome predictors (i.e., provided by classic frequentist statistics, rather than Bayesian
752 statistics). First, a PEB GLM (with only the intercept) was used to establish the posterior
753 probability distribution of each of the 14 self-connection parameters for each individual.
754 The mean of the probability distribution for each self-connection was extracted for each
755 participant, and the first principal component (as obtained by principal component analysis
756 using the *prcomp* package) was used as summary measure of the excitation/inhibition
757 balance. Subsequently, a classical (non-Bayesian) multiple regression model was used to
758 examine the relation between excitation/inhibition balance (i.e., the independent variable)
759 and ECT effectiveness. Both linear and quadratic effects of the excitation/inhibition
760 balance on ECT effectiveness were tested. All variables that showed a significant effect in
761 the above-described clinical analysis were included as a covariate in the model (i.e.,
762 baseline HAM-D score, age, presence of psychotic features, number of ECT-sessions with
763 BL electrode placement, and two binary variables indicating site membership). For post-
764 hoc analyses, identical models were built that only included patients of the separate
765 groups (i.e., noAD/BZ, AD and BZ). The same covariates were entered into the model.
766 Because the AD and BZ groups showed considerable overlap, BZ use was added as a
767 covariate in model of the AD group, and AD use was added in the model of the BZ group.
768 This was done to ensure that the effects in the AD and BZ group were independent from
769 BZ and AD use, respectively. Cohen's f^2 was used as a measure of effect size, in
770 which $0.15 \leq f^2 \leq 0.35$ indicates a medium effect size⁵⁷.

771

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776

777 **Author contributions**

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779 M.V., J.V., M.v.V., H.B., L.O., J.A.v.W., & G.A.v.W contributed to data acquisition. F.t.D.
780 primarily performed data analysis. W.B., P.Z., J.A.v.W., & G.A.v.W also made substantial
781 contributions to data analysis. F.t.D., J.A.v.W. & G.A.v.W drafted the manuscript. W.B.,
782 P.Z, C.A., M.A., A.D., L.E., P.F.P.v.E., E.v.E., P.C.R.M., K.N., I.T., D.R., P.S., M.V., J.V.,
783 M.v.V., H.B., & L.O. substantially revised the manuscript.

784

785 **Competing interests**

786 No potential competing interest was reported by the authors

787

788

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