

Neurophysiological Correlates of Borderline Personality Disorder: A Transcranial Magnetic Stimulation Study

Sven Barnow, Kathleen A. Völker, Bertram Möller, Harald J. Freyberger, Carsten Spitzer, Hans J. Grabe, and Zafiris J. Daskalakis

Background: Cortical inhibition deficits have been demonstrated in several disorders with deficits in impulsive control (e.g., attention-deficit/hyperactivity disorder [ADHD], tic disorder, Tourette syndrome) by using transcranial magnetic stimulation (TMS). With borderline personality disorder (BPD), we investigated another disorder associated with high impulsivity by TMS. We hypothesized that BPD patients display decreased cortical inhibition and/or increased cortical excitation as assessed with TMS.

Methods: Different inhibitory and excitatory TMS parameters were investigated in 19 unmedicated female BPD patients and 19 healthy control subjects matched for sex, age, handedness, and body height. Additionally, the results were controlled for ADHD symptomatology.

Results: A reduced cortical silent period (CSP) duration was found in BPD patients compared with healthy control subjects in the right cortex. Even after controlling for ADHD symptoms, this result remained significant.

Conclusions: These findings support an association between BPD and cortical inhibition deficits as indexed through TMS. The results are discussed considering basic neurobiological mechanisms that may explain our findings of decreased intracortical inhibition in BPD patients.

Key Words: ADHD, borderline personality disorder, GABA, impulsive control, inhibition, TMS

With a prevalence of 1% to 2% of the general community, borderline personality disorder (BPD) is a significant public health problem (1). Taking into account that BPD patients often show impulsive behaviors (2) and that these behaviors are controlled by neuronal networks within the prefrontal cortex (PFC) (3), deviations in morphology and in functioning of the PFC can be suggested in BPD. Several authors reported evidence to confirm this hypothesis (4-10). For example, Lyoo *et al.* (6) found a decreased frontal lobe volume in BPD patients. Tebartz van Elst *et al.* (7) demonstrated a significant volume loss of amygdala, hippocampus, the right anterior cingulate cortex, and left orbitofrontal cortex. Additionally, several studies found an association between impulsivity and a hypoactivity of the frontal lobe (11-13), while Juengling *et al.* (14) reported hyperactivity in the anterior cingulate cortex and areas of the prefrontal lobe in patients with high impulsivity and suicidal behavior. In summary, these studies demonstrated that impulsive behavior in BPD has neurophysiological correlates in terms of a frontolimbic network dysfunction. From the neurophysiological perspective, impulsive behavior may be interpreted as either diminished inhibition or enhanced excitability. A neurophysiological method assessing such cortical phenomena

might help to understand the cortical mechanisms underlying impulsivity in BPD.

One method to test inhibitory and excitatory cortical functioning is transcranial magnetic stimulation (TMS). Although different cortical areas can be tested and similar neurophysiological measures can be assessed by using TMS (15), the main target region for TMS investigation is the motor cortex. Transcranial magnetic stimulation of the primary motor cortex results in motor evoked potentials (MEP), which can be used to evaluate several important neurophysiological paradigms (16). Furthermore, TMS can be used to study cortical brain abnormalities in neuropsychiatric disorders (for summary, see 17). Previous studies focused on several impulsive control disorders such as attention-deficit/hyperactivity disorder (ADHD) and found reduced cortical inhibition especially in means of short-interval intracortical inhibition (SICI) and cortical silent period (CSP) (18-21), two inhibitory TMS paradigms. While most of these studies analyzed children with ADHD, Richter *et al.* (22) compared adult ADHD patients with healthy control subjects. They found reduced cortical inhibition (SICI) in adult ADHD patients but no differences in facilitatory measurements (rest motor threshold [RMT], intracortical facilitation [ICF]).

Short-interval intracortical inhibition represents an index of intracortical inhibitory mechanisms that can be activated by application of a subthreshold conditioning stimulus followed by a suprathreshold test stimulus after an interstimulus interval (ISI) of 2 msec to 5 msec (23). Several pharmacological studies found SICI to be mediated by γ -aminobutyric acid type A receptors (GABA_A) (24).

Cortical silent period is characterized as the duration of electromyograph (EMG) cessation as measured in the contracted target muscle in response to a TMS stimulus applied over the motor cortex. Several studies indicate CSP is mediated by γ -aminobutyric acid type B (GABA_B) neurotransmission (25,26). Additionally, there are several other TMS parameters that could be helpful to test inhibitory and excitatory cortical functioning, for example, resting motor threshold (RMT) (27), which is largely mediated by ion channel conductivity of neural membranes (28). Another

From the Department of Clinical Psychology and Psychotherapy (SB), Ruprecht-Karls University of Heidelberg, Heidelberg; and Department of Psychiatry and Psychotherapy (KAV, BM, HJF, CS, HJG), Ernst-Moritz-Arndt University of Greifswald, Greifswald, Germany; and Schizophrenia Program (ZJD), Centre for Addiction and Mental Health, Toronto, Canada. SB and KAV contributed equally to this work.

Address reprint requests to Sven Barnow, Ph.D., Department of Clinical Psychology and Psychotherapy, Ruprecht-Karls University of Heidelberg, Hauptstraße 47-51, 69117 Heidelberg, Germany; E-mail: sven.barnow@psychologie.uni-heidelberg.de.

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inhibitory TMS paradigm is transcallosal inhibition (TCI), which was found to be mediated by excitatory transcallosal output neurons projecting to contralateral inhibitory interneuron (29). Furthermore, it was suggested that TCI is associated with GABA_B receptor-mediated neurotransmission (30). Intracortical facilitation is an excitatory TMS paradigm that can be tested using a conditioning TMS stimulus and a test stimulus with an interstimulus interval of 7 msec to 20 msec, resulting in an increased MEP response (23). Intracortical facilitation seems to be generated by a net balance between weaker fast GABA_A-mediated inhibitory postsynaptic potentials (IPSP) and a stronger slow *N*-methyl-D-aspartate (NMDA)-mediated excitatory postsynaptic potential (EPSP) (30).

Reduced cortical inhibition measured by TMS paradigms has been found in several impulse control disorders including ADHD, whereas no studies have used this technique in BPD patients. In the current study, we used TMS to investigate whether or not cortical inhibition deficits or likewise enhanced facilitation are present in patients with BPD. More specifically, we hypothesized that individuals with BPD would show reduced CSP, SICI, and TCI duration compared with healthy control subjects. We also hypothesized that BPD patients would demonstrate increased cortical excitation compared with the control subjects as measured by RMT and ICF. Because a high comorbidity of BPD with ADHD was shown in previous studies (e.g., 31) and ADHD symptoms were related to diminished cortical inhibition assessed by TMS as mentioned above, we controlled our findings for current ADHD symptoms as well as for retrospective reports of ADHD symptoms during childhood.

Methods and Materials

Subjects

We recruited 24 nonmedicated right-handed female patients from the Hospital for Psychiatry and Psychotherapy of the University of Greifswald, Germany. All patients fulfilled at least five criteria of BPD according to the American Psychiatric Association (2) assessed by the Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II) (32), German version (33). The BPD participants had a mean age of 23.3 ± 5.0 years and a mean body height of 166.57 ± 6.85 cm. All patients were free of any regular psychiatric medication at the time of the study, i.e., they did not receive any antidepressive and neuroleptic medication within the last 2 weeks before investigation. Only one subject received a single dose, a sedative medication with promethazine, a histamine H1 antagonist, as acute medication within the 2-week period. Four of the patients were drug-naïve. The healthy control (HC) group consisted of young adults matched for sex, age, handedness, and body height with the BPD group. The HC subjects were recruited from the community-based sample of "The Family Study of Greifswald" (34). None of the subjects in this group had either an Axis I or Axis II lifetime disorder as assessed with the Diagnostic Expert System for Psychiatric Disorders (DIA-X) (35) and the SCID-II interview. The healthy control group had a mean age of 22.7 ± 5.0 years and a mean body height of 166.43 ± 5.11 cm.

Exclusion criteria were age under 18 or over 35 years and current substance abuse or addiction. Participants with any history of epileptic seizure or suspicion of epileptic seizure in lifetime were excluded from the study. Additionally, any other neurological disorder, pregnancy, or pieces of metal in brain or body were considered as exclusion criterion. All patients were informed about aims and risks of this study and gave written

informed consent. We could not apply TMS to three of the BPD patients because of the following reasons: one had a neurological disease, a second had a family history of epileptic seizures, and a third did not agree to the TMS procedure itself.

Because the ADHD questionnaires were not completed by two subjects, the sample size decreased to 19 persons in each group. However, there were no significant differences regarding the severity of BPD between the included and excluded patients [number of fulfilled BPD criteria ($t = -.485$, $p = .633$)].

All TMS sessions were conducted by the same scientist (K.A.V.). The left and right hemispheres were tested in randomized order. The whole session took about 1 hour. The study was approved by the Research Ethics Board of the Ernst-Moritz-Arndt-University of Greifswald in accordance with the declaration of Helsinki on the use of human subjects in experiments.

Procedure

Axis I Diagnostic. Axis I disorders were diagnosed by the DIA-X (35), which is a reliable and valid semistructured interview based on the Composite International Diagnostic Interview (CIDI) (36). To diagnose alcohol disorders, we used the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA) (37).

Axis II Disorders. Borderline personality disorder and other personality disorders were assessed by the German version of the Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II) (32) according to the criteria of the American Psychiatric Association (2). In our study, we used the combined version with questionnaire and interview which has kappa-scores of $\kappa = .41$ (cluster A) to $\kappa = .73$ (cluster C) (38).

ADHD Symptomatology. To measure the amount of adult ADHD symptoms, we used the Instrument for Assessment of Adult ADHD (German version) (IDAA) (39). This questionnaire consists of three subscales: 1) attention, 2) hyperactivity, and 3) impulsivity. All three scales have good psychometric characteristics (retest reliability: .78–.89; Cronbach's alpha: .72–.89).

Additionally, we used the Wender Utah Rating Scale (German version) (WURS-k) (40) to assess ADHD symptoms during childhood retrospectively. With a split-half reliability of $r_{12} = .85$ (Spearman-Brown) and an internal consistency of $\alpha = .91$ (Cronbach's alpha), the WURS-k has good psychometric characteristics.

Handedness. Handedness was assessed in two different ways. First, we used an item asking for handedness in our demographic questionnaire (self-rating). Second, participants were watched for their preferred handedness while performing computer tests and fulfilling questionnaires prior to the TMS session.

Transcranial Magnetic Stimulation. For the TMS procedure, we used a MAGLITE-R25 Twintop stimulator (Dantec-Medtronic, Skovlunde, Denmark) and a figure-8 coil with an outside diameter of 9 cm (half-coil).

The participants were seated in a comfortable chair during investigation. Two surface electrodes were attached on the skin over the first dorsal interosseus muscle (FDI) of each hand. Data were collected by a Keypoint commercial amplifier (Version 3.25, Dantec-Medtronic) with a bandpass of 10 Hz to 10,000 Hz. We used an auditory feedback to control the level of contraction in the target muscle.

Each session started with determination of the optimal point of stimulation on the scalp for a MEP in the target muscle. In the next step, the resting motor threshold was determined as the minimum TMS intensity necessary to produce MEPs $\geq 5 \mu\text{V}$ measured peak-to-peak on at least 5 of 10 trials of stimulation

Table 1. Mean Differences of ADHD Scores in Childhood and Adulthood Between BPD Patients and Healthy Control Subjects

	BPD (<i>n</i> = 19) Mean SD	HC (<i>n</i> = 19) Mean SD	<i>t</i> Test
WURS-k			
Sum score	29.05 (18.08)	8.84 (7.66)	^a
IDAA			
Sum score	13.74 (3.30)	6.68 (4.07)	^a
Attention	6.95 (1.93)	3.68 (2.33)	^a
Hyperactivity	3.95 (1.13)	1.74 (1.56)	^a
Impulsivity	2.84 (1.26)	1.32 (1.25)	^a

ADHD, attention-deficit/hyperactivity disorder; BPD, borderline personality disorder; HC, healthy control subjects; IDAA, Instrument for Assessment of Adult ADHD; WURS-k, Wender Utah Rating Scale.

^a*p* < .01.

delivered approximately 5 sec apart. After this, the corticomotor conduction time (CMCT) was determined by stimulation of the hemisphere of the contralateral hand with a stimulator intensity of 150% of RMT while the target muscle was slightly contracted. Corticomotor conduction time is the time interval between the stimulation and the beginning of the EMG response. Eight responses were recorded for each side.

In the next step, we measured TCI where 20 stimuli with an intensity of 80% maximum stimulator output were applied over the motor cortex. The TMS stimuli were approximately 5 sec apart from each other. The subjects were instructed to contract the ipsilateral FDI with maximum power during the TMS stimulation. The EMG activity for each stimulus and each hemisphere was recorded. The onset latency as well as the duration of transcallosal inhibition were averaged. As co-result of these tests, we calculated the transcallosal transfer time (TCT), i.e., the duration of stimuli transfer from one hemisphere to the other, as the difference between the onset latency of TCI and CMCT.

Next, CSP was assessed by applying TMS stimuli with an intensity of 110% (CSP110%) and 140% (CSP140%) of the individual RMT while the target muscle was preactivated. For each stimulus intensity, 15 stimuli were assessed. Cortical silent period was defined as the time between the onset of the MEP and the end of the inhibited EMG activity.

To control preactivation in the target muscle, the subjects were instructed to press a small ball either slightly (CMCT, CSP) or strong (TCI, TCT), which was controlled by an auditory feedback signal.

In the final step, paired-pulse stimulation was used to assess SICI and ICF according to previously published protocols (41). In particular, a conditioning stimulus with an intensity of 80% RMT was followed by a test stimulus that resulted in a MEP with an amplitude of approximately 1000 μ V. Six different ISIs were tested: 2, 2.5, 4, 7, 12, and 15 msec. The order of the ISIs was varied randomly. For each ISI and each side, we assessed eight trials with an intertrial interval of approximately 5 sec. The subjects were instructed to relax the target muscle during the testing.

Statistical Analysis

For testing the distribution of raw data, the Kolmogorov-Smirnov test was used. For all data, a normal distribution was found based on a *p*-value of >.05. To investigate group differences in inhibition and facilitation between the BPD and the HC groups, we used a one-tailed *t* test for independent groups. Additionally, the effect size Cohen's *d* was computed.

To compare the two groups in regard to ADHD symptoms, another *t* test for independent groups was calculated. To specify the impact of ADHD symptoms on the possible differences between both groups, the ADHD sum scores for adulthood (IDAA) and childhood (WURS-k) symptomatology were included as covariates in an analysis of covariance (ANCOVA). Because of the high intercorrelation between the two ADHD scores, two separate ANCOVAs were computed. For all tests, significance was determined at a value of *p* < .05.

Results

Transcranial magnetic stimulation was well tolerated by all included subjects. The group comparison, including the TMS parameters RMT, CSP, TCI, TCT, SICI (2, 2.5, and 4 msec ISI), and ICF (7, 12, and 15 msec ISI) in both hemispheres, revealed a significant CSP reduction in the right cortex in BPD patients as compared with HC subjects: (*t* test, CSP110%: *p* = .010; CSP140%: *p* = .027). We found mid- to high-range effect sizes (Cohen's *d*) of *d* = .80 for CSP110% (right cortex) and of *d* = .65 for CSP140% (right cortex). For none of the other parameters (RMT, TCI, TCT, SICI, and ICF) have significant group differences been found.

The comparison of the self-reported childhood and adulthood ADHD scores between the BPD group and the HC subjects resulted in significant differences in all five ADHD scores (WURS-k sum score, IDAA sum score, IDAA subscale attention, IDAA subscale hyperactivity, IDAA subscale impulsivity) with higher scores in the BPD group (Table 1).

As a result of the analysis of variance (ANOVA), including adult ADHD symptomatology as covariate, significant differences in CSP110% in the right cortex between the BPD and HC groups were found, while the scores regarding CSP140% were no longer statistically significant. Again, no significant differences for any other of the analyzed TMS parameters have been found. The results of the ANCOVA with the IDAA sum score as covariate are displayed in Table 2 and Figure 1.

Table 2. ANOVA: Differences Between BPD Patients and Healthy Control Subjects in Inhibitory and Excitatory TMS Parameters Controlled for Adult ADHD Scores

	BPD (<i>n</i> = 19) Mean SD	HC (<i>n</i> = 19) Mean SD	<i>F</i> (<i>df</i> = 2)	<i>p</i>
RMT				
lc	37.53 ± 8.12	35.53 ± 6.25	.780	.466
rc	37.89 ± 8.21	36.53 ± 6.41	.236	.791
CSP				
lc110%	95.76 ± 27.78	98.71 ± 38.55	.668	.519
lc140%	169.57 ± 38.27	168.82 ± 28.36	.009	.992
rc110%	91.50 ± 31.91	118.30 ± 35.05	5.398	.009 ^a
rc140%	174.05 ± 31.14	192.52 ± 25.61	1.969	.155
TCI				
lc	16.11 ± 3.18	16.62 ± 5.17	.120	.887
rc	16.34 ± 4.28	17.46 ± 5.85	.227	.798
TCT				
lr	21.20 ± 2.92	20.41 ± 3.06	.454	.639
rl	20.75 ± 2.24	20.23 ± 3.84	.182	.834

ADHD, attention-deficit/hyperactivity disorder; ANOVA, analysis of variance; BPD, borderline personality disorder; CSP, cortical silent period; HC, healthy control subjects; lc, left cortex; lr, left-right; rc, right cortex; rl, right-left; RMT, resting motor threshold; TCI, transcallosal inhibition; TCT, transcallosal transfer.

^a*p* < .01.

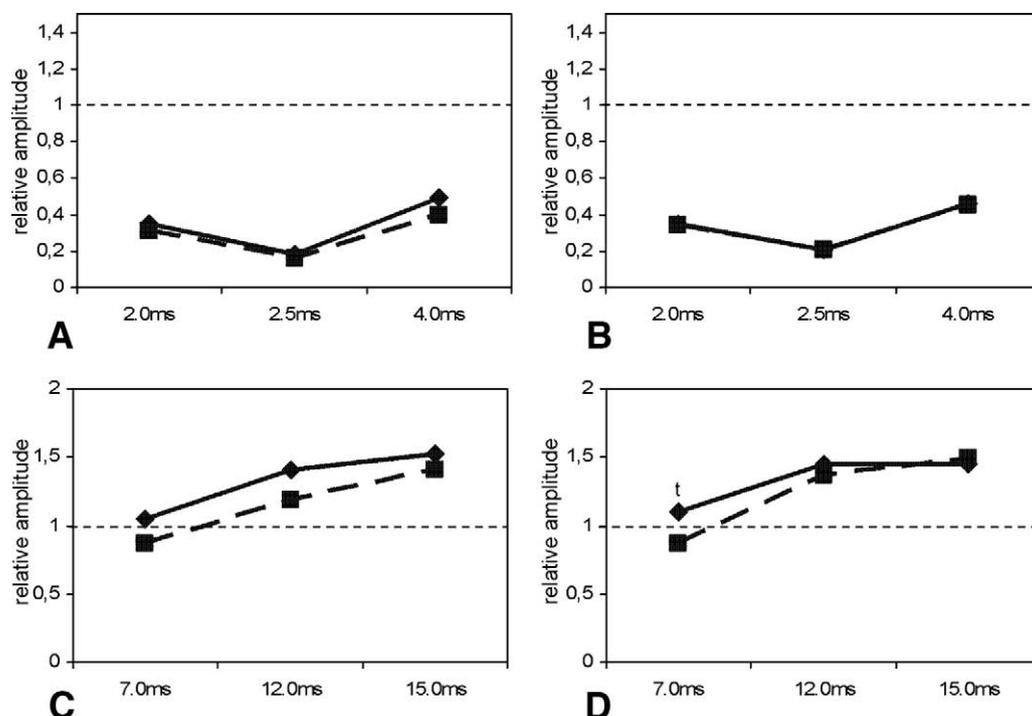


Figure 1. Differences in paired-pulse TMS [relative amplitude = (pp-amplitude in mV/baseline-amplitude in mV)] stimulation between BPD patients and healthy control subjects controlled for adult ADHD scores. **(A)** ISIs of 2.0, 2.5, and 4.0 msec left cortex (SICI); **(B)** ISIs of 2.0, 2.5, and 4.0 msec right cortex (SICI); **(C)** ISIs of 7.0, 12.0, and 15.0 msec left cortex (ICF); and **(D)** ISIs of 7.0, 12.0, and 15.0 msec right cortex (ICF). Solid lines and squares, BPD group ($n = 19$); dashed lines and rhombuses, healthy control subjects ($n = 19$); $t: p < .10$. ADHD, attention-deficit/hyperactivity disorder; BPD, borderline personality disorder; ICF, intracortical facilitation; ISI, interstimulus interval; pp, paired-pulse; SICI, short interval intracortical inhibition; TMS, transcranial magnetic stimulation.

Reevaluating our analyses by including childhood ADHD symptomatology as covariate, the results were similar with significant differences for the CSP140% ($F = 4.713$, $df = 2$, $p = .015$) and a trend toward a significant difference for CSP110% ($F = 2.955$, $df = 2$, $p = .065$). No other TMS score reached significance.

The exclusion of the subject who received promethazine as acute medication within the 2-week period before investigation did not change our results.

Discussion

To the best of our knowledge, this is the first study investigating if individuals with BPD show differences in inhibitory and excitatory TMS parameters in comparison with healthy control subjects. Our main finding was a significantly reduced CSP in the right motor cortex of BPD patients. Because a high comorbidity of BPD with ADHD was shown in previous studies (31) and ADHD symptoms were related to diminished cortical inhibition as assessed with TMS (20,22,42), we controlled our results by including current and childhood ADHD symptoms as covariates. These analyses revealed similar results with a significantly reduced CSP duration at 110% when controlling for adult ADHD symptoms and at 140% when controlling for childhood ADHD symptoms (all right cortex). However, it remains unclear why the effect sizes were different in both analyses, and further replication is needed to reconcile if these differences are attributable to a relatively small sample size or methodological problems (e.g., different variance and measurement errors of ADHD measures) or are due to actual differences in excitability in this patient population.

A reduced CSP is concordant with studies showing a CSP reduction in patients with tic disorder (TD), another disorder characterized by poor impulse control (19). Several authors suggested that CSP is mediated by GABA_B receptors (41). An influence of γ -aminobutyric acid (GABA) on the phenomenology of BPD seems reasonable, as GABA is the main inhibitory neurotransmitter, and decreased GABA activity could potentially result in impulsive behavior problems and affective instability, both key features of BPD (43). Moreover, several studies found a higher activity of the amygdala in response to negative stimuli in BPD patients (e.g., 44,45), and the amygdala has high levels of GABA receptors, suggesting an influence of GABA in this context (43).

Furthermore, it was also suggested that the basal ganglia may influence CSP and that CSP reflects the functioning of a cortico-striato-thalamo-cortical motor loop (46). In regard to the neuropsychological function of the basal ganglia, Haber (47) emphasized the pivotal role of the basal ganglia in the integration of motivation, cognition, and emotion for motor planning and execution of goal-directed behavior. Disturbance of these basal ganglia functions may lead to an inability to maintain and focus specific behaviors, as well as an inability to adapt specific behaviors appropriately to external and internal cues. Such behavioral problems can be seen in BPD. In regard to CSP, an integrative network theory, as proposed by Haber (47), provides an opportunity to link cortical inhibition tested in the motor cortex with dysfunction of cortical and subcortical structures as described in BPD (47).

Our finding of a CSP reduction for the right, but not for the left, hemisphere is indirectly supported by a recently published study by Irle *et al.* (48), who found a reduced right parietal cortex

volume in patients with BPD. The authors interpreted their results as indicating a neurodevelopmental deficit in the right hemisphere that may have been caused by several traumatic life events of these patients (48). Additionally, they reported an increased leftward asymmetry as a protective factor in BPD patients with posttraumatic stress disorder (PTSD) for the development of disabling psychotic syndromes. A study by Boutros *et al.* (49) that analyzed the cortical excitability in cocaine-dependent subjects also found right hemispherical CSP differences (CSP prolongation) in a subgroup of subjects with a history of cocaine-induced paranoia. While psychotic symptoms are also known in BPD patients, there might be an association between these symptoms and the right hemispherical asymmetry. However, we did not specifically assess psychotic symptoms and the interpretation of these hemisphere differences should be considered with care.

In summary, the reported CSP reduction in individuals with BPD suggests a deficit in the right hemisphere. This deficit was not accounted for by comorbid ADHD in childhood or adulthood, which is known to be highly comorbid with BPD. Since CSP is mostly mediated by GABA_B, reduced CSP in BPD patients may refer to a deficit in GABA_B receptor neurotransmission (41). So far, there is no evidence in recent literature for an alteration of the GABAergic system in BPD (50), while different neurotransmitter systems have been discussed as being important for the pathophysiology of BPD, e.g., serotonin (50), dopamine (51), and glutamate (52). Further studies may also consider GABA neurotransmission and its importance in the etiology of BPD. The deficiency of GABA_B receptors might be associated with the clinical phenomenon of an enlarged tolerance against benzodiazepines in BPD patients.

Limitations of this study are the relatively small sample size and the exclusion of male subjects. To find medium effects with a power of 80%, 30 patients with BPD would have been needed, and to find small effects we would have needed to include 60 patients. Thus, in this study, we were only able to identify large effects. Another important limitation is that we did not include a clinical comparison group (e.g., patients with ADHD). Thus, statements about the specificity of our findings for BPD cannot be made, although we controlled for ADHD symptoms. It has to be critically mentioned that we cannot exclude the possibility that the analyzed patients ever took a stimulant medication such as methylphenidate (MPH), regarding their high ADHD scores. The long-term effects of MPH on motor cortical excitability are not yet fully known, so an influence of the assessed parameters cannot be completely excluded. However, none of the included patients reported such a treatment when asked for earlier psychopharmacological treatments. Furthermore, it is possible that our nonmedicated BPD sample was less disturbed than BPD patients who receive regular medication. However, analyzing the amount of fulfilled BPD criteria, we did not find evidence for having an especially mildly disturbed sample (SCID-II interview mean score = 7, SD = 1.37). Additionally, the nonmedication of BPD patients was part of the treatment concept for personality disorders in our department where the patients were recruited. A strength of this study was the application of a large variety of TMS parameters to assess a wider spectrum of possible indicators for a disturbed cortical excitability. And by excluding patients with current medication, we eliminated the confounding effects of pharmacological treatment. Finally, a further strength was that we matched both study groups for important confounding factors.

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