

# Psychophysiological responses to group cognitive-behavioral therapy in depressive patients

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## Research article

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# **Abstract**

## **Background**

Cognitive-Behavioral Therapy (CBT) has a significant adjunctive effect in the treatment of Major Depressive Disorder (MDD), however its uses as monotherapy is less explored, mainly the group-based approaches.

## **Methods**

We assessed the responses of distinct psychophysiological domains after a intervention using group-based CBT (gCBT, 16 weeks) in drug-free patients with mild-moderate MDD ( $n = 20$ ; women = 11) and to compare with a healthy control group ( $n = 25$ , women = 13).

## **Results**

Treatment resulted in 65% of response and 55% of remission rates. Reductions in depressive and anxiety symptoms and increase in self-esteem and sleep quality were observed as responses of gCBT. After treatment patients regulated their previous deregulated salivary cortisol awakening response (CAR) and sleep quality to healthy parameters. These improvements were correlated among themselves and dependent of remission condition. Remitted patients showed large progresses than non-remitted patients, who significantly changed only serum cortisol and self-perceived depressive symptoms. Further, better baseline sleep quality was predictor of remission.

## **Conclusion**

These psychophysiological changes in response of gCBT support its use as tool with low cost and no side effects for treatment of mild-moderate major depression, as well as suggests a stronger exploration of these psychological domains in psychotherapies and stimulates furthers studies of neurobiology of MDD and alternatives treatments.

## **Trial registration**

U1111-1215-4472. Registered 21 August 2018, <http://www.ensaiosclinicos.gov.br/rg/RBR-3npbf8/>

# **Background**

The recognition and uses of alternative and complementary therapies of pharmacological treatments, such as psychotherapy, physical exercise, nutraceutical and psychedelic substances, have been increasing in the management of depressive symptoms [1–5]. Despite antidepressants are still the most adopted treatment for Major Depressive Disorder (MDD), patients have shown a significant preference for psychotherapies over pharmacotherapy [6, 7], probably due to the relative low efficacy of these drugs, which are not efficient to all patients [8–10], and due to the induction of undesirable side effects, which

may imply a reduction in adherence to treatment [11]. Consequently, the MDD prevalence has increased worldwide [8, 10, 12].

Among the psychotherapeutic approaches Cognitive-Behavioral Therapy (CBT) is the most used modality for the treatment of MDD [13, 14] and shows a significant adjunctive effect to pharmacological treatment, helping in the reduction of depressive symptoms and MDD recurrence [1, 15]. However, studies analyzing CBT as monotherapy for the treatment of MDD are less conclusive and its efficacy has been related to MDD severity [16, 17]. Compared to individual CBT, group CBT offers some advantages, such as reduced cost and sharing the experiences, which can help in more effective and faster acceptance of their own problems. However, this modality of CBT is less used and studied [18, 19].

The MDD cognitive theory points out that the patients have unfair thoughts and beliefs about themselves, an improper self-concept, lower self-esteem and feelings of shame. Moreover, it proposes that these cognitive aspects negatively modulate emotional, physiological, and behavioral reactions [20, 21]. Therefore, the CBT aims to improve the thoughts on self-concept and self-esteem [22, 23], which consequently contributes to the recovering of positive emotions and behaviors, as well as to the adjustment of physiological systems [20, 24, 25]. Another benefit of CBT is its potential to identify and treat comorbidity symptoms [20, 24, 26], such as anxiety [27–29] and sleep disturbances [27, 30, 31].

Although MDD diagnosis does not include pathophysiological characteristics [27], changes in the Hypothalamus-Pituitary-Adrenal (HPA) axis function and cortisol levels been observed in MDD patients [32–34]. Cortisol changes seem to correlate with sleep disturbances, high anxiety levels and rumination thoughts in depressive patients, closing a dysfunctional positive feedback system [35–37]. Therefore, the cortisol has been proposed as an important biomarker of MDD for diagnosis, prognosis, and follow-up [38, 39]. However, studies that have measured the effects of CBT as a monotherapy on cortisol levels of MDD patients are few and inconsistent [40, 41].

Thus, this study investigated the responses of distinct psychophysiological domains, such as depression and anxiety symptoms, self-esteem, sleep quality and cortisol levels (salivary and serum), in MDD patients under group CBT monotherapy treatment. We expected to find a reduction of depressive and anxious symptoms, associated with increases in self-esteem and in sleep quality, as well as an adjustment of cortisol levels, especially in remitted patients.

## Methods

This open-label trial was conducted at the Federal University of Rio Grande do Norte (UFRN) between 2018–2019. It has been approved by the UFRN Human Ethics Committee (# 2628,202) and registered at <http://clinicaltrials.gov> (U1111-1215-4472). The procedures of this study comply with the ethical standards of the relevant national and institutional committees for human experimentation and with the Declaration of Helsinki of 1975, revised in 2008. All subjects provided written informed consent prior to participation and it was ensured freedom to withdraw from the study at any time and without any prejudice. All study's information has been kept confidential.

## Volunteers

The recruitment of volunteers was performed by advertising on radio, social and academic media. All subjects have undergone a full clinical evaluation performed by a trained psychiatrist including anamnesis and mental health evaluation assessed by Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) and the Hamilton Depression Assessment Scale. After screening, the volunteers were grouped as follows:

**Patients group (PG):** 30 volunteers (16 women and 14 men) with mild to moderate depressive episode without psychiatric, neurological, or physical (metabolic and inflammatory) comorbidities were included in this group and selected to start the treatment. Other exclusion criteria were the previous use of antidepressant and current use of antidepressants, anxiolytic, corticoids, or drugs with action on neurovegetative functions, mood, and cognition. Therefore, the patients were drug-free during this study.

**Control group (CG):** 25 healthy volunteers (13 women and 12 men) with similar socio-demographic characteristics of the patients group, without history or current diagnosis of physical (metabolic and inflammatory), neurological or mental disease, and no use of regular medication with action on neurovegetative functions, mood and cognition. This group did not receive treatment or intervention.

## Study design

All volunteers (PG and CG) slept, individually, one night at the Laboratory of Neurobiology and biological rhythms of UFRN, when the Pittsburgh Sleep Quality Index (PSQI) [42] was assessed. In the following morning, around 6 a.m., the saliva and blood were collected to measure the salivary cortisol awakening response (CAR) and serum cortisol, respectively. Prior the patients started the treatment, the psychometric scales were assessed: Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI) and Rosenberg Self-Esteem Scale (RSE). Over the following 16 weeks, patients underwent the treatment. After that, up to one week from the end of treatment, patients slept once again in the sleep lab. Sleep quality was assessed by PSQI and blood and saliva were collected in the following morning. A new clinical evaluation with the same psychiatrist was conducted and the psychometric scales (BDI, BAI and RSE) and HAM-D were assessed.

## Treatment

Patients were treated with group Cognitive-Behavioral Therapy (gCBT) in monotherapy for 16 weeks; 12 weekly sessions and two fortnightly sessions (reinforcement and closing sessions). The duration of each session was about 2 hours and patients comprised 3 therapeutic groups with 10 individuals per group, in average. The therapy protocol was adapted from [43] and [44], and applied by a team headed by a trained psychologist with expertise in the cognitive-behavioral approach, a co-therapist, and an observer.

As an ethical consideration, individual sessions were held in case of decompensating or risk of suicide. On average, there was one individual session per patient. At the end of the study patients that had not

achieved remission were included as outpatients in Psychology Service or/and psychiatry at Hospital Universitário Onofre Lopes, both from UFRN.

## Instruments

Hamilton Depression Assessment Scale [45] was used to MDD diagnosis, to assess its severity and its remission. It is a semi-structured interview for identification of frequency and intensity of depressive symptoms performed by a trained psychiatrist. HAM-D is one of the most usual tools to assess depressive symptoms and, because of that, was adopted as the primary outcome measure in this trial [46, 47]. HAM-D has 4 categories of classification: a) mild major depression  $10 < \text{scores} < 13$ ; b) moderate:  $14 < \text{scores} < 17$  and c) severe:  $\text{scores} > 17$  [48]. The Beck Depression Inventory [49] is a 21 items, self-reported instrument that assesses depressive symptoms during the last week and proposes their classification in four levels: "Minimal" (0–11 scores), "mild" (12–19 scores), "moderate" (20–35 scores) and "severe" symptoms (36–63 scores). It was validated for adult Brazilian clinical population [50] ( $\alpha = 0.93$ ). The Beck Anxiety Inventory [51] is a 21 questions, self-completion scale, which measures somatically, affectively and cognitively the anxiety level during the last week and proposes its classification into 4 levels as following: "minimum" (0–10 scores), "mild" (11–19 scores), "moderate" (20–30 scores) and "severe" (31–63 scores). This instrument was validated to adult Brazilian population and was proved suitable for use in clinical population ( $\alpha = 0.83$ –0.92) [52]. Rosenberg Self-Esteem Scale [21] is a 10 items self-completion instrument to measure self-concept traits. The total score ranges from 0 to 40. It was validated to adult Brazilian population ( $\alpha = 0.90$ ) [53]. In this study conventional or non-inverted correction was adopted. Pittsburgh Sleep Quality Index (PSQI) is a self-assessment instrument that has 7 components and it is used to measure sleep quality. The overall score ranges from 0 to 21 points, in which can be categorized into good sleep quality (0–4 points), poor sleep quality (5–10 points) and suggestive of sleep disorder (greater than 10 points). This instrument was validated to adult Brazilian population [54] ( $\alpha = 0.82$ ).

## Collection and dosage of biological material

The salivary cortisol awakening response is a feedforward mechanism that prepares the individual to daily activities, therefore has minor influence of acute stressors. CAR changes have been associated with dysfunction of the HPA axis, observed in some mental illnesses [55, 56]. On the other hand, Serum cortisol is highly influenced by an enormous sort of stressors and suffers from time-of-day modulation, thus its measurement has an acute value. Therefore, these two measures were select and analyzed aiming at helping in the consolidation of cortisol as biomarker of MDD [38, 57].

To account for the circadian oscillation in cortisol levels, both saliva and blood were always collected about 6 a.m. Volunteers were in fasting for approximately 8 hours. Using Salivette® devices (Sarstedt Numbrecht, Germany), two saliva samples were collected by the volunteers under the researcher supervision. The 1st collection was done immediately at awakening and the 2nd was done after 30 minutes. During collection participants were restricted to bed and were instructed to rest and not eat or drink. Blood collections were performed, using disposable perforating material (needle and syringe),

immediately after saliva collections by trained laboratory technicians or researcher. Salivary cortisol was measured by DRG® Salivary Cortisol ELISA kit SLV-4635 and Serum cortisol by DRG® Cortisol ELISA Kit 1887.

## Statistical analysis

Depressive (BDI) and anxiety symptoms (BAI), sleep quality (PSQI), self-esteem (RSE), serum cortisol (SC) and cortisol awakening response (CAR) were the quantitative dependent variables evaluated in this study. Groups (PG and CG) and patient's remission (remitted: R and non-remitted: NR) were considered categorical independent variables. Sociodemographic characteristics, such as gender, age, education, and income were investigated as covariates. The CAR was calculated from the change (%) in salivary cortisol between 0 and 30 minutes after awakening [56].

The effect of sociodemographic characteristics was assessed by Wilcoxon sum rank test (for age) and chi-square test (for gender, education level and income). The effect of intervention was assessed by Wilcoxon sign rank test both considering the patients group (PG) as a whole, as well as stratifying it by remission condition (remitted patients [R] and non-remitted [NR]). In order to check whether the changes achieved with the intervention were comparable with a healthy pattern, we performed a Wilcoxon sum rank test comparing the baseline and post-treatment values to a healthy control. The effect sizes ( $r$ ) and its bootstrapped confidence interval (CI 95%, 1,000 resamples) are reported as  $r$  [lower limit, upper limit], and were obtained from the *rcompanion* package. The correlations between biomarkers after the treatment were assessed for remitted and non-remitted patients using Spearman's correlation ( $\rho$ ). Finally, a binary logistic regression was performed to find potential baseline predictors of remission, using non-remitted patients as reference (NR = 0; R = 1). Nagelkerke's pseudo- $R^2$  and OR is reported as importance measures of the prediction.

All analyzes were performed using R (4.0.2), assuming a significance level of  $p < .05$ .

## Results

### Sample characteristics and study workflow

From the total of 385 volunteers, 55 were selected in the screening phase (CG: 25 and PG: 30). All volunteers were Brazilian and young adults, was observed in the groups a slightly biased towards women (PG = 55%, CG = 52%), further, most part of both groups was undergraduate students and had a low income (Additional file 1). Sociodemographic characteristics showed no difference between groups (GC and PG) (Additional file 1). Patients showed in average a mild level of major depression (HAM-D =  $12.8 \pm 3.55$ ) before the treatment (Additional file 1) and from the 30 patients who started the treatment, 20 completed the 16 weeks proposed. The consolidated standards for clinical trial reports (CONSORT) are shown in Fig. 1.

## Insert Fig. 1 around here

## Overall effect of group cognitive behavioral therapy

The group cognitive behavioral therapy induced large changes, with 65% of response (that means reduction in HAM-D > 50%) and 55% of remission rate. After treatment, patients showed a moderate to large significant decrease in depressive symptoms (HAM-D:  $V = 127$ ,  $p = .002$ ,  $r = -.682$  [CI - .818, - .445]; BDI:  $V = 209$ ,  $p < .0001$ ,  $r = -.868$  [CI - .879, - .827]), moderate reductions in anxiety (BAI:  $V = 199.5$ ,  $p < .0001$ ,  $r = -.789$  [CI - .879, - .590]) and in PSQI total scores, that means a moderate improvement of sleep quality (PSQI:  $V = 147$ ,  $p = .008$ ,  $r = -.602$  [CI - .816, - .304]), further a moderate increase in self-esteem (RSE:  $V = 15.5$ ,  $p = .002$ ,  $r = .682$  [CI .427, .841]). No change was found for serum (SC:  $V = 130$ ,  $p = .368$ ) or awakening cortisol (CAR (%)):  $V = 142$ ,  $p = .173$ ) (Fig. 2A, Additional file 2).

## Insert Fig. 2 around here

When stratifying the patient group by the condition of remission after gCBT, the remitted patients showed significant large improvements in depressive (HAM-D:  $V = 45$ ,  $p = .009$ ,  $r = -.805$  [CI - .889, - .666]; BDI:  $V = 66$ ,  $p = .001$ ,  $r = -.883$  [CI - .892, - .886]) and anxiety symptoms ( $V = 65$ ,  $p = .005$ ,  $r = -.859$  [CI - .892, - .727]), self-esteem ( $V = 1$ ,  $p = .008$ ,  $r = .814$  [CI .591, .889]) and sleep quality ( $V = 42.5$ ,  $p = .020$ ,  $r = -.721$  [CI - .892, - .395]), in addition to a marginal decrease in cortisol awakening response ( $V = 55$ ,  $p = .056$ ,  $r = -.591$  [CI - .889, - .134]). No changes were found for serum cortisol ( $V = 24$ ,  $p = .465$ ). In contrast, the only changes showed by non-remitted patients were large decreases in serum cortisol ( $V = 43$ ,  $p = .012$ ,  $r = -.810$  [CI - .897, - .533]) and self-perceived depressive symptoms ( $V = 44$ ,  $p = .008$ ,  $r = -.850$  [CI - .897, - .653]). No changes were found for depressive symptoms (HAM-D:  $V = 21$ ,  $p = .270$ ), self-perceived anxiety symptoms ( $V = 37.5$ ,  $p = .085$ ), sleep quality ( $V = 37$ ,  $p = .096$ ), self-esteem ( $V = 9$ ,  $p = .232$ ) and CAR ( $V = 27$ ,  $p = .652$ ) (Fig. 2B, Additional file 3).

After treatment, for remitted patients depressive scores (HAM-D), which is assessed by the psychiatrist, was correlated with the self-perceived depressive symptoms (BDI) ( $\beta = .69$ ,  $p = .029$ ). Moreover lower depressive symptoms were correlated with lower self-perceived anxiety symptoms (HAM-D  $\beta = .76$ ,  $p = .007$  and BDI  $\beta = .72$ ,  $p = .015$ ) and higher self-esteem (HAM-D  $\beta = -.69$ ,  $p = .037$  and BDI  $\beta = -.74$ ,  $p = .005$ ). In addition, lower self-perceived depressive and anxiety symptoms was also correlated with better sleep quality (PSQI) (BDI  $\beta = .65$ ,  $p = .028$  and BAI  $\beta = .63$ ,  $p = .029$ ). Also, better sleep quality was correlated with higher self-esteem ( $\beta = -.85$ ,  $p = .013$ ). For non-remitted patients, significant correlations were restricted to BDI, BAI, and RSE. Specifically, larger RSE correlated with lower BDI ( $\beta = -.86$ ,  $p = .002$ ) and BAI ( $\beta = -.78$ ,  $p = .012$ ), and the two latter were positively correlated between them ( $\beta = .83$ ,  $p = .01$ ) (Fig. 3).

## Insert Fig. 3 around here

### Comparisons with a healthy control group

When compared to a healthy control group (CG), before the intervention, patients group (PG) scored higher in HAM-D ( $W = 0$ ,  $p < .0001$ ,  $r = -.866$  [CI - .881, - .817]), presented worse sleep quality ( $W = 80.5$ ,  $p$

= .0001,  $r = -.580$  [CI = -.744, -.359]), high levels of serum cortisol ( $W = 130$ ,  $p = .005$ ,  $r = -.408$  [CI = -.635, -.119]) and reactivity of cortisol awakening response ( $W = 136$ ,  $p = .009$ ,  $r = -.389$  [CI = -.626, -.099]). Comparing the PG after the treatment with CG, only HAM-D ( $W = 66.5$ ,  $p < .0001$ ,  $r = -.644$  [CI = -.818, -.397]) and serum cortisol ( $W = 137$ ,  $p = .01$ ,  $r = -.385$  [-.639, -.073]) remained significantly different, suggesting a gCBT-induced adjustment of sleep quality ( $W = 169$ ,  $p = .064$ ) and CAR reactivity ( $W = 194$ ,  $p = .201$ ). However, it must be highlighted that there was a .22-point decrease in Hamilton effect size (Additional file 2, Fig. 4).

## Insert Fig. 4 around here

### Predictors of remission

Between psychophysiological outcomes, only the baseline sleep quality ( $B = -.482$ ,  $OR = .62$ ,  $p = .039$ , Nagelkerke's pseudo- $R^2 = .379$ ) predicted remission, where lower values of PSQI before the intervention, that means better sleep quality, are associated with remission achievement (Fig. 5, Table 1). Moreover, the sociodemographic characteristics showed no influence on remission (Additional file 1).

Table 1

Baseline predictors of remission condition after group Cognitive-Behavioral Therapy (gCBT), assessed by a binary logistic regression.

Variable	B	OR	p	Pseudo- $R^2$
PSQI	<b>-.482</b>	<b>.617</b>	<b>.039</b>	<b>.379</b>
SC	-.002	.998	.502	.030
CAR (%)	.002	1.002	.253	.092
BDI	-.047	.954	.460	.038
BAI	.015	1.015	.786	.005
RSE	.18	1.018	.848	.002
HAM-D	-.306	.736	.069	.256

Bold text stands for p-value < 0.05; Pittsburgh Sleep Quality Index (PSQI), Serum cortisol (SC; µg / dL), Salivary cortisol awakening response (CAR; %), Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI), Rosenberg self-esteem scale (RSE), Hamilton Depression Assessment Scale (HAM-D).

## Insert Table 1 around here

## Insert Fig. 5 around here

## Discussion

In this study, we observed a remission rate of 55% for patients diagnosed with mild-moderate major depression after 16 weeks of group Cognitive-Behavioral therapy (gCBT) as monotherapy. This response was followed by reductions in self-perception of depressive symptoms and anxiety and increases in sleep quality and self-esteem. After treatment, patients regulated their previous deregulated salivary cortisol awakening response and sleep quality to healthy parameters. Secondary analysis showed that these improvements were dependent of remission condition, and they were correlated among them. Remitted patients showed stronger responses of these outcomes plus a reduction of salivary cortisol awakening response, whereas non-remitting ones showed larger reduction in serum cortisol levels and self-perceived depressive symptoms. Moreover, a better sleep quality before treatment was predictive of remission achievement.

Distinct remission rates for CBT monotherapy as treatment for MDD are observed in the literature. Some factors can contribute to this discrepancy in remission after CBT treatment, such as age, severity of disease, previous use of antidepressants, duration of CBT and the instruments used to measure remission [17, 58–60]. However, in this present study we demonstrated a rate slightly above the level usually seen in literature; we can speculate that the remission rate observed in this study was achieved due to the adoption of the group approach, as well as due to the homogeneity of groups. Those were composed of young undergraduate students; therefore, it could increase the identification among patients and the quality of their social support. The social support is seen as an active mechanism for resilience [61, 62] and it should be stimulated for management of MDD.

Moreover, 65% of patients showed a response to treatment and besides moderate reduction in the depressive scores analyzed by a specialist; the self-reported depressive symptoms were significantly large reduced after gCBT as well, even for patients who did not achieve a complete remission. Recent studies in the fields of personalized medicine and precision psychiatry have suggested that individualized treatments according to the patients' psychophysiological and socio-economic demands probably have larger chances to improve response and remission rates [16, 17, 63]. In view of this trend and intending to better understand the neurobiology of MDD, we assessed potential responses to gCBT through several social and psychophysiological domains, such as anxiety level, self-esteem, sleep quality, cortisol (serum and CAR). However, the sociodemographic characteristics did not influence the result of treatment.

After gCBT, the patients showed significant improvements in anxiety symptoms. The moderate anxiety levels found at baseline decreased to mild levels after intervention, especially in remitted patients. Moreover, strong positive correlations between improvements in depressive and anxious symptoms were found independent of remission condition. Taking into account the positive feedback between depression and anxiety, which is mediated by a dysfunctional hyperactivation of amygdala [64, 65], the simultaneous improvements in these symptoms seem critical to a good treatment response, possibly avoiding relapse [66, 67].

We also observed an increase of self-esteem in response to treatment, specifically in remitted patients, together with correlations between increases in self-esteem and reduction of depressive and anxious

symptoms, which were observed independent of remission condition. Other studies also pointed out the importance of the improvement in self-esteem after group cognitive psychotherapies [23, 68, 69]. Therefore, regardless of being low self-esteem the cause or the consequence of negative mood, the correlation between them must be considered in psychotherapy approaches [22, 70, 71].

Before the treatment, patients disclosed worse sleep quality than the control group of healthy volunteers, showing suggestive sleep disturbance or poor sleep quality. After the intervention we noticed an improvement of sleep quality, when the patients were able to reach healthy patterns of sleep quality. However, this overall change seems to be due to the large decrease of PSQI score, which means an improvement of sleep quality, found for remitted patients, in contrast to the marginal decrease found for non-reddited. Moreover, for those who achieved remission, it was observed a moderate correlation between improvements in sleep quality and depressive symptoms and a better sleep quality before treatment was predictive of remission achievement. These results may contribute to the understanding of the relationship between changes in sleep quality and depressive mood [72]. Sleep complaints tend to occur before the first depressive episode of MDD; in addition, its persistence after treatment is associated with higher rates of recurrence [73–75]. Also, it is suggested that increased levels of anxiety are related to the presence of sleep disorders in young adult population with major depression [76]. Therefore, these results suggest the inclusion of tools to improve sleep quality in CBT treatment for major depression and highlight the importance of its measurements before treatment and at follow-ups.

Moreover, at baseline patients showed hypercortisolemia and increased salivary cortisol awakening response when compared to healthy controls. Hyperactivity of HPA axis is an alteration usually seen in young MDD patients [77, 78] and it is also a predictor of low response of CBT and disease recurrence [12, 41, 79, 80]. Some studies suggested that hypercortisolemia results from the impairment of the negative feedback loop of the HPA axis [81, 82]. An improvement in CAR was observed to remitted patients as response of treatment, while a reduction in serum cortisol was found for non-reddited. Despite this, only CAR reactivity was regulated to healthy control levels after the treatment, which is an interesting result since it is a stronger marker of dysfunction of the HPA axis and its change is associated to mental illnesses [55, 56]. Although the regulated HPA axis function is critical for body-mind homeostasis, few studies analyze it and part of them failed in finding an adjustment of HPA axis after psychotherapy treatment for MDD [41, 83]. Furthermore, cortisol changes is not usually considered during antidepressant choice, so the mode of action of this drugs on the HPA axis is complex and depends on the type of antidepressant and the duration of treatment [84, 85].

Considering some limitations, such as the sample size and the lack of a placebo-controlled group, we must highlight the relevant results found in this open-label clinical trial on distinct psychophysiological outcomes after gCBT intervention. Therefore, this study stimulates the use of group-based CBT approaches for the treatment of mild-moderate major depression, a tool with low cost and no described side effects. Moreover, our results support further studies that may explore several psychophysiological domains in MDD aiming to improve treatments. Finally, we also suggest that anxious symptoms, self-esteem, and the sleep quality should be better addressed in psychotherapies.

## **Declarations**

### **Ethics approval and consent to participate**

All procedures were approved by the ethical committee of the Federal University of Rio Grande do Norte, Brazil (#2628,202). Participants became aware of the study procedures and provided informed written consent prior to participation.

#### **Consent for publication**

Not applicable.

#### **Availability of data and materials**

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

#### **Competing interests**

The authors declare that they have no competing interests.

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## **Authors' contributions**

NLGC, YMV and NGS planned the clinical trial; ACLL did volunteers screening; YMV conducted treatment; ACMG and GMSJ carried out statistical analysis; all authors contributed to the manuscript.

## **Author Agreement Statement**

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

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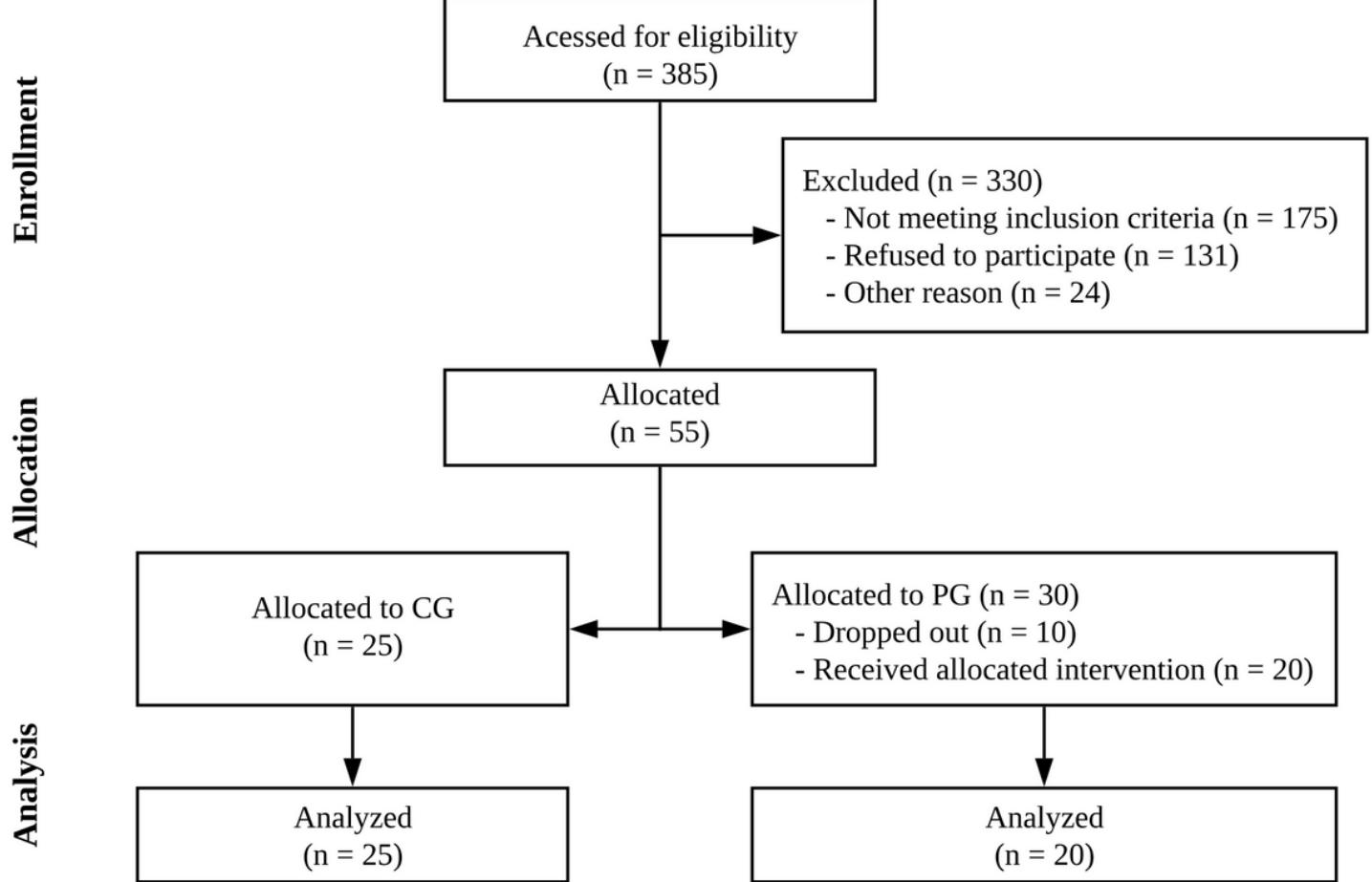
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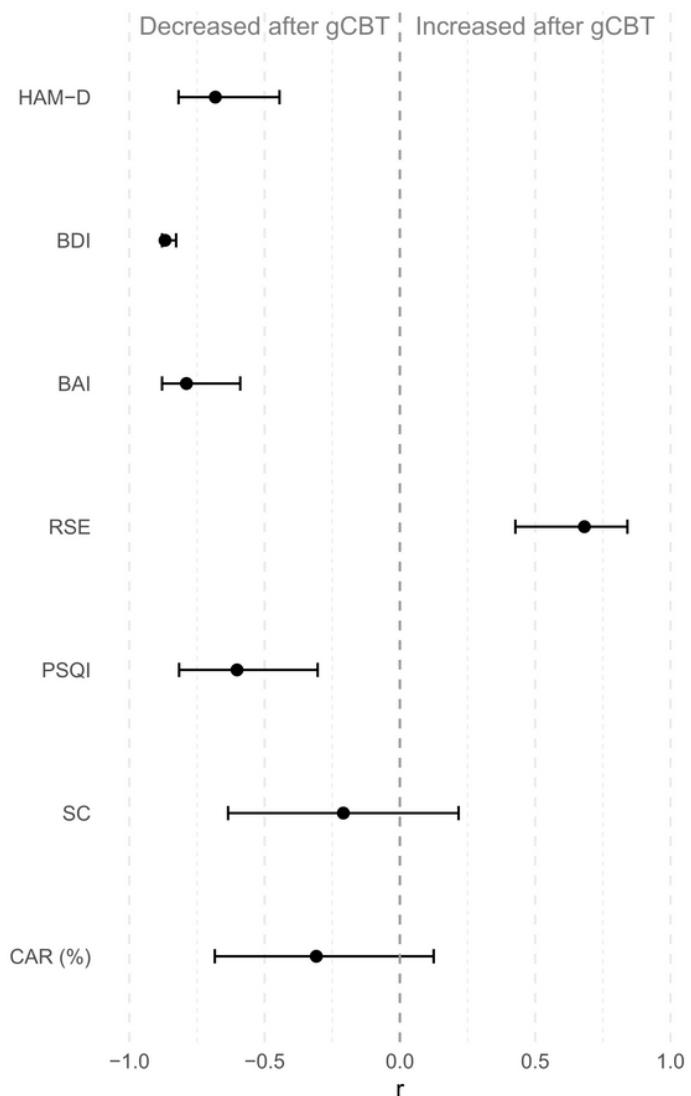
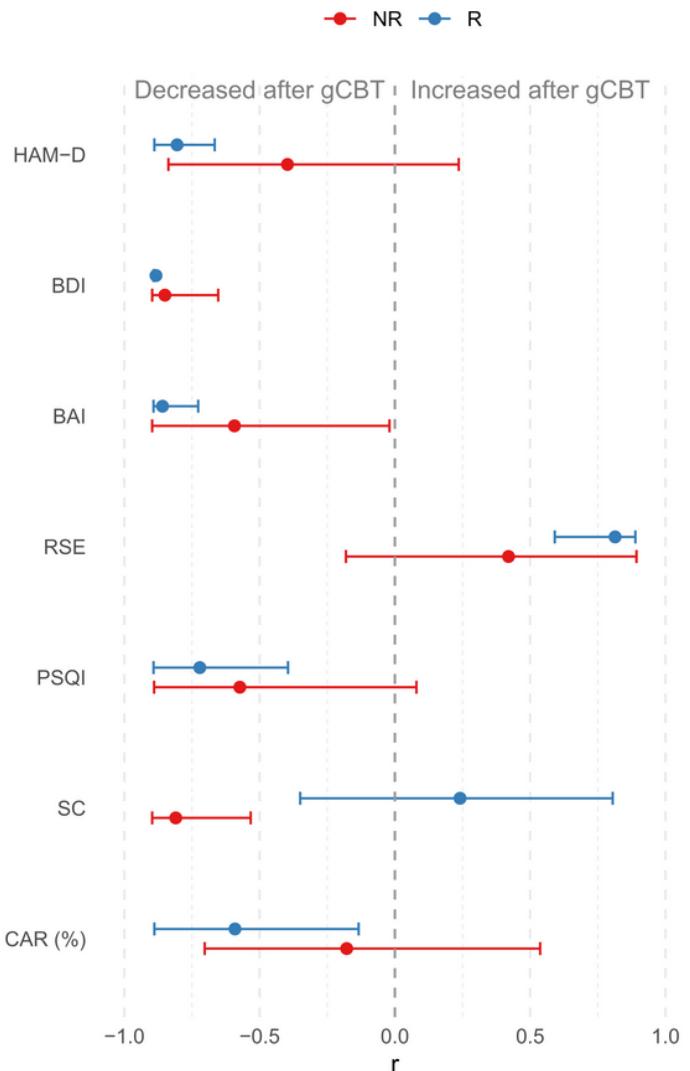
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## Figures

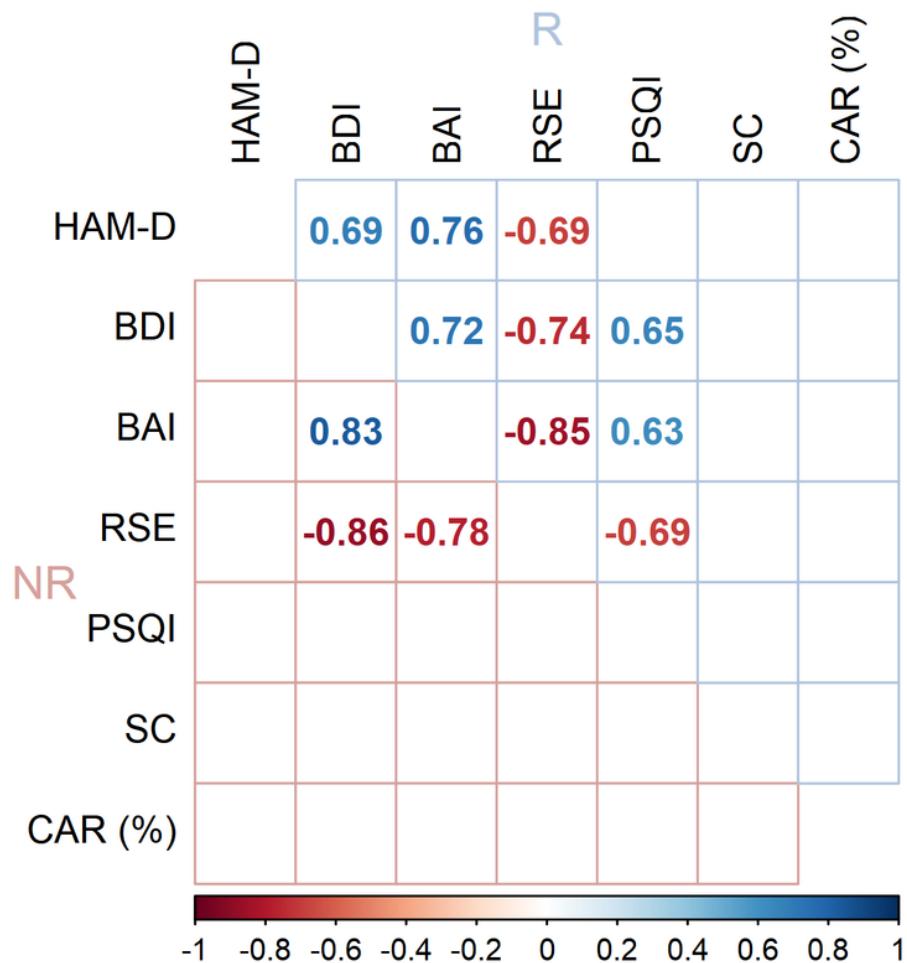


**Figure 1**

The consolidated standards of clinical trial reports (CONSORT) for control group (CG) and major depressive patients (PG) in an open-label clinical trial using group Cognitive-Behavioral Therapy as monotherapy treatment.

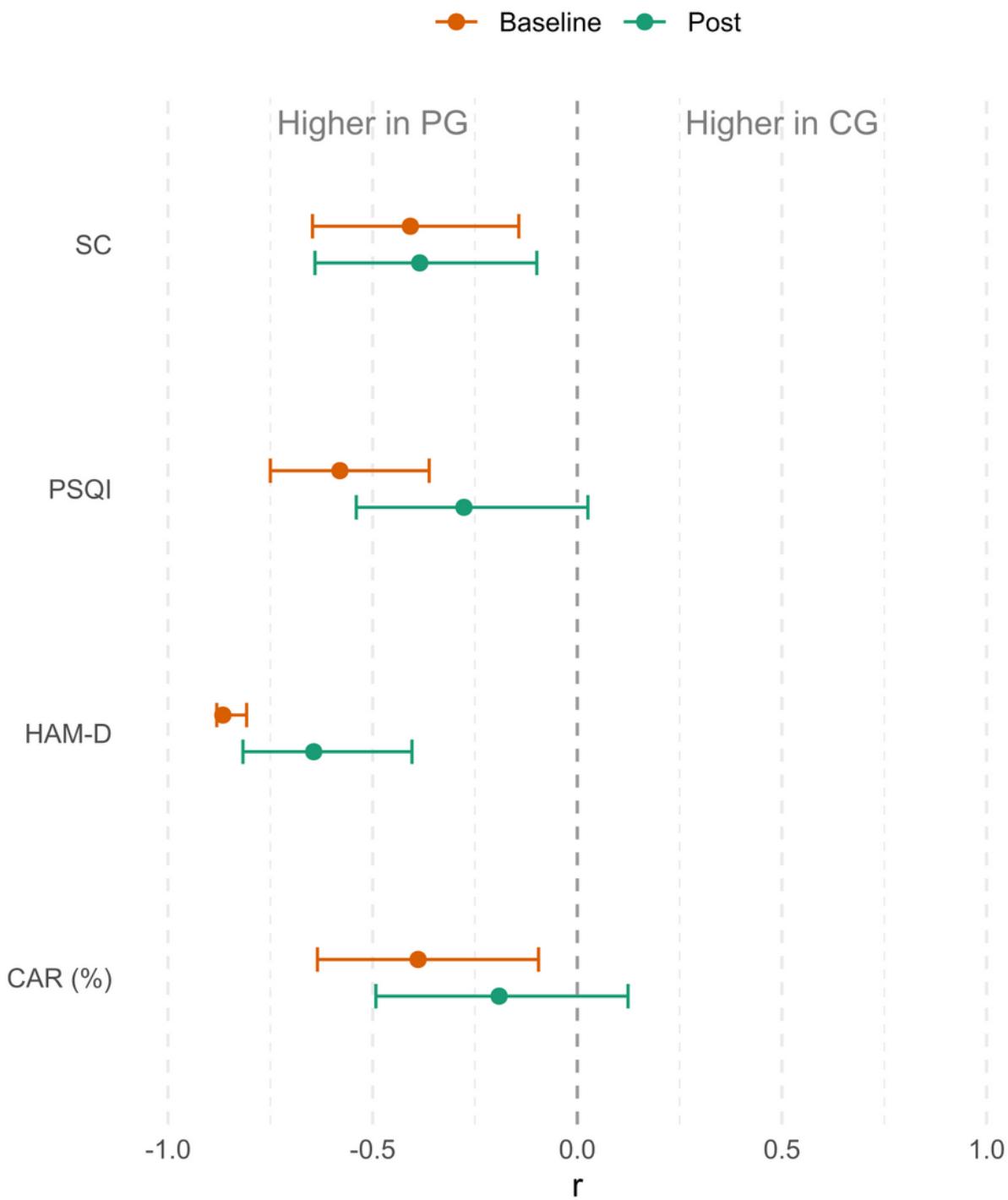
**A****B****Figure 2**

Effect size ( $r$ ) and 95% bootstrapped confidence interval of psychophysiological outcomes (A) within patients' group as a whole after group Cognitive-Behavioral Therapy (gCBT), and (B) patients' group stratified in remitted (R: blue) / non-remitted (NR: red) after gCBT. Hamilton Depression Assessment Scale (HAM-D), Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI), Rosenberg self-esteem scale (RSE), Pittsburgh Sleep Quality Index (PSQI), Serum cortisol (SC;  $\mu\text{g}/\text{dL}$ ), Salivary cortisol awakening response (CAR; %).



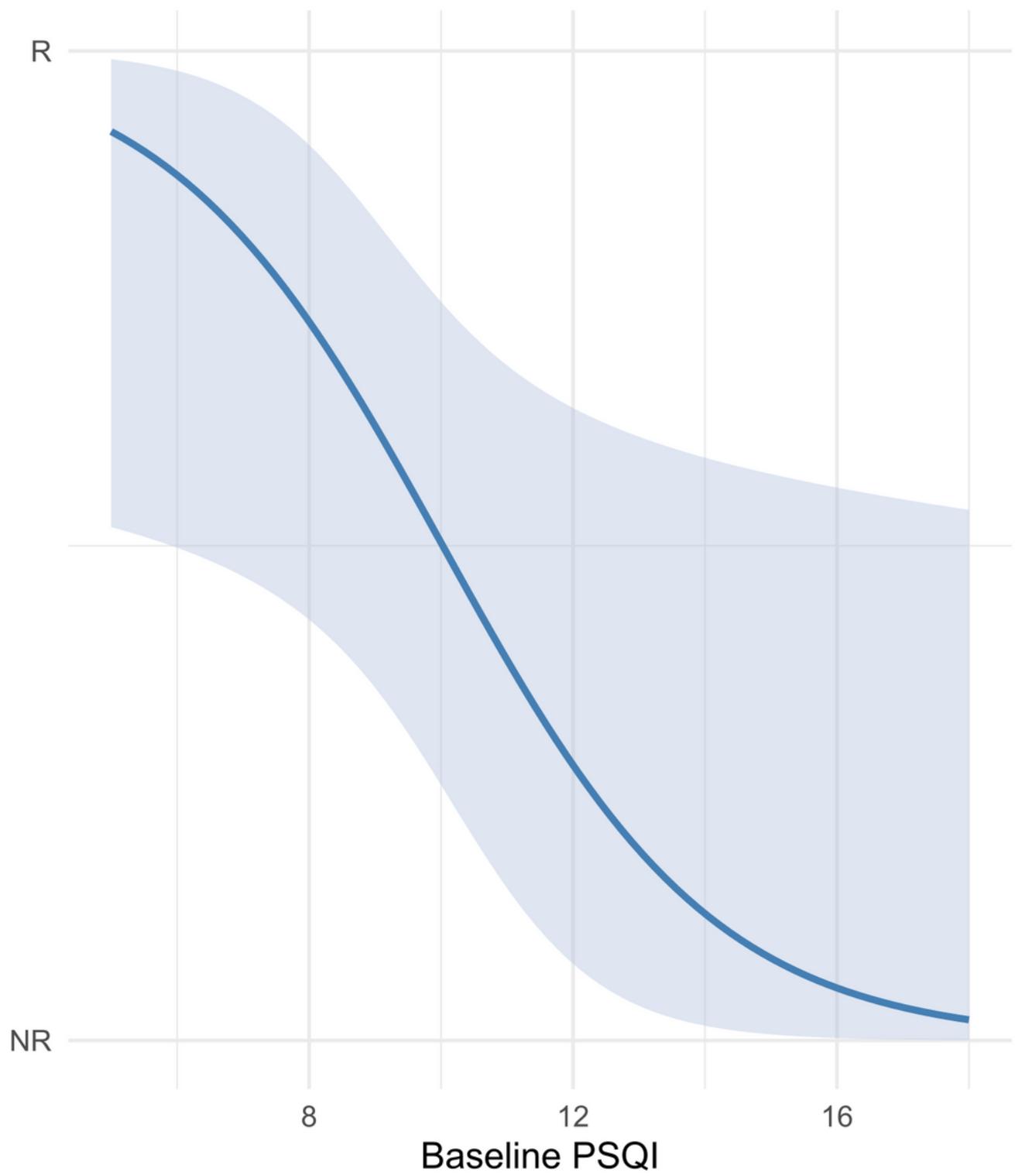
**Figure 3**

Correlations (Spearman's  $\rho$ ) between psychophysiological outcomes in non-remitted (NR, light red grid at the lower panel) and remitted (R, light blue grid at the upper panel) patients. Only significant correlations ( $p < .05$ ) are shown. Colors of plotted  $\rho$  values denote the direction of correlation (red = negative; blue = positive). Hamilton Depression Assessment Scale (HAM-D), Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI), Rosenberg self-esteem scale (RSE), Pittsburgh Sleep Quality Index (PSQI), Serum cortisol (SC;  $\mu\text{g}/\text{dL}$ ), Salivary cortisol awakening response (CAR; %).



**Figure 4**

Effect sizes ( $r$ ) and bootstrapped 95% confidence intervals of psychophysiological outcomes at baseline (orange) and after (green) group Cognitive-Behavioral Therapy (gCBT) of patients group (PG) in comparison to a healthy control group (CG). Hamilton Depression Assessment Scale (HAM-D), Pittsburgh Sleep Quality Index (PSQI), Serum cortisol (SC;  $\mu\text{g}/\text{dL}$ ), Salivary cortisol awakening response (CAR; %).



**Figure 5**

Baseline PSQI as predictor of remission outcome. As it increases, the greater is the odds of non-remitting.

## Supplementary Files

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