Letter to the Editor

Pretreatment Cardiac Vagal Tone Predicts Dropout from and Residual Symptoms after Exposure Therapy in Patients with Panic Disorder and Agoraphobia

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Exposure therapy is a well-established and effective treatment for pathological anxiety. However, high dropout and nonresponder rates call for the investigation of individual differences that mediate treatment response [1]. Among physiological individual differences, cardiac vagal tone (CVT) seems a promising candidate to predict treatment response: CVT has been linked to cognitive, affective, social, and health functioning levels [2] and low CTV has been found in a variety of anxiety disorders [3]. To test the association between CVT and treatment response, we followed two lines of argument. First, low CVT has been associated with a deficit in extinction learning which is considered an underlying mechanism of exposure therapy [e.g., 4]. Given that pathological anxiety is also associated with an extinction learning deficit [5], CVT may qualify as a factor moderating this association. That is, anxiety patients with low CVT may show less extinction during exposure therapy and, thus, may more likely show residual symptoms. Second, CVT has been linked to self-regulation capacity [2] and, thus, may impact the likelihood of dropout from exposure therapy during which a patient's self-regulation capacity is extraordinarily challenged.

Accordingly, we investigated the association between pretreatment CVT and residual symptoms after exposure therapy and dropout from exposure therapy in a sample of 228 patients with panic disorder and agoraphobia (PD/AG). These PD/AG patients underwent a standardized and manualized treatment focusing on exposure in vivo in a randomized controlled trial carried out in multiple centers [6, 7]. For the current research question, patients were grouped into those who were (1) fully recovered or (2) showed residual symptoms according to clinician ratings after completion of treatment, and (3) treatment dropouts. Clinician ratings were standardized using the Clinical Global Impression Scale (CGI) that measures the overall severity of a disorder with scores that range between 1 (no disorder) and 7 (among the most severely ill patients). The assessment of pretreatment CVT as indexed by heart rate variability (HRV) was based on electrocardiogram data collected during a relaxation period of a highly standardized Behavioral Avoidance Test (BAT [8]) prior to therapy. The root mean square of successive differences (RMSSD) and high-frequency (HF) HRV (frequency band: 0.15–0.40 Hz) were determined using HRV analysis (see online suppl. material for more information about participants, treatment, outcome assessment, HRV assessment, and data analysis; for all online suppl. material, see www.karger.com/doi/10.1159/000487599).

Thirty-nine patients (17.1%) dropped out from therapy prior to postassessment. In patients completing treatment, postassessment CGI scores lower than 3 indicated no more clinically relevant symptoms (i.e., full recovery) in 28 patients (12.3%), and CGI scores of 3 or more indicated residual symptoms in 161 patients (70.6%). Neither the group with residual symptoms nor the treatment dropout group differed from the fully recovered group with regard to baseline levels of symptom severity (see online suppl. Table S1). As shown in Figure 1, however, the groups differed with regard to pretreatment HRV. The group with residual symptoms had lower pretreatment HRV than the fully recovered group: RMSSD: $t(187) = 2.27$, $p = 0.024$; HF-HRV: $t(187) = 2.35$, $p = 0.020$. Likewise, the treatment dropout group had lower pretreatment HRV than the fully recovered group: RMSSD: $t(65) = 2.69$, $p = 0.009$; HF-HRV: $t(65) = 2.33$, $p = 0.023$.

To predict residual symptoms, binary logistic regressions were conducted using either RMSSD or HF-HRV scores to indicate HRV together with sex and age as well as CGI scores as indicators of baseline symptom severity. Fully recovered patients served as a reference group. The Wald criterion indicated that only HRV made a significant contribution to predict residual symptoms: RMSSD: 4.27, $p = 0.039$; HF-HRV: 4.25, $p = 0.039$ (see online suppl. Table S2 and text). The same setup for binary logistic regressions was applied to predict treatment dropout as opposed to full recovery and, again, the Wald criterion indicated that only HRV made a significant contribution to predict treatment dropout:
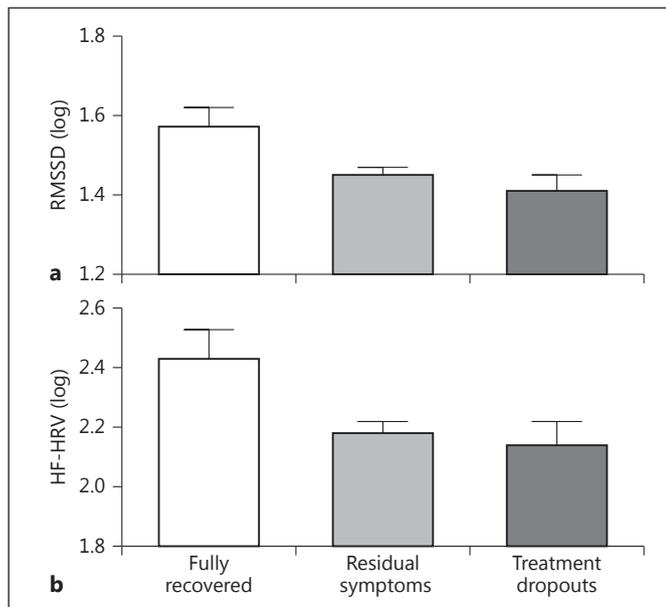
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Fig. 1. Pretreatment levels of heart rate variability (HRV) in the fully recovered group, the group with residual symptoms, and the treatment dropout group. Bar charts represent means and standard errors of logarithmized values from the root mean square of successive differences (RMSSD; **a**) and high-frequency (HF)-HRV (**b**).

RMSSD: 4.72, $p = 0.030$; HF-HRV: 3.40, $p = 0.065$ (see online suppl. Table S3 and text).

These findings indicate that PD/AG patients with low pretreatment CVT are more likely to show residual symptoms after completing exposure-focused therapy. Previous research showed that low CVT is associated with a deficit in safety learning during fear extinction training [e.g., 4]. Both CVT [9] and extinction learning [10] are mediated by inhibitory pathways from the prefrontal cortex to brainstem regions mediated by the amygdala. According to the model of neurovisceral integration [9], this inhibitory cortico-subcortical network enables the organism's adaptation to changing environments (e.g., to the absence of an expected threat) by integrating autonomic, attentional, and affective systems. Thus, PD/AG patients with lower levels of prefrontal cortex activity as indexed by CVT may experience less effective fear extinction and, thus, may more likely show residual symptoms after completing exposure-focused therapy.

In addition, low pretreatment CVT also predicted treatment dropout in the present study. Entering an exposure situation in which a patient confronts what they most fear (up to and including in some cases the fear of dying) and have long since avoided certainly demands high levels of self-regulation from PD/AG patients. Patients with particularly low pretreatment CVT may have lower levels of self-regulatory capacity and, therefore, more pronounced difficulties in entering and/or remaining in a feared situation. This assumption is further strengthened by the finding that pretreatment CVT is particularly low in patients stating motivational reasons for dropout, e.g., "too afraid to enter exposure situation" (see online suppl. Fig. S1 and text). Thus, PD/AG patients with low

CVT may benefit from increased guidance by the therapist during exposure exercises [8]. Indeed, results from this clinical trial showed that patients who are accompanied by a therapist profit more from exposure therapy than those without guidance [7], especially if pronounced situational avoidance behavior has to be overcome during treatment [8]. In the case of CVT, such tailored treatments are feasible for the practitioner because CVT can be increased by different interventions such as meditation, exercise training, or biofeedback. In conclusion, PD/AG patients with low CVT may benefit from the implementation of such low-intensity interventions prior to undergoing exposure therapy.

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