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Running for extinction? Aerobic exercise as an augmentation of exposure therapy in panic disorder with agoraphobia

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ABSTRACT

Exposure-based Cognitive Behavioral Therapy (eb-CBT) represents the most evidence-based psychotherapeutic approach in anxiety disorders. However, its efficacy may be limited by a delay in onset of action and a substantial number of patients does not respond sufficiently to treatment. In this context, aerobic exercise was found to be effective in reducing clinical anxiety as well as to improve (elements of) disorder-specific CBT in some mental disorders. We therefore investigated the effect of aerobic exercise supplementary to an eb-CBT in panic disorder and agoraphobia (PD/AG). 77 patients with PD/AG performed a 30 min treadmill task with moderate or low intensity (70% or 30% of the maximal oxygen uptake [VO_{2max}]) prior to five exposure sessions within a standardized seven-week CBT. At baseline, after completing the treatment period (post) and six month after post (follow-up), several measures of (un)specific psychopathology (Hamilton Anxiety Rating Scale [Ham-A], Mobility Inventory [MI], Panic and Agoraphobia Scale [PAS], Agoraphobic Cognitions Questionnaire [ACQ], Body Sensations Questionnaire [BSQ]) were established to assess for clinical changes. All patients experienced a significant improvement of symptoms from baseline to post (for all measures $p < .001$) but repeated-measures analyses of variance found a trend towards a significant time × group interaction in the Ham-A in favor for the moderate intense exercise group ($f[1, 74] = 4.15$, $p = .045$, $\alpha = .025$). This trend, however, disappeared at follow-up since the low-intense exercise group further improved significantly in Ham-A after post. Our findings therefore might point to an accelerating effect of moderate-intense exercise within an exposure-based CBT for AG/PD.

1. Introduction

Psychotherapy and second-generation antidepressants currently represent the first-line treatment options in anxiety disorders (e.g. Bandelow et al., 2012). In this field, exposure-based cognitive behavioral therapy (CBT) has already been established for years in the daily routine and has to be regarded as the best evidence-based psychotherapeutic procedure for these conditions (Kaczkurkin and Foa, 2015). Although the efficacy of disorder-specific CBT was proven in numerous randomized-controlled trials, a few clinical aspects limit enthusiasm to some extent. Available data point to only moderate effects on symptoms of social anxiety disorder (SAD), generalized anxiety disorder (GAD) or panic disorder (PD) with/without agoraphobia (AG) and a significant number of patients do not respond to treatment (Hofmann and Smits, 2008; Taylor et al., 2012). Moreover, due to the protracted changes in cognition and behavior, CBT may show a general delay in onset of action of up to several weeks or months.

For these reasons, current research focused on strategies eligible to facilitate the efficacy of exposure-based CBT in anxiety disorders. Augmentation of exposure via pharmacological interventions (e.g. by using the NMDA-partial agonist d-cycloserine) therefore has gained substantial interest in this context and several modifications of psychological techniques have been discussed in order to optimize fear extinction (Mataix-Cols et al., 2017; Pittig et al., 2016).

In addition, growing evidence also points to a substantial impact of physical activity in the treatment of clinical anxiety. Randomized-

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controlled trials found an overall moderate effect of several-week aerobic exercise programs on disorder-specific symptomatology in PD, GAD or SAD (Stubbs et al., 2017) and single bouts of exercise demonstrated acute anxiolytic activity in specific phobia or PD (Lindenberger et al., 2017; Ströhle et al., 2009). Several biological and psychological aspects such as reduction of anxiety sensitivity, changes in serotonergic and endophinergic systems, improvement of self-efficacy or exercise-induced exposure to fear-related bodily sensations were suspected to be mediating mechanisms of these findings (Asmundson et al., 2013). Furthermore, available data suggest that physical activity also may enhance exposure training by facilitating the extinction of fear. As reported by several studies, exercise was found to elevate levels of brain-derived neurotrophic factor (BDNF; e.g. Neeper et al., 1996; Van Kummer and Cohen, 2015) that in turn plays a prominent role in extinction learning (Andero and Ressler, 2012). In accordance with this hypothesis, one preclinical trial found wheel-running to be significantly associated with increased extinction learning in mice whereby the duration of training and the amount of extinction learning were correlated positively to each other (Siette et al., 2014). Despite these promising findings, clinical trials focusing on exercise-induced augmentation of extinction learning in distinct mental disorders are rare. To date, only one study investigated the immediate impact of exercise on in-vivo disorder-specific exposure in Posttraumatic Stress Disorder (PTSD). Within a small sample of only nine patients, a single bout of 70% VO_{2max} exercise directly prior to sessions of prolonged exposure (PE) has shown to be significantly more effective than PE alone (Powers et al., 2012).

The aim of the present study therefore was to investigate the additional effect of moderate-intense aerobic exercise (70% VO_{2max}) on exposure in patients with PD/AG who underwent a manualized exposure-based CBT. In the light of former findings in this field, we hypothesized that this type of aerobic exercise would be associated with a stronger amplification and acceleration of psychotherapy than a less intense exercise condition.

2. Material and methods

2.1. Design

The present study was conducted as a multi-center trial at three centers in Germany: Department of Psychiatry and Psychotherapy, Campus Charité Mitte, Charité – Universitätsmedizin Berlin; Department of Psychology, Humboldt Universität Berlin and Institute of Clinical Psychology and Psychotherapy, Technische Universität Dresden. It was approved by the local ethics committee (registration number: EA1/223/10) and registered (ClinicalTrials.gov Identifier: NCT01928810). Patients were recruited over a period of 1.5 years. A total of 77 patients with PD/AG were subsequently allocated to one of the two treatment conditions by applying a single randomization. The randomization was reciprocally accomplished by selected staff members of the different study centers via the assignment of a random number to one of the two treatment conditions. There were more random numbers than necessary and therefore it was impossible to predict the allocation of patients. Considering the nature of the trial, patients could not be blinded to intervention but were blind to hypotheses. Therapists and assessors were blind to condition.

2.2. Sample size calculation

According to a study using a pharmacological approach to augment exposure-based CBT in patients with PD/AG we expected an interaction effect of $\eta_p^2 = .18$ for the primary outcome measures (Siegmund et al., 2011). With an alpha-level of 0.05 and power of 0.95 (one tailed), power analysis using G*Power (Faul et al., 2009) resulted in a sample size of 64 patients. The addition of further 14 patients for an expected dropout rate of 20% led to a required sample size of $n = 78$.

2.3. Participants

Participants were recruited via specialized outpatient units at the participating centers. Diagnosis of PD/AG was made according to the Diagnostic and Statistical Manual of Mental Disorders, 4th ed. (DSM-IV) (American Psychiatric Association, 2000) and was verified by applying the Composite International Diagnostic Interview (CIDI) for DSM-IV (Essau and Wittchen, 1993). The following criteria were obligate to be included in the study: age 16–65 years, Hamilton Anxiety Scale (Ham-A; Hamilton, 1959) ≥ 18, Clinical Global Impression (CGI; Guy, 1976) ≥ 4 and being able to attend all therapy sessions. Exclusion criteria were changes in pharmacological treatment within the last four weeks, ongoing psychotherapy, suicidality, diagnosis of psychotic or bipolar disorder, borderline personality disorder, and active alcohol dependence. Other mental comorbidities were acceptable if PD/AG represented the main diagnosis. Medical contraindications for exposure-based CBT or exercise (e.g. severe cardiovascular, musculoskeletal, pulmonary or neurological disorders) were assessed via recording a detailed medical history by the study physician (JP). Moreover, cardiopulmonary fitness of participants was ensured by a spiroergometry that was performed prior to the start of the trial (see also “exercise interventions”). For explorative analyses the amount of physical activity in minutes per week (defined as activity that made subjects sweat or getting out of breath) was obtained via two questions derived from the “German Health Update 2009” survey (Lampert et al., 2012).

2.4. Psychotherapy

2.4.1. CBT

All patients received a manualized exposure-based CBT (Gloster et al., 2011; Lang et al., 2012) consisting of twelve sessions over a time period of seven weeks (two sessions à 100 min per week). The treatment included empirically verified components such as psychoeducation, cognitive reframing and interoceptive exposure. In addition, therapist-guided in-vivo exposure were conducted during session 6, 7, 8, 10 and 11. The first three exposure situations were standardized (bus, shopping center, forest) and the last two sessions were chosen individually by visiting the patients' most relevant agoraphobic context.

2.4.2. Therapists

The therapist team consisted of 31 psychologists (four of them were male). Eight of them were certified psychotherapists while the others were in training for psychotherapy. They all underwent a two-day training consisting of detailed instructions for applying the manual (Lang et al., 2012) and including several practical exercises. A videotape of each therapist performing a central therapy exercise (thought experiment) was rated for adherence as well as competence and served as basis for becoming licensed as a study therapist. This procedure was based on the procedure within the “MAC” study published by Gloster and colleagues (Gloster et al., 2009). In order to control for treatment integrity, all therapy sessions (except for exposure) were videotaped and analyzed by two trained master students of psychology. Therapists showed good adherence and competence (adherence: $M = 6.00$, $SD = 1.59$, competence: $M = 5.49$, $SD = 1.42$) on the therapist adherence and competence rating scale for PD/AG (Gloster et al., 2008). There were no significant differences between both study groups (see below) concerning adherence ($f[1,40] = 0.60$, $p = .45$) and competence ($f[1,40] = 0.07$, $p = .79$).

2.5. Exercise interventions

2.5.1. Determination of optimum training level

In order to determine the optimum training level as well as to definitively exclude any somatic contraindications to physical strain, every patient underwent a modified Bruce treadmill spiroergometry (Knubben et al., 2007) prior to the start of psychotherapy. Patients were