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Neural activation in stress-related exhaustion: Cross-sectional observations and interventional effects

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A R T I C L E I N F O

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A B S T R A C T

The primary purpose of this study was to investigate the association between burnout and neural activation during working memory processing in patients with stress-related exhaustion. Additionally, we investigated the neural effects of cognitive training as part of stress rehabilitation. Fifty-five patients with clinical diagnosis of exhaustion disorder were administered the *n*-back task during fMRI scanning at baseline. Ten patients completed a 12-week cognitive training intervention, as an addition to stress rehabilitation. Eleven patients served as a treatment-as-usual control group. At baseline, burnout level was positively associated with neural activation in the rostral prefrontal cortex, the posterior parietal cortex and the striatum, primarily in the 2-back condition. Following stress rehabilitation, the striatal activity decreased as a function of improved levels of burnout. No significant association between burnout level and working memory performance was found, however, our findings indicate that frontostriatal neural responses related to working memory were modulated by burnout severity. We suggest that patients with high levels of burnout need to recruit additional cognitive resources to uphold task performance. Following cognitive training, increased neural activation was observed during 3-back in working memory-related regions, including the striatum, however, low sample size limits any firm conclusions.

1. Introduction

It is well documented that stress-related exhaustion is associated with impaired cognitive functioning (Eskildsen et al., 2015; Jonsdottir et al., 2013; Ohman et al., 2007; Oosterholt et al., 2012; Sandström et al., 2005; van Dam et al., 2011). Less is known about the neural underpinnings of these cognitive deficits, but a few studies are available, showing both structural and functional brain changes. Specifically, reduced grey matter volume and cortical thickness has been observed in the prefrontal cortex (PFC), the anterior cingulate cortex (ACC), and the superior temporal gyrus, along with decreased striatal and increased amygdala volumes (Blix et al., 2013; Savic, 2015; Savic et al., 2017). Also, reduced functional connectivity between amygdala and medial PFC, ACC, dorsolateral PFC and motor cortex has been found (Golkar et al., 2014; Jovanovic et al., 2011). During working memory (WM) processing, reduced prefrontal activation has been observed in patients with stress-related exhaustion, as compared to healthy controls and patients with depression (Sandström et al., 2012). Although longitudinal follow-ups are scarce, one recent study suggests that the stress-related structural changes in the PFC and the striatum may be at least partly reversible (Savic et al., 2017).

We have recently shown that a 12-week process-based cognitive training intervention can strengthen cognitive function in patients with stress-related exhaustion (Gavelin et al., 2015). We observed improved performance on a trained task, as well as evidence of generalizations of training effects within the trained domains (i.e. near transfer) to WM updating and episodic memory. These results are in line with several studies showing promising results suggesting that cognitive training

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may enhance WM capacity and executive functioning in healthy adults, as well as in clinical conditions associated with WM impairments (Iacoviello et al., 2014; Jaeggi et al., 2008; Owens et al., 2013; Sandberg et al., 2014; but see also Lindenberger et al., 2017). In healthy adults, the associated functional brain response following WM training has shown to include both increased and decreased neural activation in task-relevant regions, such as frontal, parietal and striatal areas (Brehmer et al., 2011; Dahlin et al., 2008; Hempel et al., 2004; Jolles et al., 2010; Kühn et al., 2013; Salminen et al., 2016; Schneiders et al., 2012, 2011; Westerberg and Klingberg, 2007). However, for patients with stress-related exhaustion, no studies have so far investigated the neural changes associated with cognitive training.

The primary purpose of this study was to investigate the association between the key symptom of stress-related exhaustion, i.e. burnout, and functional neural response during WM processing. Based on Sandström et al. (2012), we hypothesized that higher levels of burnout would be associated with decreased activation in the PFC. The secondary purpose of the study was to extend our previous work and examine the neural mechanisms underlying the positive effects of process-based cognitive training in patients with stress-related exhaustion, relative to a treatment-as-usual control condition (Gavelin et al., 2015). We hypothesized that training-related changes in activation would be observed in the frontoparietal regions associated with WM, particularly the PFC and the intraparietal and superior parietal cortex (Constantinidis and Klingberg, 2016), along with an increase in functional brain response in the striatum (Dahlin et al., 2008; Salminen et al., 2016).

2. Methods

2.1. Participants and procedure

This study was part of a three-armed randomized trial, evaluating the effects of additional cognitive or aerobic training to regular multimodal rehabilitation on cognition in patients with stress-related exhaustion. Participants and procedure in the overall trial have previously been described in detail (Gavelin et al., 2015). The study was conducted in accordance with the Declaration of Helsinki and approved by the Umeå Regional Ethical Review Board (Dnr 2010-53-31). All participants provided written informed consent prior to the start of the study.

All participants had confirmed diagnosis of exhaustion disorder (ED), according to the International Classification of Diseases and Related Health Problems (ICD-10, code F43.8A). A total of 161 patients were recruited consecutively to the overall study trial. A subsample of 60 patients also conducted functional magnetic resonance imaging (fMRI) at baseline and were included in the present study. The participants included in the MR-sample were representative of the overall sample with respect to age, educational level, sex, level of burnout, depression and anxiety. Five participants were excluded from analysis, two due to missing data from the fMRI scanning sessions and three due to missing behavioral data, resulting in a total of 55 participants.

All patients participated in a 24-week multimodal group stress rehabilitation program as part of the Stress Rehabilitation Clinic's usual care. The stress rehabilitation program consisted of 22 group sessions and two individual meetings with the group therapist. The program was based on cognitive behavioral therapy fostering cognitive-, behavioral- and emotional skills, psychoeducation on stress reactions, sleep and recovery, as well as on individual vocational return-to-work strategies and prescription of physical activity. After 12 weeks of rehabilitation, a randomization by rehabilitation group was conducted to one of three conditions; multimodal rehabilitation with (1) no additional training (serving as control group); (2) the addition of computerized cognitive training and; (3) the addition of aerobic training (indoor cycling). The added training was performed during the last 12 weeks of multimodal rehabilitation, with three weekly training sessions.

Twenty-seven patients in the MR-sample completed the post-intervention assessment: 11 in the control group, ten in the cognitive training group and six in the aerobic training group. The effects of the aerobic training intervention have been evaluated elsewhere (Eskilsson et al., 2017), however, these participants are included in the analyses of burnout and related neural activation. Background characteristics are presented in Table 1 and a flowchart depicting the study design is displayed in Fig. 1. For a detailed description of the characteristics of the aerobic training group, see Eskilsson et al. (2017).

Table 1
Background characteristics.

Measure	Baseline sample ($n = 55$)	Longitudinal sample ($n = 21$)	
		Cognitive training group ($n = 10$)	Control group ($n = 11$)
Sex (female/male)	46/9	6/4	10/1
Age			
Mean (SD)	42.85 (8.97)	41.50 (7.18)	39.09 (9.44)
Range	22–60	26–51	22–58
Education level			
Elementary school	5.5%	0%	0%
High school	34.5%	60%	54.5%
University	60.0%	40%	45.5%
HAD depression			
≤ 10	84%	80%	73%
> 10	16%	20%	27%
HAD anxiety			
≤ 10	53%	20%	64%
> 10	47%	80%	36%

Note. HAD = Hospital Anxiety and Depression Scale (Zigmond and Snaith, 1983); score > 10 indicates identified cases of depression and anxiety respectively.

2.2. Cognitive training intervention

The home-based computerized cognitive training program has previously been described in detail (Gavelin et al., 2015). Briefly, participants trained on six tasks, chosen to target the cognitive functions known to be affected by long-term stress, i.e. executive function, short term-, working- and episodic memory (Deligkaris et al., 2014). Each training session was approximately 15–20 min long. Two tasks targeted updating ability, requiring participants to continuously update WM representations (Miyake et al., 2000). Both updating tasks used visual stimuli, consisting of either lists of single letters or words belonging to different semantic categories. Two tasks targeted shifting ability, requiring participants to classify digits as odd/even or higher/lower than five, or to classify letters as vowel/consonant or beginning/end of the alphabet, depending on the accompanying cue (Rogers and Monsell, 1995). One task targeted visuospatial short-term memory. In this task, participants were presented with a four-by-four grid of green squares that turned red, one-by-one. After presentation, participants were asked to recall the sequence in the correct order. One task targeted episodic memory binding. The participants were presented with lists of triplets consisting of an object, a location and a color. After presentation, they were given the location as a cue and asked to recall the associated color and object in a multiple choice format. All tasks except for the shifting tasks were adaptive so that when participants reached 80% correct answers, they moved up to a more difficult level. Feedback on task performance was given after each task.

2.3. Assessment of training gains

Letter memory running span was used as the criterion task, measuring training gains in the WM updating function. This task was included in the training program, as well as in the pre- and posttest assessments. Ten lists of single letters (A–D) were presented serially on the computer screen. After presentation, participants were asked to