



Long-term effects of cognitive behavior therapy on brain activation in spider phobia[☆]

Anne Schienle^{a,b,*}, Axel Schäfer^a, Rudolf Stark^b, Dieter Vaitl^b

^aDepartment of Clinical Psychology, University of Graz, Graz, Austria

^bBender Institute of Neuroimaging, University of Giessen, Giessen, Germany

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ABSTRACT

This functional magnetic resonance imaging study investigated long-term effects of cognitive behavior therapy (CBT) in individuals suffering from spider phobia. Ten female patients who had shown positive immediate CBT effects were invited to take part in a 6-month follow-up investigation. Here, the patients, along with eight non-phobic females, were presented with the same pictures depicting spiders, generally disgust-inducing, generally fear-inducing and neutral content, which they had viewed 6 months earlier. Patients' self-report and overt behavior indicated a positive long-term clinical improvement. Related hemodynamic changes included an increase in medial orbitofrontal cortex (OFC) activity. As the medial OFC is involved in emotion-related learning, especially in the representation of positive stimulus-outcome associations, we conclude that the medial OFC effect constitutes the neuronal basis of the lasting positive CBT outcome. Activity to disorder-irrelevant pictures decreased across the sessions in the lateral OFC and in the insula, which most likely reflects general habituation.

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1. Introduction

Behavior therapy with exposure in vivo is currently the most effective intervention method for individuals suffering from spider phobia (Choy et al., 2007). The patients are taught to approach spiders until the experienced anxiety diminishes substantially and to correct their misattributions about the animal. Positive immediate, as well as long-term effects for cognitive behavior therapy (CBT), are well documented (Öst et al., 1991, 1997; Arntz and Lavy, 1993; Hellström and Öst, 1995; Öst, 1996; Gotestam and Hokstad, 2002; Koch et al., 2004). All authors reported that the immediate treatment gains were either maintained or even improved over a follow-up period of up to 12 months.

To our knowledge there are no published functional magnetic resonance imaging (fMRI) studies on long-term CBT effects in spider phobia. Three investigations focused on short-term effects (Paquette et al., 2003; Straube et al., 2006; Schienle et al., 2007). The observed therapy-related changes included activation reductions in the dorso-lateral prefrontal cortex, the parahippocampus, the insula and the anterior cingulate cortex (Paquette et al., 2003; Straube et al., 2006). These changes were interpreted to reflect a therapy-induced normalization of psychophysiological hyperactivation. Schienle et al. (2007) reported augmented medial orbitofrontal cortex (OFC) activation directly after successful CBT. Considering that the OFC is central for the rapid (re)learning of stimulus-reinforcement associations and the self-

regulation of emotions (Kringelbach and Rolls, 2004), the main therapeutic effect was understood as cognitive restructuring. This process refers to the patient's ability to modify irrational beliefs about spiders, one's own behavioral possibilities during exposure, and the associated emotional distress.

In order to investigate the temporal stability of this therapy effect, we invited the successfully treated patients to a 6-month follow-up session. We tested whether the immediate therapy-induced changes (reduced scores on a phobia-specific self-report measure, learned approach behavior, more positive affective ratings for spider pictures and medial OFC activation) would still be present in the follow-up session. Also, we analyzed brain activation changes to disorder-irrelevant pictures with disgust-inducing and fear-inducing content in order to be able to differentiate therapy-specific effects from general habituation effects.

2. Methods

2.1. Subjects

We invited 14 treated spider-phobic females who had participated in an fMRI study on short-term CBT effects (Schienle et al., 2007). Ten participants (mean age = 29.1 years, S.D. = 11.5) were available for the 6-month follow-up session (three subjects declined participation: two of them had moved away, and one subject had experienced a reoccurrence of phobic symptoms; one subject did not reply to the invitation). Prior to CBT the females had suffered from spider phobia according to DSM-IV (American Psychiatric Association, 1994). Eight non-phobic women with a comparable mean age ($M = 24$ years, S.D. = 3.7; $t(11,2) = 1.3$, $P = 0.22$) also agreed to participate in the fMRI investigation. All subjects were medication-naïve and right-handed. They gave written informed consent after the nature of the experiment had been explained to them. The ethics committee of the German Society of Psychology approved this study.

[☆] The study was carried out at: Bender Institute of Neuroimaging.

* Corresponding author. University of Graz, Clinical Psychology, Universitätsplatz 2/III, A-8010 Graz, Austria. Tel.: +43 316 380 5086; fax: +43 316 380 9808.

E-mail address: anne.schienle@uni-graz.at (A. Schienle).

Table 1
Behavioral and affective responses before therapy (session 1) and in the 6-month follow-up investigation (session 2).

Session	Patients (M, S.D.)		Controls (M, S.D.)	
	1	2	1	2
SPQ	21.8 (1.6)	4.3 (2.2)	2.6 (1.7)	3.3 (2.9)
Behavior test	4.7 (1.9)	12.0 (0.0)	12.0 (0.0)	12.0 (0.0)
Spider pictures				
Arousal	7.3 (0.9)	2.9 (1.2)	2.8 (1.8)	2.1 (1.1)
Valence	1.9 (1.0)	6.3 (1.3)	7.4 (1.5)	6.4 (2.3)
Fear	5.9 (3.0)	2.4 (1.2)	1.6 (0.9)	1.9 (1.4)
Disgust	7.1 (2.5)	2.7 (1.2)	2.0 (1.1)	2.3 (1.3)
Disgust pictures				
Disgust	5.9 (2.5)	6.0 (2.5)	5.0 (2.9)	5.1 (2.0)
Arousal	4.7 (2.1)	5.0 (2.4)	4.5 (2.1)	4.5 (2.0)
Fear pictures				
Fear	4.2 (2.4)	3.7 (2.1)	3.3 (2.3)	3.6 (1.8)
Arousal	4.6 (2.3)	4.7 (2.2)	4.4 (2.4)	4.6 (1.6)
Neutral pictures				
Valence	6.8 (1.6)	6.6 (1.6)	7.6 (0.7)	7.4 (0.8)
Arousal	1.1 (0.3)	1.1 (0.3)	1.4 (0.7)	1.5 (1.4)

2.2. Procedure

The course of the investigation has been previously described in detail (Schienle et al., 2007). In a first diagnostic session, participants underwent a clinical interview (Margraf, 1994), a questionnaire assessment (Spider Questionnaire (SPQ), Klorman et al., 1974) and a behavioral approach test (BAT). A spider was put in a transparent container and placed 5 m from the subjects, who received points based on their behavior (1 point = no movement, 12 points = removing the spider from the box and holding it in their hands for 20 s). Inclusion criteria for the patient sample were clinically relevant phobic symptoms and pronounced avoidance behavior in the BAT. Females were classified as non-phobic when they were able to hold the spider in their hands without any problems. Clinically relevant depression, dependence on alcohol and drug abuse led to exclusion from the study.

In the first fMRI session, the subjects were exposed to a total of 160 pictures depicting spiders, generally disgust-inducing, generally fear-inducing and neutral content (Lang et al., 1997; Schienle et al., 2007). Each picture was shown for 1.5 s within a block consisting of 40 pictures of the same category. Within a block the pictures directly followed each other in a randomized sequence. Each block was shown six times during the course of the experiment in a quasi-randomized order with the restriction that no more than two categories of the same type followed each other. There were no pauses between the blocks. The total experiment lasted 24 min. The pictures were viewed by means of a mirror attached to the head coil (visual field = 18°). After the scanning, subjects rated their impression of the 40 pictures from each category on four nine-point Likert scales for the dimensions arousal, valence, fear and disgust (range: 1–9, with '9' indicating that the subject felt very aroused, pleasant, anxious and disgusted).

The CBT (Öst, 1996; Öst et al., 1997) was scheduled in the following week after the first fMRI session. The second fMRI session was repeated 1 week after the treatment. The findings for the short-term CBT effects are reported elsewhere (Schienle et al., 2007). The patients of the therapy group underwent a third fMRI session 6 months after successful CBT completion (same course as session 1). The control subjects were invited after a comparable waiting period.

2.3. Imaging and statistical analysis

Brain images were acquired using a 1.5 Tesla whole-body tomograph (Siemens Symphony, Erlangen, Germany) with a standard head coil. For the functional imaging

a total of 492 volumes were registered using a T₂*-weighted gradient echo-planar imaging sequence (EPI) with 30 slices covering the whole brain (slice thickness = 5 mm, no gap, interleaved, TE = 60 ms, flip angle = 90°, field of view = 192 mm × 192 mm, matrix size = 64 × 64). The orientation of the axial slices was parallel to the AC–PC line. The first six volumes were discarded to control for saturation effects. For the preprocessing and statistical analyses, SPM2 (Wellcome Trust Centre for Neuroimaging, University College London, UK) implemented in Matlab (Mathworks, Inc., Natick, MA, USA, release 12) was used, which is based on the general linear model (GLM). Slice time correction, realignment and normalization to the standard space of the Montreal Neurological Institute brain were performed. Smoothing was executed with an isotropic three-dimensional Gaussian filter with a full width at half maximum of 9 mm. The four experimental conditions Spider, Disgust, Fear and Neutral were each modeled by a boxcar function convolved with a hemodynamic response function in the GLM. The six movement parameters of the rigid body transformation applied by the realignment procedure were introduced as covariates in the model. Serial correlations were controlled by an AR(1) process; the high pass filter was set at 512 s.

The effects of the symptom provocation in the first (1) and the follow-up session (2) were studied with a group level random-effects analysis for the contrasts Spider1 > Neutral1, and Spider2 > Neutral2. Then, we analyzed response changes across the sessions by means of paired *t*-tests (separately for patients and controls). Two-sample *t*-tests were conducted in order to compare the groups with each other. General habituation effects were investigated by analyzing response changes across sessions for the contrasts Disgust > Neutral and Fear > Neutral separately for phobic and control subjects.

We computed voxel intensity tests for the following regions of interest (ROIs): amygdala, insula, medial/lateral OFC. The ROIs had been defined by the anatomical parcellation of the normalized brain (single-subject high-resolution T1 volume of the Montreal Neurological Institute) as described by Tzourio-Mazoyer et al. (2002). Based on this assignment between anatomical structures and voxel coordinates, we created masks with the MARINA software (Walter et al., 2003). The results were considered statistically significant for *t*-values with $P \leq 0.005$ for a region of interest (ROI) with at least five contiguous voxels (see Straube et al., 2006).

3. Results

3.1. Verbal and behavioral responses

3.1.1. Symptom severity and affective ratings for spider pictures in the two sessions

We computed paired *t*-tests separately for the spider-phobic group and the control group in order to investigate response changes over time. The patients showed a pronounced decrease in symptom severity (SPQ, behavioral approach test, affective ratings for the spider pictures) from session 1 (directly before CBT) to session 2 (follow-up session) (all $P < 0.01$). The non-phobic participants gave comparable estimates for the spider pictures in the two sessions and had stable SPQ and BAT scores (all $P > 0.35$). Relative to the controls, the patients scored higher on all phobia-relevant measures in the first session (df(16); all $P < 0.001$). There were no statistically significant group differences in the follow-up session (see Table 1).

3.1.2. Affective ratings for disorder-irrelevant pictures

We analyzed changes in affective ratings via 2 × 2 analyses of variance separately for each picture category (factors: group and session). Neither the main effects for group nor the interaction effects group × session reached statistical significance (Table 1).

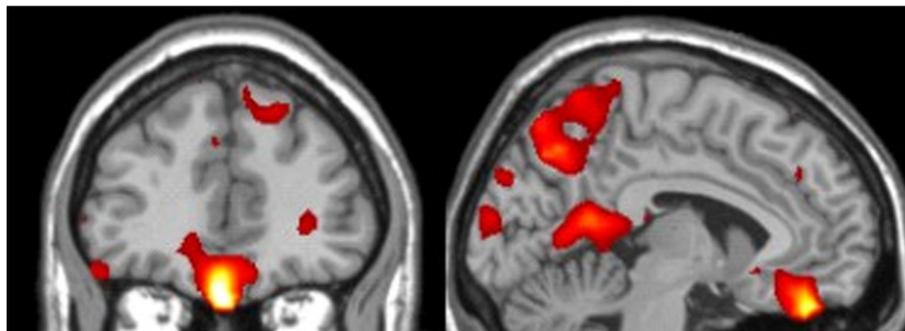


Fig. 1. Brain activation in the follow-up session relative to the first session in the patients (contrast: Spider > Neutral).

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