NeuroImage: Clinical 26 (2020) 102219

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Cortical oxygenation during exposure therapy – in situ fNIRS measurements in arachnophobia

David Rosenbaum[a,*], Elisabeth J. Leehr[b], Julian Rubel[c], Moritz J. Maier[d], Valeria Pagliaro[a], Kira Deutsch[a], Justin Hudak[a,e], Florian G. Metzger[a], Andreas J. Fallgatter[a,f], Ann-Christine Ehlis[a,f]

[a] Department of Psychiatry and Psychotherapy, University Hospital of Tuebingen, Tuebingen, Germany
[b] Department of Psychiatry, University of Muenster, Muenster, Germany
[c] Psychotherapy Research Lab, Psychology and Sport Sciences, Justus-Liebig-University Giessen, Giessen, Germany
[d] Fraunhofer IAO | Center for Responsible Research and Innovation, Berlin, Germany
[e] Center on Mindfulness and Integrative Health Intervention Development, University of Utah, Salt Lake City, UT 84112, United States
[f] LEAD Graduate School & Research Network, University of Tuebingen, Tuebingen, Germany

ARTICLE INFO

Keywords:
Functional near-infrared spectroscopy (fNIRS)
Exposure Therapy
Psychotherapy research
Arachnophobia
Phobia
Change mechanism

ABSTRACT

Exposure therapy is a well-studied and highly efficacious treatment for phobic disorders. Although the neurobiological model of fear is well underpinned by various studies, the mechanisms of exposure therapy are still under discussion. Partly, this is due to the fact that most neurophysiological methods like fMRI are not able to be used in the natural therapeutic settings.

The current study used in situ measurements of cortical blood oxygenation (O_2Hb) during exposure therapy by means of functional near-infrared spectroscopy. 37 subjects (N = 30 completers) underwent exposure therapy during 5 adapted sessions in which subjects were exposed to *Tegenaria Domestica* (domestic house spider – experimental condition) and *Dendrobaena Veneta/ Eisenaia hortensis* (red earthworm – control condition).

Compared to the control condition, patients showed higher O_2Hb levels in the anticipation and exposure phase of spider exposure in areas of the cognitive control network (CCN). Further, significant decreases in O_2Hb were observed during the session accompanied by reductions in fear related symptoms. However, while symptoms decreased in a linear quadratic manner, with higher reductions in the beginning of the session, CCN activity decreased linearly. Further, higher anxiety at the beginning of session one was associated with increased O_2Hb in the CCN. This association decreased within the following sessions.

The current study sheds light on the neuronal mechanisms of exposure therapy. The results are discussed in light of a phase model of exposure therapy that posits a role of cognitive control in the beginning and routine learning at the end of the therapy session.

1. Introduction

Exposure therapy is one of the most efficacious treatments for phobic disorders, showing large effect sizes in meta-analysis either as a stand-alone treatment or in combination with other interventions (Etten and Taylor, 1998; Gould et al., 1997; Wolitzky-Taylor et al., 2008). With respect to the etiology of phobias, genetic (preparedness) as well as environmental factors (learning processes) play a role. Habituation – the reduction of a responsiveness after repeated stimulus presentation (McSweeney and Swindell, 2002) – has perennially been proposed to be the key mechanism of therapeutic change in exposure therapy. However, this assumption has been challenged by some findings (Barlow, 2004; Blakey and Abramowitz, 2016; Craske et al., 2008; Deacon et al., 2010; Hood et al., 2010; Meulders et al., 2016; Milosevic and Radomsky, 2008; Oliver and Page, 2008; Parrish et al., 2008; Rentz et al., 2003; Sy et al., 2011). As an alternative model that may explain the evidence in rodent models better, the inhibitory learning model of extinction proposes that the learned association of conditioned stimulus and unconditioned stimulus stays intact and that instead, the subject learns to inhibit the association (Craske, 2015; Craske et al., 2014). Other influences into the treatment of anxiety disorders come from cognitive accounts. For example, the role of experienced control over fearful stimuli has been highlighted by studies that found fear reduction when patients used the possibility to escape from exposure (De Silva and Rachman, 1984, 1984; Rachman et al., 1987). Cognitive approaches such as the Emotion Processing Theory of

* Corresponding author: Calwerstraße 14, 72076 Tübingen, Germany.
E-mail address: david.rosenbaum@med.uni-tuebingen.de (D. Rosenbaum).

https://doi.org/10.1016/j.nicl.2020.102219
Received 30 October 2019; Received in revised form 14 February 2020; Accepted 17 February 2020
Available online 19 February 2020

Foa and Kozak (1986) propose that pathological fear stems from excessive response elements in the fear structures (e.g. schema) and impairments in the processing of fear relevant information (Foa and Kozak, 1986). Successful modification of these structures - e.g. by means of exposure therapy - includes the activation of the fear memory by fear-relevant information and the incompatibility of the available information with the fear structure (e.g. "I can control the spider"), so that the fear-structure can be changed (Foa and Kozak, 1986).

The neurobiological model of anxiety disorders highlights hyperactivity of para-/limbic areas – such as the amygdala and insula – and prefrontal areas such as the dorsolateral prefrontal cortex (dlPFC) during exposure to fearful stimuli (Hermann et al., 2007; Maren and Quirk, 2004; Michałowski et al., 2017; Münsterkötter et al., 2015; Schweckendiek et al., 2011; Wendt et al., 2008; Zilverstand et al., 2017). In addition, higher activity in the dorsal anterior cingulate cortex (ACC), insula, thalamus, visual areas and bed nucleus of the stria terminalis were observed in phobic patients compared to healthy controls during the anticipation of fearful stimuli (Straube et al., 2007), but prefrontal hyperactivity within phobic subjects during exposure to fearful stimuli has not been consistently reported (Etkin and Wager, 2007; Hermann et al., 2009; Johanson et al., 2006). In conclusion, exposure therapy affects areas of the fear network that are active which includes the amygdala as the core-structure of the fear network, the thalamus, hippocampus and somatosensory areas (Amano et al., 2010; Messina et al., 2013; Myers and Davis, 2007; Quinn and Fanselow, 2006; Sotres-Bayon et al., 2004, 2006). Changes from pre- to post-treatment include decreases in fear-network activation (Messina et al., 2013). Interestingly, the areas of the fear-network comprise brain structures relevant for the formation of emotion – such as limbic structures – as well as areas involved in the regulation of attention and deployment of cognitive control, such as the dlPFC. While the role of limbic structures in the fear response is underpinned by consistent evidence, the role of areas that are related to the regulation of fear is not that clear. Generally, the brain areas related to emotion regulation and cognitive control are labeled as the cognitive control network (CCN). However, the role of areas that are part of the CCN such as the dlPFC, inferior prefrontal gyrus (IFG) and angular gyrus, in the regulation of fear seems to be more complex and may differ between anxiety disorders (Duval et al., 2015; Etkin et al., 2015; Hariri et al., 2000; Hermann et al., 2009; Patel et al., 2012). In general, the CCN plays a central role in tasks that require effortful cognitive control (Maier et al., 2018, 2019, Rosenbaum et al., 2018a, 2018b), and is involved in successful emotion regulation (Etkin et al., 2015; Goldin et al., 2008; Rosenbaum et al., 2018b, 2018d). However, CCN activity might also be present in maladaptive emotion regulation strategies such as expressive suppression of emotions, although the related activity pattern is distinguishable from adaptive emotion regulation strategies (Cutuli, 2014; Goldin et al., 2008). On a meta-analytical level, no evidence exists for the involvement of the CCN in pre-post-treatment comparisons for exposure therapy (Messina et al., 2013). Further, with respect to extinction learning and exposure therapy, the ventromedial prefrontal cortex (vmPFC), which is not part of the CCN, has been highlighted (Herrmann et al., 2017). However, the vmPFC is connected to areas of the lateral prefrontal cortex and stimulation of posterior left prefrontal cortex areas has been shown to increase extinction learning (Raij et al., 2018). Additionally, the evidence that highlights the importance of the CCN in the regulation of emotion (Etkin et al., 2015; Kohn et al., 2014) somewhat questions that the CCN is not related to psychotherapeutic processes in exposure therapy at all and implies a more complex relationship of the role of the CCN in psychotherapeutic processes.

Some explanation for the inconsistent evidence of functional changes within the CCN from pre- to post-treatment in exposure therapy comes from a neurobiological emotion regulation model proposed by Etkin et al. (2015). In their model, the authors differentiate between model-free emotion regulation, which is realized by the vmPFC and ventral ACC, and model-based emotion regulation, which additionally requires areas of the CCN. During model-free emotion regulation, emotion is regulated merely by experience dependent alterations in the value of behavior, while in model-based regulation internal models are used for guidance of behavior (Etkin et al., 2015). Therefore, the involvement of the CCN in psychotherapeutic processes might depend on how far such internal models are used during a specific point of time. Such models might be absent at the beginning of a therapy (as no internal models have been developed through therapy), may be present after the first session, or at the beginning of the session (when the therapist has developed a model with the patient), and may be absent again at the end of the therapy, as routines have been built and no model-based guidance is needed anymore (Kelly and Garavan, 2004). Further, the implementation of model-based processing within exposure therapy might differ between therapeutic accounts, which might further explain the mixed evidence. Within the cognitive account (e.g. CBT), schema-based processing theories emphasized the role of cognitive processes in anxiety (Clark and Beck, 2010) and use many techniques that emphasize model-based emotion regulation. Indeed, the use of cognitive techniques such as reappraisal has been shown to increase the effects of standard exposure (Sloan and Telch, 2002). Further, model-based regulation of fear in arachnophobia has been shown to be related to activity within the CCN (Hermann et al., 2009; Johanson et al., 2006). As model-based processing might differ through different stages of therapy, it might be necessary to develop research strategies that allow the measurement of neuronal activity over the course of treatment.

On a neuronal level CBT has been shown to influence fear-related brain areas in phobic subjects. For example, the studies of Paquette et al. (2003) and Soravia et al. (2016) both showed that CBT reduced activation of prefrontal areas, such as the dlPFC and Brodmann area 8, and fear-related para-/limbic areas, such as the thalamus, parahippocampus and cingulate cortex during fear-provocation paradigms (Paquette et al., 2003; Soravia et al., 2016). However, while in accordance with the observation of reduced activation of the limbic system, Schienle et al. (2007) found reduced activity of the amygdala and insula following CBT, but also increased activity in the medial orbitofrontal cortex (OFC) directly after CBT (Schienle et al., 2007) and 6 months following treatment (Schienle et al., 2009).

Although it is hypothesized that CBT increases prefrontal control over limbic areas (Brooks and Stein, 2015), the data so far doesn't show a clear picture for exposure therapy. New insights might be gained by assessing neurophysiological data directly during the therapeutic process in situ. Yet, the paradigms and adaptations used so far are not comparable to the therapeutic environment of psychotherapy. The first studies employing in situ measurements during exposure were conducted using virtual reality and functional near-infrared spectroscopy (fNIRS) (Deppermann et al., 2017, 2016; Landowska et al., 2018). In the study of Landowska et al. (2018), 15 acrophobic subjects were assessed during exposure in virtual reality with a portable fNIRS device (Landowska et al., 2018). In their preliminary study, the authors observed no difference between the experimental condition and a control condition in the first two sessions of virtual reality exposure, but during the third session, increases in medial prefrontal cortex activity were observed. Nonetheless, their results may be limited with respect to the relative small sample size and the duration of the block design (120 s).

In the current study, we investigated the effects of CBT-based graduated exposure therapy on cortical oxygenated blood concentrations (O_2Hb) in areas of the Cognitive Control Network (CCN) by means of fNIRS. To this end, 37 patients with arachnophobia were treated by a CBT therapist in a cross-over waiting list design while being measured with fNIRS during 5 adapted exposure sessions with domestic house spiders (*Tegenaria Domestica)*. Additionally, exposure trials with red earthworms (*Dendrobaena Veneta/ Eisenaia hortensis*) were assessed as

control conditions. In the current investigation, we analyzed differences between the two experimental conditions (spiders vs. earthworms), changes over the different sessions (first vs. second vs. third vs. fourth vs. fifth) and changes within sessions (beginning vs. middle vs. end of session) during the anticipation of the exposure and the actual exposure.

In accordance with the above outlined studies (Etkin et al., 2015; Hermann et al., 2009; Johanson et al., 2006; Kohn et al., 2014; Paquette et al., 2003), we hypothesized that we would find increased levels of O_2Hb in the CCN – and especially in the dlPFC – during anticipation of and during (spider) exposure trials, in comparison to control trials at the beginning of the therapy. Further, we assumed that CCN activity would be more pronounced during the beginning, in comparison to the middle and end of the session, as prefrontal activity has been shown to decline through CBT (Paquette et al., 2003; Soravia et al., 2016) and more model-based emotion regulation should be present at the beginning of the therapy (Etkin et al., 2015). With respect to differences between sessions, we explored differences with an open hypothesis: Usually, in graduated exposure, anxiety drops over a session and rebounds in the next session, as a more difficult step in handling the feared object becomes the goal (e.g., watching the spider in the first session from a distance vs. holding the jar with the spider in the hand in the second session). Due to this design, comparable hemodynamic changes should be observed between sessions, as the fear response and decline is similar. However, it is possible that some kind of generalization takes place, and changes over sessions (e.g. reduced dlPFC activity) might be observed. Therefore, we explored the changes over sessions with an undirected hypothesis.

2. Material and methods

2.1. Participants

$N = 37$ spider phobic patients participated in this study. Subjects were recruited via email and flyers. Seven subjects dropped out of the study; one due to personal reason, four due to lack of time and two due to problems with the treatment such as fast progress and problems in reducing avoidance. Both of the latter subjects dropped out after session 3 (see supplementary Figure 1). The ethics committee at the University Hospital and University of Tuebingen approved this project and all subjects gave written informed consent. The study protocol is registered at ClinicalTrials.gov (NCT03653923). Exclusion criteria were acute physical illness, neurological disorders, substance abuse, chronic or acute diseases that affect brain functioning such as diabetes or kidney failure, cardiac arrhythmia or other cardiac diseases. Out of the 37 subjects, 89% were female; the average age was 28.74 years (SD = 8.03), with 17.79 (SD = 4.023) years of education. All patients fulfilled criteria for specific phobia / arachnophobia according to the Structural Clinical Interview for DSM IV (SCID) (American Psychiatric Association, 2013; Wittchen et al., 1997). Comorbid diagnoses in the sample were: previous episode of major depressive disorder (10.81%) and other phobic disorders (29.7%) (e.g. acrophobia, panic disorder). Three subjects had a psychotherapeutic treatment in their past, before they participated in the study. Two of these subjects were familiar with the concept of exposure therapy.

The sample had typical initial values (see Table 1) on questionnaire measures of spider phobia such as the Spider Phobic Questionnaire (SPQ), Spider Beliefs Questionnaire (SBQ) and the Fear of Spiders Questionnaire (FSQ) and in measures of behavioral avoidance (BAT) (Arntz et al., 1993; Klorman et al., 1974; Muris and Merckelbach, 1996). BAT assessment before treatment indicated relevant fear and avoidance: 33.3% of the sample were maximally able to watch a spider in a jar from a distance of 5 m, 50% from a distance of 2 m, 6.7% from a distance of 0.5 m, 10% were able look at the spider from the near distance until fear and avoidance was no longer tolerable. No subject was able to touch the spider with a hand or pen.

Table 1
Study characteristics at the beginning of the study.

	mean	SD	Min	max
Age (years)	28.74	8.03	19	48
Sex (percent female)	89%			
Spider Phobic Questionnaire (total score)	20.7	3.9	12	29
Spider Beliefs Questionnaire (total score)	54.56	12.54	32.5	79.38
Fear of Spiders Questionnaire (average)	4.10	0.86	2	5.33
Behavioral Avoidance Test	3	1.20	1	6

2.2. Study protocol

In total 37 arachnophobic patients and 30 healthy controls (primary assessment only) were recruited for this project via email lists of the University Hospital of Tuebingen and University of Tuebingen. Phobic subjects were randomly allocated to a waiting list ($n = 19$) or treatment group ($n = 18$). Groups switched after the first phase (after approximately 4 to 5 weeks) of the study, when the treatment of the treatment group was completed: The treatment group had a waiting period and the waiting group was treated. The second study phase again took approximately 4 to 5 weeks. This cross-over design was used to allow the combined analysis of the in-session fNIRS data of both study groups that is presented in the paper at hand (see Fig. 1). At the beginning of the study, subjects had a baseline measurement consisting of the assessment of demographic variables and behavioral and psychometric assessments of spider phobia. Spider phobia was measured with questionnaires (SPQ, SBQ and FSQ) and a behavioral avoidance test. During the behavioral avoidance test (BAT), subjects were confronted with a living spider in increasing difficulty and were told to give a stop signal when the fear was no longer endurable: (1) Spider is 5 m away (in a jar), (2) Patient watches pictures of spiders while the spider is 5 m away, (3) spider is 2 m away (in a jar), (4) spider is 0.5 m away (in a jar), (5) spider is directly in front of the subject (in a jar), (6) spider is taken out of the jar into a larger tub, (7) patient touches the spider with a pen, (8) the spider is on the (covered) hand of the patient, (9) patient touches the spider with his finger, (10) spider moves on the hand of the patient, (11) spider moves up the arm of the patient. Behavioral avoidance was measured by computing the sum of achieved steps.

Further, subjects participated in a combined EEG-fNIRS measurement in which 40 film clips (10 s length) of spiders or house animals were presented (results of this part will be reported elsewhere). The measurement took 1 to 1.5 h. After the baseline measurement, the treatment group had the first contact with the therapist during which the rationale for the treatment was presented. After the baseline measurement the treatment group had 5 sessions of exposure therapy while being measured with fNIRS (see also treatment and procedures section). During an intermediate survey following the treatment, subjects again participated in the combined EEG-fNIRS measurement and completed

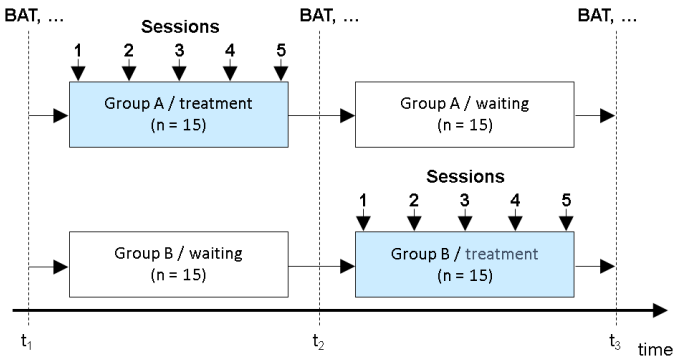

Fig. 1. Study design of the project. In the current article, the fNIRS measurements during the 5 sessions of exposure therapy are reported combined for both study groups (blue boxes).

behavioral and psychometric assessments. Further, the waiting group had their first contact with their therapist. Afterwards, the waiting group was treated and the treatment group had a waiting interval before the final assessment took place. Here again, subjects completed behavioral and psychometric assessments and participated in the combined EEG-fNIRS measurement. A healthy control group was further recruited that only participated once in the EEG-fNIRS measurement to allow a comparison between the patients and healthy controls. As the current study deals with the in-session changes during exposure therapy, this data is not presented.

2.3. Treatment

All subjects of this study were treated by the same (male) licensed CBT therapist according to German law with further 2 years practical experience after the exam. After the corresponding baseline measurement, treated patients had their first therapeutic contact with the therapist: approximately 30 min during which psychoeducation on models of phobic fears, exposure therapy, problems about fear avoidance and anxiety coping strategies (relaxation, controlled breathing, attention refocusing, reframing, metacognitive detachment, mindfulness, positive self-instructions) were discussed. Further, worksheets on the coping strategies were provided to the patients. During the treatment, subjects sat on a comfortable chair in front of a table with the NIRS machine behind them. The therapist was sitting beside the subjects at an approximate angle of 45°. During each session 20 exposure trials and 20 control trials, each with a length of 40 s were assessed with random order of sequence. Each trial consisted of (1) an optional therapeutic talk/intervention, (2) a rating of fear and disgust in anticipation of the trial, (3) an (randomized) instruction on what kind of trial – exposure or control – would follow, (4) an anticipation phase of at least 8 s during which the therapist prepared the animals (spiders or earth worms), (5) the exposure trial of 40 s length and (6) a final rating on fear, disgust and avoidance during the trial. At the beginning of the trial, the animals were located beside the table out of the patient's view. After the instruction on which trial would follow, the therapist took the corresponding animal, prepared it for the exposure, and finally placed it in front of the subject after the 8 s of the anticipation phase. Afterwards, the therapist manually started the exposure trial of 40 s. During the therapeutic interventions, the therapist instructed the patient on performing the exposure and how to deal with problems. Techniques such as attention focusing, behavioral chaining, positive verbal feedback, cheerleading, cognitive reframing, model learning, reducing direct and indirect avoidance, education on spider behavior and metaphors were used. To control for these variables, the therapist noted the technique used and the corresponding trial. In total, each subject had 5 sessions with increasing difficulty of exposure task. In the first three trials of session one, the subject watched the spider, which was located in a jar held by the therapist from approximate 0.5 m away. For the remaining trials, the subject was 0.3 m away. In Session 2, subjects had to hold the jar by themselves. During session 3, subjects were instructed to touch the spider with a wooden pick of 20 cm length. The pick was shortened to 10 cm after trial 3 and to 3 cm after trial 6. The animals were located in a bowl, which stood directly in front of the subjects (approximately 30 cm). Session 4 was similar to session 3 but subjects touched the spider with their hand. During session 5, the therapist took the spider out of the bowl, started the exposure trial, and encouraged the spider to move over to the subject's hand. In the first 6 trials, the spider moved from the therapist's to the patient's hand and back during the trial. Afterwards, subjects handled the spider themselves using both hands. Note that in some cases, the spider moved from hand to hand while in other cases, the spider sat still on the subject's hand. All exposure tasks were done in the same manner with the earthworms during the control conditions. The treatment sessions were delivered with one session per week on average, resulting in a 4 to 5 week treatment phase. We did not deliver more than one session per day, as the treatment is exhausting and the wearing of the fNIRS cap becomes uncomfortable after one hour.

2.4. Animals

For fear exposure, the largest local spider species, *Tegenaria Domestica,* was used. Male and female spiders were captured by volunteers in the wild. Only adult spiders were used. The range of the soma length (prosoma and opisthosoma) was 1 to 1.5 cm, leg to leg span was 5 to 8 cm. Spiders were housed in boxes ($15 \times 14 \times 25$ cm) with appropriate furnishings (paper roll for housing, dried leafs as hiding places, wooded ground). The spiders were fed approximately one time per week with *Acheta domesticus.* The spiders were used in order, which provided different spider-subject-allocation and ensured maximal recovery time for the animals. We used *Tegenaria Domestica* as it is the largest local spider and, for most subjects, the most feared, due to its relatively massive black body and relatively strong “hairy” legs.

Additionally, as control animal, *Dendrobena Veneta/ Eisenaia hortensis* was used. Approximately 150 animals were bought online and kept in a ($50 \times 40 \times 30$ cm) box filled with compost soil. The earthworms were fed with used and washed coffee grounds and the compost soil was replaced partly every 2 weeks. We used red earthworms as control animals, as most subjects do not fear them, despite some having disgust when confronted with worms. The animals are easy to keep, as familiar to most subjects as spiders are and most importantly, they are invertebrates like spiders, but are different enough to not be associated with spiders, as insects might be.

After the end of the study, the spiders were released in their natural habitats. The earthworms were released into the compost of the clinic garden, the spiders were released into different locations of the cellars where they were found.

2.5. fNIRS

Cortical oxygenated (O_2Hb) and deoxygenated (HHb) blood was assessed with a continuous wave, multichannel NIRS system (ETG-4000 Optical Topography System; Hitachi Medical Co., Japan) with a temporal resolution of 10 Hz. Data was recorded with a semiconductor laser and avalanche diodes at two wavelengths (695 20 and 830 20 nm) with 4.0 0.2 mW for each wavelength at each optode. We used two frontal and one parietal probeset as described in Rosenbaum et al. (2018) (see supplementary Figure 2) with reference points at F3 and F4 for the frontal probesets and Pz for the parietal probeset (Rosenbaum et al., 2018d) according to the international 10–20 system (Jasper, 1958). The probesets were integrated in electrode caps, which were positioned at the reference points Fpz and Cz for each subject. The probeset placement covered areas of the bilateral inferior frontal gyrus (IFG), bilateral dorsolateral prefrontal cortex (dlPFC) and the superior parietal lobule (SPL). Corresponding brain areas of each channel were extrapolated from reference points based on the Colin 27 template (Singh et al., 2005; Tsuzuki et al., 2007; Tsuzuki and Dan, 2014).

After export of the NIRS data, changes in O_2Hb and HHb were computed by means of a modified Beer-Lambert law. Data preprocessing was performed with MATLAB 2017a (MathWorks Inc, Natick, USA). First we used a bandpass filtering (0.001 to 0.1 Hz) based on DCT-II and inverse DCT-II filters, then the correlation based signal improvement (cbsi) algorithm by Cui et al. (2010) was used to reduce movement artefacts (Cui et al., 2010). Through the cbsi-algorithm, the signals of O_2Hb and HHb were included in one signal of corrected O_2Hb, which is why only this data was used for further analysis. Afterwards, we interpolated single artefact-loaded channels after visual inspection and used an ICA-based reduction of teeth clenching artefacts. In 10% of the measurements, the exposure induced many high amplitude artefacts that could not be corrected by the ICA procedure. In these cases, we corrected the data by a PCA reduction of the first component (Brigadoi et al., 2014). Finally, a second bandpass filtering (0.01 Hz to

0.1 Hz) was performed before the data was z-transformed and a correction of the global signal by means of a Gaussian PCA kernel filter was done (Zhang et al., 2016). The global signal correction was needed because exposure therapy is associated with high arousal levels in the beginning of the therapy session that would confound the O_2Hb level changes due to neuronal activity. Event-related averages were computed over the first, second and third 33% of the exposure blocks, separately for the anticipation phase and actual exposure phase. The anticipation phase was averaged with a 15 s baseline correction in a 65 s window, with an extracted mean activity between 0 and 10 s of the time window. The exposure phase was averaged within the same window, with an extracted mean activity between 10 and 50 s. Data was averaged in 5 regions of interest (ROI) comprising the SPL, bilateral dlPFC and IFG. ROIs were selected according to previous studies on the CCN (Rosenbaum et al., 2018c, 2018d, 2018e).

2.6. Data analysis

Changes in fear of spider-related questionnaires from pre to post-treatment were assessed with a repeated measurement analysis of variance (ANOVAs). Next, ANOVAs were used to track changes in rated fear, disgust and avoidance and fNIRS data during the exposure therapy sessions. Behavioral ratings were analyzed for the experimental factors: session (first to fifth), session phase (first vs. middle vs. end of session) and condition (worm vs. spider).

Additionally, we analyzed the therapeutic techniques that were used and noted by the therapist qualitatively. In the notes of the therapist, only deviations from the general procedure described above (e.g. instructing the patient, psychoeducation) were noted and analyzed, as the specific techniques (e.g. reframing, acceptance) differed between subjects. Therefore, it is important to note that some techniques (e.g. model learning, direct instructions, cheerleading/positive reinforcement) might be underrepresented as they were part of the standard procedure. Qualitative data was categorized into 9 interventions: Socratic questioning (e.g. “What do you think could happen in the worst scenario?… How likely is this from a realistic point of perspective?…”), cognitive reframing (e.g. of catastrophic cognitions), acceptance (e.g. of negative emotions), attention regulation (e.g. in detail description of the spider), self-verbalization/instruction (e.g. formulation of self instructions “I will take my finger and touch the spider”), model learning (e.g. the therapist shows how to handle the spider during the therapeutic talk), chaining (e.g. the subject is asked to perform a subtask of a complex behavior), motivational interviewing (e.g. the therapist and patient talk about the positive aspects of overcoming the fear) and control of body function (e.g. controlled breathing or relaxation). Interventions were instructed during the therapeutic talk phase before the next trial began. We analyzed the frequency of the intervention implementation by chi^2-tests for different comparisons: We checked if the implementation of any intervention differed between sessions and session phases and if specific intervention techniques (e.g. attention regulation vs. model learning) differed in their implementation between sessions and session phases.

Hypotheses with respect to fNIRS data were assessed for the anticipation and exposure phase separately with the factors: session (first to fifth), session phase (first vs. middle vs. end of session) and ROI (bilateral dlPFC, bilateral IFG, SPL). For reasons of simplicity, we directly computed the contrast between the experimental condition and control condition (difference between spider and worm blocks). We used polynomial contrasts as post-hoc tests as we hypothesized a linear decrease in hemodynamic responses during the session. Correction for multiple comparisons for post-hoc comparisons was performed with the procedure of Armitage-Parmar (Sankoh et al., 1997).

To investigate the relationship between behavioral ratings and O_2Hb levels within the CCN, we further conducted an exploratory analysis in which we modeled the ratings as a dependent variable from the session, session phase and O_2Hb level within the CCN. To this end, we used hierarchical linear models with three levels of nesting (session phase within sessions and session within subjects). Random intercepts were modeled and the O_2Hb levels were used as continuous covariates. For reasons of simplicity, we only modeled the ratings of responsive anxiety during spider trials. All analysis was carried out with the lme4 package in R. Note that we did not investigate the relationship between the use of therapeutic techniques, anxiety and cortical blood oxygenation, as intervention use and anxiety ratings might be confounded (the more anxious a patient is the more guidance the therapist will offer) and the research questions would extend the scope of this article. The analysis of this research question would further require higher sample sizes for the statistical analysis.

3. Results

Seven subjects dropped out of the study. Reasons given were: personal changes in workload due to external events and in two cases emotional overload due to treatment and the included fast progress in the graduated fear levels (see supplementary material Fig. 1). The results include the completers only. Data of 150 sessions – 30 subject each completing a 5 session exposure therapy – were analyzed.

3.1. Efficacy compared to waiting list: questionnaires and behavioral avoidance test

As expected, the treatment was effective as indicated by time by group interactions of the questionnaire data: SBQ ($F(2,56)=62.209$, $p<.001$, $\eta_p^2=0.69$), FSQ ($F(2,56)=86.760$, $p<.001$, $\eta_p^2=0.93$), SPQ ($F(2,56)=45.492$, $p<.001$, $\eta_p^2=0.62$) and BAT ($F(2,56)=158.544$, $p<.001$, $\eta_p^2=0.92$). All interactions indicated a relatively stable symptom severity during the waiting time in the waiting control group and a significant reduction in symptom severity through the treatment (see Fig. 2). Correspondingly, pre-post effect sizes from the beginning of the study to the end were high in all measures (SBQ ($t(29)=9.71$, $p<.001$, $d = 4.33$), FSQ ($t(29)=15.847$, $p<.001$, $d = 4.17$), SPQ ($t(29)=13.942$, $p>.001$, $d = 3.25$), BAT ($t(29)=36.163$, $p<.001$, $d = 6.60$) and the waiting list control group showed stable symptom severity during the waiting phase with exception of a moderate reduction in the SBQ (SBQ ($t(14)=2.447$, $p<.05$, $d = 0.44$), FSQ ($t(14) = 0.330, p > .1, d = 0.05$), SPQ ($t(14) = 0.816, p > .1, d = 0.13$, BAT ($t(14) = -0.323, p > .1, d = 0.08$).

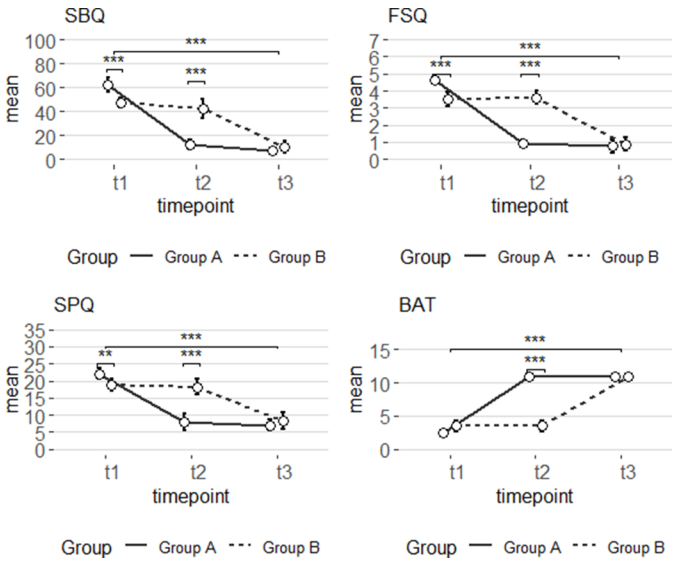

Fig. 2. Changes in symptom severity as assessed by questionnaires and behavioral avoidance test in the treatment and waiting phase in both study groups. * $p < .05$, ** $p < .01$, ***$p < .001$.

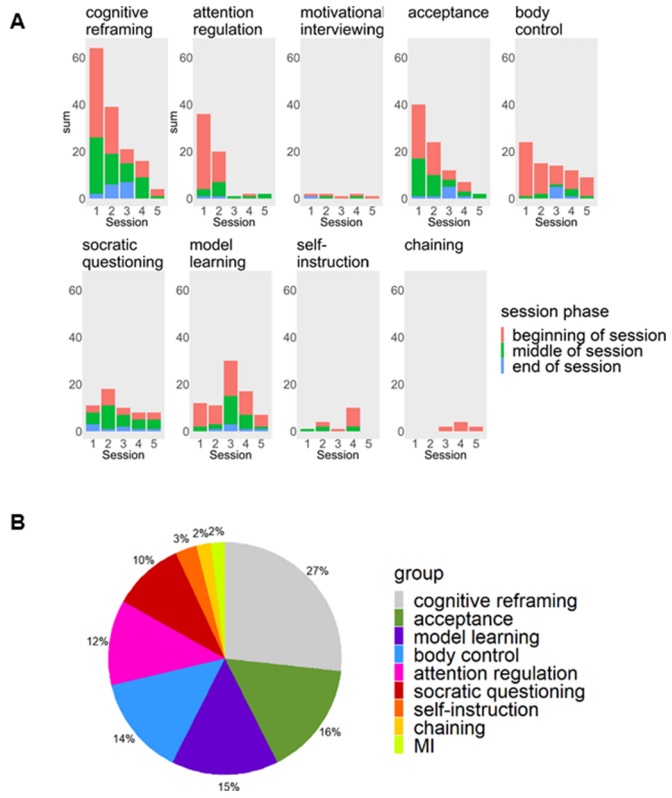

Fig. 3. Frequency of implemented additional interventions between the experimental trials: A) Split by session and session phase for each intervention. B) Number of used interventions in total during the treatment.

3.2. Therapeutic techniques

The analysis of the qualitative data itself revealed some interesting characteristics of the treatment. First, additional intervention use decreased from session to session (session 1 = 36%, session 2 = 25.2%, session 3 = 17.4%, session 4 = 14.8%, session 5 = 6.6%, $\chi^2(4) = 115.235$, $p < .000$) and most of the interventions were performed during the first phase of the sessions (beginning of session = 59.8%, middle of session = 31.4%, end of session = 8.7%; $\chi^2(2) = 216.98$, $p < .000$). Second, interventions differed significantly in their realization in total ($\chi^2(8) = 267.03$, $p < .000$), within different sessions ($\chi^2(32) = 142.01$, $p < .000$, see supplementary Table 1, see Fig. 3A) and within the different session phases ($\chi^2(16) = 50.304$, $p < .000$, see supplementary Table 2, see Fig. 3A). Further, in 26 of 150 sessions no additional intervention was used at all.

Most frequently cognitive reframing, acceptance and model learning was used (see Fig. 3B), followed by body control, attention regulation and socratic questioning. Techniques such as self-instruction, chaining and motivational interviewing were rarely used and only at the beginning of the session as they were only used when heavy problems with performing the task were present. In the same way, body control and attention regulation were used predominantly in the beginning of the session, as they need less cognitive resources than cognitive techniques and can be implemented in high-stress states. The use of cognitive reframing, acceptance, attention regulation and body control decreased from session to session, while chaining, motivational interviewing, self-instructing, socratic questioning and model learning were used consistently (see Fig. 3A).

3.3. Behavioral data

In line with prior work, we observed a decline in avoidance, anticipatory and responsive anxiety/disgust during the sessions, as indicated by significant interactions of conditions by session phase for responsive anxiety ($F(2,58) = 280.843$, $p < .001$, $\eta_p^2 = 0.91$), responsive disgust ($F(2,58) = 92.04$, $p < .001$, $\eta_p^2 = 0.76$) and avoidance ($F(2,58) = 15.725$, $p < .001$, $\eta_p^2 = 0.35$) and a main effect of session phase for anticipatory anxiety ($F(2,58) = 59.694$, $p < .001$, $\eta_p^2 = 0.67$) and anticipatory disgust ($F(2,58) = 38.138$, $p < .001$, $\eta_p^2 = 0.56$).

The interaction of session phase and condition in responsive anxiety, disgust and avoidance was characterized by a linear (anxiety: $F(1,29) = 357.183$, $p < .001$, $\eta_p^2 = 0.93$, disgust: $F(1,29) = 100.191$, $p < .001$, $\eta_p^2 = 0.78$, avoidance: $F(1,29) = 16.227$, $p < .001$, $\eta_p^2 = 0.36$) and quadratic relationship (anxiety: $F(1,29) = 15.289$, $p < .001$, $\eta_p^2 = 0.35$, disgust: $F(1,29) = 16.170$, $p < .001$, $\eta_p^2 = 0.36$, avoidance: $F(1,29) = 14.107$, $p < .001$, $\eta_p^2 = 0.33$), respectively, indicating higher decreases from the first to the second third, than from the second to the last third (see supplementary Figure 4). In the same way, the main effect of session phase for anticipatory anxiety and disgust was characterized by a linear (anxiety: $F(1,29) = 15.289$, $p < .001$, $\eta_p^2 = 0.35$, disgust: $F(1,29) = 38.554$, $p < .001$, $\eta_p^2 = 0.57$) and quadratic decrease (anxiety: $F(1,29) = 29.397$, $p < .001$, $\eta_p^2 = 0.50$, disgust: $F(1,29) = 27.968$, $p < .001$, $\eta_p^2 = 0.49$,), respectively.

Further, we observed a significant interaction of session, session phase and condition for responsive anxiety ($F(8,232) = 3.194$, $p < .01$, $\eta_p^2 = 0.10$). Post-hoc analysis revealed that this three-way interaction was mainly driven by a quadratic decrease between the sessions and a linear decrease over the session phases in anxiety ratings ($F(1,29) = 11.186$, $p < .01$, $\eta_p^2 = 0.28$). However, the interaction with the quadratic term of session phase also reached significance ($F(1,29) = 6.645$, $p < .05$, $\eta_p^2 = 0.19$). These effects were driven by high symptom reduction in the first therapy phase during the first therapy session and, subsequently, reductions in initial symptom severity at the beginning of the following sessions and consequently reduced decline (see Fig. 4, supplementary Tables 3 and 4).

3.4. fNIRS data

All following reported fNIRS results are based on this experimental contrast: the difference of the experimental and control condition. With respect to the anticipatory phase, our results showed a clear main effect of the condition contrast as represented by a highly significant constant term ($F(1,29) = 21.361$, $p < .001$, $\eta_p^2 = 0.42$) indicating higher O_2Hb levels during anticipation of spider trials in the CCN. Main effects for the contrast were found for session phase ($F(2,58) = 5.030$, $p < .05$, $\eta_p^2 = 0.15$) and ROI ($F(4,116) = 4.298$, $p < .01$, $\eta_p^2 = 0.13$). The effect of session phase was characterized by a linear decrease ($F(1,29) = 7.397$, $p < .05$, $\eta_p^2 = 0.20$) (see Figs. 5 and 6) and the effect of ROI by a fourth order polynomial relationship ($F(1,29) = 9.944$, $p < .01$, $\eta_p^2 = 0.25$). The latter effect was driven by higher O_2Hb levels in the left IFG, left DLPFC and SPL than in the right IFG and right DLPFC. Post-hoc comparisons further indicated that the experimental contrast was not significantly different from zero in the right IFG at all (see Fig. 7). Further, we observed an interaction of session by session phase ($F(8,232) = 2179$, $p < .05$, $\eta_p^2 = 0.07$) which was driven by a quadratic relationship from the first to the fifth session of the linear decrease in O_2Hb levels over the session phases ($F(1,29) = 9.819$, $p < .01$, $\eta_p^2 = 0.25$). While there was a considerable decrease in the contrast of spider vs. worm trials in the CCN in sessions two to four, O_2Hb levels stayed stable during anticipation across the session during sessions one and five (see Figs. 5& 6).

With respect to the actual exposure, again we observed a significant constant term ($F(1,29) = 8.191$, $p < .01$, $\eta_p^2 = 0.22$), a significant effect of session phase ($F(2,58) = 3.497$, $p < .05$, $\eta_p^2 = 0.11$) and a significant effect of ROI ($F(4,116) = 10.604$, $p < .001$, $\eta_p^2 = 0.26$). As for the anticipation phase, during the exposure, differences between spider trials and worm trials decreased during the session ($F(1,29) = 6.013$, $p < .05$, $\eta_p^2 = 0.17$) and the ROI effect was driven by a fourth order polynomial relationship ($F(1,29) = 8.244$, $p < .01$, $\eta_p^2 = 0.17$) indicating higher effects in the left IFG, left DLPFC and SPL than in the ROIs of the right

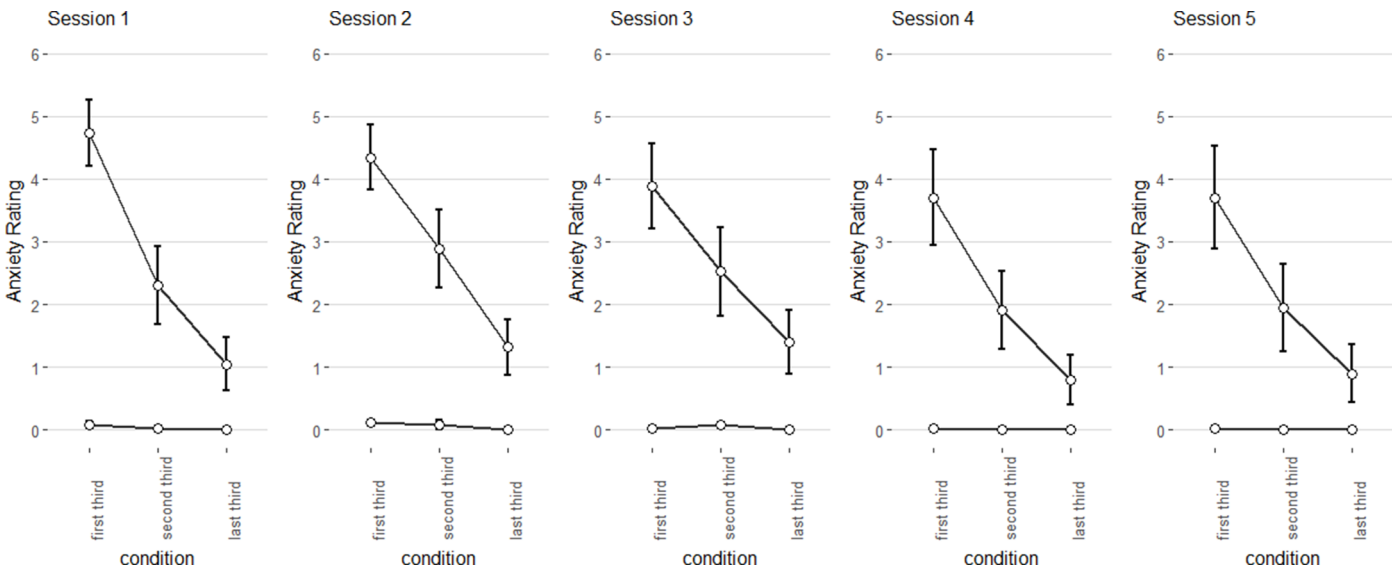

Fig. 4. Anxiety ratings during spider trials (higher lines) and worm trials (lines near zero) from session one (left) to five (right). Of course, control conditions did not provoke anxiety, which is why a legend skipped.

hemisphere. However, an also significant linear contrast for the main effect of ROI ($F(1,29) = 17.370$, $p < .001$, $\eta_p^2 = 0.375$) indicated higher effects in the SPL than in the frontal ROIs. Post-hoc analysis further indicated that the contrast was only different from zero in the left DLPFC and SPL after correction for multiple comparisons (see Fig. 7).

3.5. Exploratory analysis

First, we analyzed the relationship between O_2Hb levels during the 10 s anticipation phase and responsive anxiety ratings. In addition to the already examined effects of session and session phase on anxiety ratings, results indicated that higher anxiety ratings were associated with higher O_2Hb levels in the first session phase of session one (as indicated by the main effect of O_2Hb). Further, we found a negative

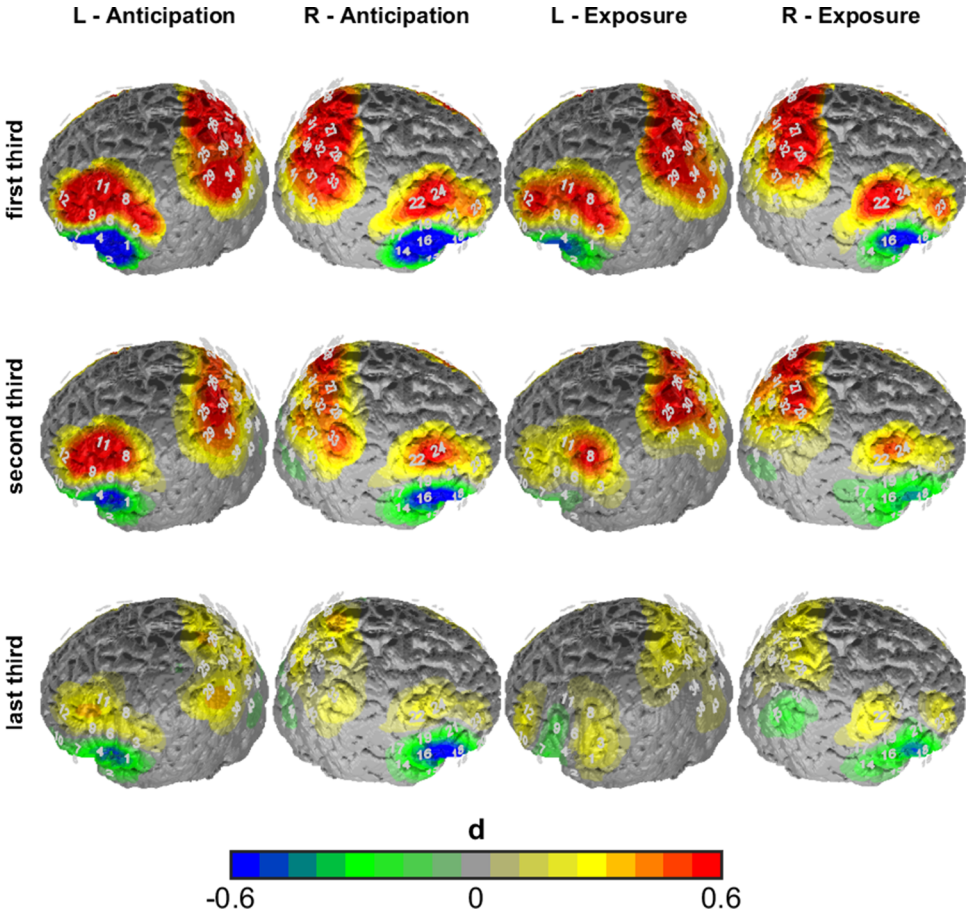

Fig. 5. Activation maps for the exposure contrast (spider vs. control) during the anticipation (left columns) and exposure (right columns) for the different session phases (top to bottom). Differences are plotted as effect sizes in Cohen's d. Warm colors indicate higher activation during the spider trials, while cold colors indicate higher activation in control trials.

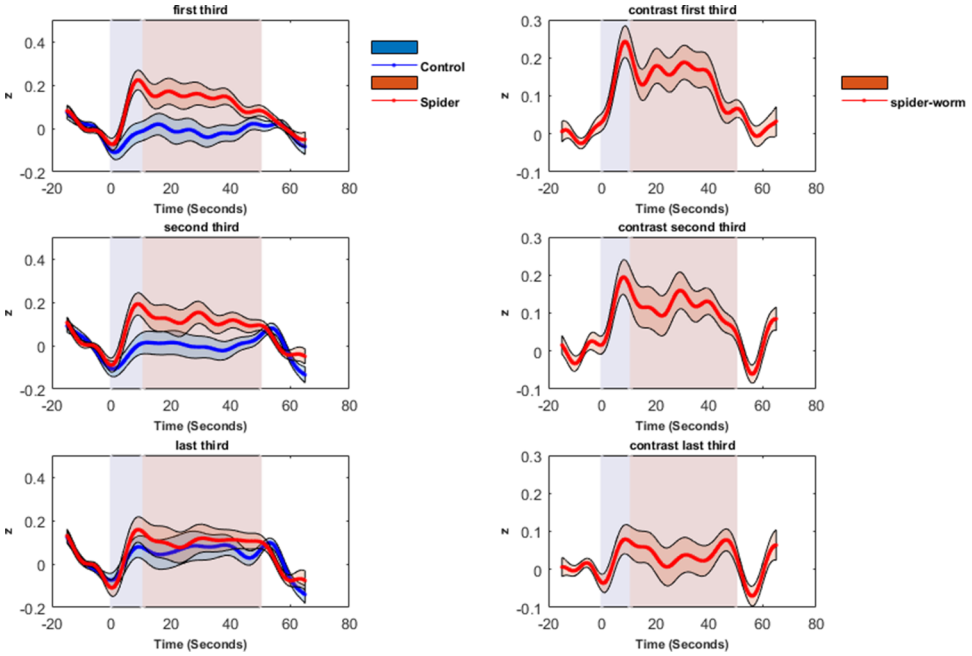

Fig. 6. Hemodynamic responses (mean over all ROIs) in the different session phases. From top to bottom (first to last third), left side = for spider (red) and control (blue) trials, right side = contrast between spider and control trials, blue shaded = anticipation phase, red shaded = exposure phase, shaded area around the hemodynamic trajectories indicated one standard error of the mean.

association between O_2Hb levels and anxiety ratings with increasing session numbers, as indicated by the negative interaction of session with O_2Hb levels (see Table 2).

With respect to O_2Hb levels during the exposure phase, no association between O_2Hb levels and anxiety ratings were found (all $p > .2$).

4. Discussion

The aim of the study at hand was to investigate in situ changes in hemodynamic responses of the cognitive control network (CCN) during exposure therapy in arachnophobia. To this end, 30 subjects completed treatment in an adapted exposure therapy while cortical concentration of oxygenated blood was assessed with functional near-infrared spectroscopy (fNIRS). As expected, significant and treatment specific reductions in symptom severity and behavioral avoidance were found. Importantly, the treatment did affect behavioral (avoidance and other fear behavior), affective (emotional fear reactions) and cognitive (beliefs and spider related cognitions) anxiety domains as assessed by the questionnaires and behavioral avoidance test. With respect to additional interventions implemented between the exposure trials, those comprised predominantly cognitive-behavioral techniques such as

Table 2
Fixed effects of the model predicting anxiety ratings, including 450 observations, 30 subjects and 5 sessions per subject. *** = $p < .001$, ** = $p < .01$, * = $p < .05$.

Fixed effects:	Estimate	Std. Error	Df	t value	Pr(> |t|)	
(Intercept)	1.79	0.25	32.02	7.076	5.00E-08	***
Phase	−1.48	0.06	416.13	−22.179	<2e-16	***
Session	−0.15	0.04	4.04	−3.251	0.0308	*
O_2Hb	0.77	0.38	423.87	2.023	0.0437	*
Phase: O_2Hb	−0.34	0.33	415.66	−1.027	0.3051	
Session: O_2Hb	−0.40	0.16	422.60	−2.412	0.0163	**
Phase:Session:O_2Hb	0.15	0.13	422.56	1.167	0.2438	

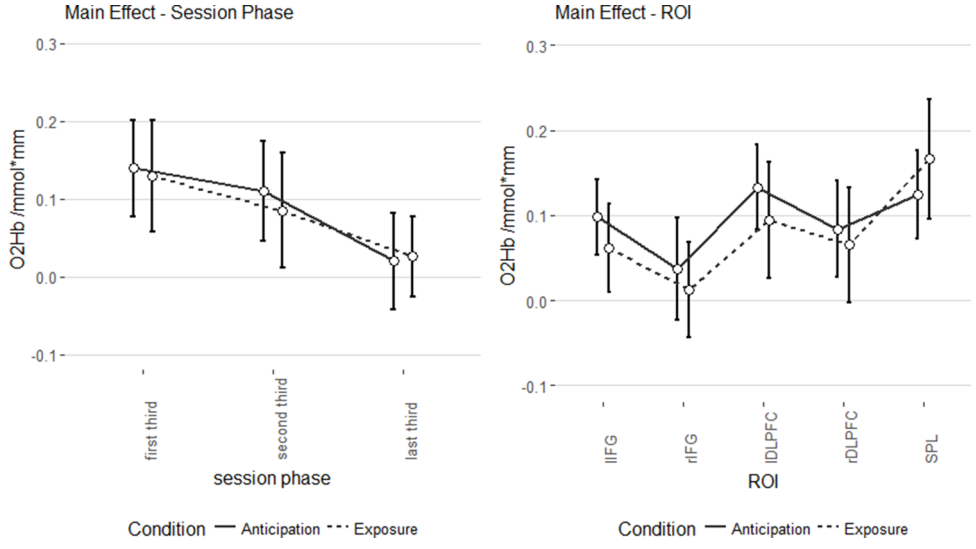

Fig. 7. The effects of session phase (left) and ROI (right) on cortical oxygenated blood concentrations during the anticipation and exposure phase on the experimental contrast (spider vs. control). Displayed are difference scores in the experimental contrast.

cognitive reframing and acceptance. Interventions were mainly implemented in the first session and at the beginning of the session and decreased during each session and over the course of the treatment in general, except for interventions that were used rarely and only in difficult situations (e.g. motivational interviewing). Furthermore, within each session, anxiety ratings as well as activity in the CCN declined from the beginning of the session to the end of the session. However, while anxiety ratings showed a linear-quadratic decrease, reflecting higher symptom reductions from the beginning of the session to mid-session than from mid-session to the end of the session, CCN activity decreased linearly. In addition, we measured fNIRS during the anticipation of the following exposure trial and the actual handling during the exposure task itself. Interestingly, the effects of the anticipation and exposure phase on cortical blood oxygenation were rather similar. In both analyses, we found significant effects of the experimental contrast, with higher blood oxygenation during spider trials than control trials, reductions of the experimental contrast during the session and ROI dependent effects. Consistently, we observed higher effects of the experimental contrast in the left IFG, left DLPFC and SPL than in the right IFG and right DLPFC. We observed an interaction of session phase with session, for the experimental contrast, exclusively in the anticipation phase. Post hoc contrast revealed that the linear decrease in O_2Hb levels over the session phases was dependent on the session. Decreases in the experimental contrast during the anticipation of spider trials over the session phases were absent in the first and last session, but were present in sessions two to four. Finally, in an exploratory analysis we showed that anxiety ratings and O_2Hb levels during the anticipation phase were positively associated in the beginning of the first session, and that this association weakened from session one to session five.

Our behavioral results are in line with previous investigations, showing that exposure therapy is an effective treatment for phobic disorders (Carpenter et al., 2018; Feske and Chambless, 1995; Hofmann et al., 2012; Meulders et al., 2016; Podină et al., 2013; Wolitzky-Taylor et al., 2008). Interestingly, our adapted design showed highly effective symptom reduction, although it was adapted to the NIRS environment. We used relatively short blocks (40 s) of exposure, against the indication that exposure trials should be sufficiently long to allow at least a 50% reduction in symptoms during the treatment. During such short trials, anxiety levels, in most cases, did not fall from high to moderate levels. Instead, steady decreases in anxiety occurred from trial to trial, implicating that patients may improve similarly from relatively short exposure trials with longer rest times as from one long session of exposure. Importantly, this result is well in line with the results of Rachman et al. (1987), who showed that patients profited from exposure therapy even when they escaped from the therapy session at the time their fear was highest (De Silva and Rachman, 1984; Rachman et al., 1987). It may be the case that the relatively short exposure trials increase the sense of controllability for the patients, which in turn may foster symptom reduction. Furthermore, from our fNIRS data we conclude that the actual exposure begins with the anticipation of the trial itself, as steep increases in cortical blood oxygenation began in the anticipation phase and stayed stable during the exposure phase, rather than increase further. In future studies it might be interesting to see how far interventions directly designed for the anticipation phase might increase anticipatory emotion regulation and improve exposure treatment itself.

Our in situ fNIRS measurements showed the expected pattern of decreases in O_2Hb levels in the CCN, which complements the data on pre-post imaging studies showing decreased activity in prefrontal areas following psychotherapy (Ipser et al., 2013; Paquette et al., 2003; Soravia et al., 2016). Interestingly, our results did not show an increase in any area of the CCN. We interpret these patterns as a phase model of exposure therapy. During the beginning of the therapy session, subjects are motivated to confront themselves with their feared object. However, to do so, they need to control their urge to avoid the situation and they need to cope with their subjectively overwhelming anxiety symptoms by using model-based (Etkin et al., 2015) inhibitory top-down control that is guided by plans and strategies provided by the psychotherapist. Interestingly, this interpretation is further supported by the analysis of additional techniques implemented between trials: at the beginning of the therapy and the beginning of the session, more interventions were implemented than at the end of each session and the end of treatment, suggesting that the therapist provided more model-based guidance at the beginning of the session. During the sessions, subjects used high stress coping strategies such as controlled breathing (body control) and attention focusing to stay in the situation and deal with the animals. Consequently, high effortful inhibitory control was necessary for the subjects to implement model-based emotion regulation, which would be reflected by activity in the CCN (Rosenbaum et al., 2018a, 2018b). In line with this, Hermann and colleagues found increased activity in the dlPFC when arachnophobic subjects were asked to downregulate their emotion (Hermann et al., 2009). Further, Johanson found increased activity in areas of the CCN in phobic subjects that did not panic during exposure to phobic material and increases in CCN areas after CBT in initially panicking patients (Johanson et al., 2006). By staying in the situation and experiencing schema-incongruent situations (e.g. “the spider won't jump out of the jar”, “I am in control of the situation/my emotions”, “the spider is small and breakable”, “the spider runs away from me”) and reductions of anxiety by habituation, expectations are further adapted and less top-down control is needed. This may be accompanied by a reduction of effortful control and CCN activity. At the end of the therapy session, mechanisms of routine learning might take place, as subjects become familiar with the handling of the spiders. Importantly, from studies of routine learning, we know that areas of cognitive control such as the prefrontal cortex and parietal cortex are especially active in the beginning of the learning process (Kelly and Garavan, 2004). It is thought that areas of the CCN build up a scaffolding framework that guides supervised learning during unskilled effortful tasks (Petersen et al., 1998). With practice, cortical performance becomes more efficient and task-related areas that are not related to cognitive control are activated without the scaffolding framework (Kelly and Garavan, 2004). In light of Etkin's emotion regulation theory, emotion regulation might switch from a model-based to a model-free emotion regulation, which would be accompanied by a switch from CCN activity to ventral ACC and dorsomedial PFC activity (Etkin et al., 2015). This interpretation is further supported by our exploratory analysis. In addition to the general positive association between O_2Hb levels during the anticipation phase and anxiety ratings, a negative interaction between O_2Hb and session was observed, indicating a decline in the positive association from session one to five. With respect to the scaffolding framework, we would argue that in the beginning of session one, higher cognitive control (model-based emotion regulation) was necessary to face the spiders, reflecting the positive association of CCN activity and anxiety ratings. Over the course of treatment, less effortful control is needed, which would decrease the relationship between the CCN and anxiety ratings. Yet, no such relation was found for the O_2Hb levels during the actual exposure phase, which limits the validity of this argument. One explanation for this might be that inter-subject variability during the exposure phase (10–50 s after baseline correction) was higher (see Fig. 6) and therefore less reliable. Alternatively, it may reflect a special role of the CCN during the anticipation phase in terms of an anticipatory emotion regulation.

A further alternative interpretation of our data would be that the higher activity in the CCN might reflect avoidance instead of cognitive control. As avoidance is reduced during the session, activity within the CCN decreases. We do not believe that this is the case due to two arguments. First, the time period during which the symptoms and CCN activity decrease are different. Avoidance and anxiety showed steep and high decreases in the beginning of the session and lower decreases at the end of the session, while CCN activity decreased linearly in a steady

manner. Second, the linear decrease in symptoms during the session was more or less comparable across sessions, while the decline during the anticipation phase varied as a function of session, showing no decrease in the first and last session. We interpret the lack of decline in terms of the scaffolding framework. During the first session, subjects might not have gained enough practice for the scaffolding network to fall away. During session two to four, the practice in handling of the spider was routinized resulting in decreases in activity. The last session of therapy falls a bit out of the range here. However, it might be the case that holding the spider freely in the hands was again challenging, which would result in an increase in effortful control. Alternatively, the CCN activity during session five could reflect monitoring of hand movements rather than emotion regulation, as the association between CCN activity and anxiety ratings was negatively related to the number of sessions.

Interestingly, our experimental contrast of the fNIRS data showed highest effects in the left frontal cortex and SPL during the anticipation and exposure phase. Generally, lateralisation effects and effects between different ROIs must be interpreted with caution in fNIRS experiments as data might differ due to different optical path lengths and regional anatomical differences. However, assuming that our results have not been influenced by such factors, our data could imply a special role of the left IFG, left DLPFC and SPL in the therapeutic rationale used in this study. The right IFG has been previously associated with response suppression (Cieslik et al., 2015; Hornberger and Bertoux, 2015) and left hemisphere dominance has been associated with increased approach motivation (Davidson and Tomarken, 1989; Rutherford and Lindell, 2011), inhibition in emotional Stroop (Hung et al., 2018) and response inhibition (Ocklenburg et al., 2011). However, hemispheric specificity is to date a matter of controversy and usually complex tasks require activity in both hemispheres, also in respect to inhibition (Blasi et al., 2006; Hung et al., 2018; Ocklenburg et al., 2011; Spielberg et al., 2008). It will be an interesting endeavor for future studies to investigate in how far lateralization effects during exposure are related to specific facets of inhibition, such as emotional, cognitive or response inhibition, interference inhibition or cancelation.

Despite these promising findings, some limitations must be considered. Although fNIRS has some important advantages that make it possible to assess oxygenated blood levels during movement, the penetration depth and spatial resolution are far lower than those of fMRI (Haeussinger et al., 2014, 2011). With fNIRS it is not possible to assess limbic and mesolimbic structures that are related to emotion regulation and the fear response (Haeussinger et al., 2014; Tsuzuki et al., 2007). Therefore, our results are restricted to the limited probe set that covered parts of the CCN. Yet, imaging studies on subcortical limbic areas already showed that subcortical activation declines through psychotherapy (Åhs et al., 2017; Goossens et al., 2007; Strigo et al., 2010).

Further, although we investigated a healthy control group in the baseline assessment only, we did not include a healthy control group that was treated in the exposure paradigm. Such a comparison would be interesting, however, it might not make sense to treat subjects without phobia in such an extensive treatment program (6 h) as confounding variables might be induced (e.g. boredom in the healthy controls). The comparisons of the healthy control subjects with the patients in this group during the symptom provocation paradigm will be reported elsewhere, as the comparison would extend the scope of a single article. Our design resulted in two treatment-related dropouts, as the design was not adaptable to patients that did not respond within the restricted number of trials and the restricted duration of the session. As the NIRS probeset becomes uncomfortable to wear after a certain duration, sessions were designed to be finished after one hour.

A final limitation concerns the generalizability of our findings. We decided to use Arachnophobia patients as a type of specific phobia in the investigation of exposure therapy. This was due to relatively easy care of the study animals and adaptability of the exposure setting within the fNIRS laboratory. It might be the case that different exposure therapy settings (e.g. in vivo vs. *in situ*; specific phobia vs. generalized anxiety disorder) might be, to different extents, adaptable to the NIRS laboratory setting. But, they may be grounded on different neuronal networks. However, as we believe that our data shows increased CCN activity in terms of a scaffolding network in model-based emotion regulation, the results of this study may be generalizable to other types of exposure therapy and other related psychotherapeutic techniques, if our data truly reflects emotion regulation related top-down activity.

Importantly, our interpretation of the data in terms of model-based emotion regulation in a scaffolding network is at this point rather speculative although it is plausible from the literature on emotion regulation and routine learning. However, many confounding variables might have influenced the findings and we did not assess effortful control during the experiment. It will be up to future investigations to make effortful model-based emotion regulation measureable on a trial to trial basis to further support our interpretation. Furthermore, we did not investigate the relationship between additional intervention implementation, anxiety ratings and cortical blood oxygenation, as the sample size is suboptimal for such an analysis and the research question would extend the scope of this article. Nonetheless, this research question is elementary and holds a high potential for future studies. Such a study would clearly help to clarify the inconsistent findings on CCN related changes through exposure therapy. Further, in future studies it might be interesting to investigate if stimulation of the CCN at the first phase of exposure therapy is especially effective, as model-based emotion regulation is needed. Such clinical applications might hold the potential to increase the efficacy as well as the stability of exposure therapy.

5. Conclusions

Our adaptation of exposure therapy for 40 s block lengths showed comparable effect sizes in treatment efficiency to those seen in typical exposure therapy. We observed elevated levels of cortical blood oxygenation within the cognitive control network during experimental trials. Furthermore, the size of this experimental effect decreased during the session, implying a decrease in effortful control. To the knowledge of the authors, the study at hand is the first study to investigate in situ cortical blood oxygenation in a psychotherapy setting, and shows very promising results for the future application of the technique in psychotherapy research.

Statement of ethics

The ethics committee at the University Hospital and University of Tuebingen approved this project and all subjects gave written informed consent. All used methods and procedures in this study were in accordance to the current guidelines of the World Medical Association's Declaration of Helsinki.

Financial disclosures

Ann-Christine Ehlis was partly supported by IZKF Tübingen (Junior Research Group 2115–0–0). David Rosenbaum and Florian Metzger were partly supported by STORZ MEDICAL AG. The authors have no conflicts of interest to declare.

CRediT authorship contribution statement

David Rosenbaum: Formal analysis, Funding acquisition, Data curation, Writing - original draft. **Elisabeth J. Leehr:** Formal analysis, Funding acquisition, Data curation, Writing - original draft. **Julian Rubel:** Formal analysis, Funding acquisition, Data curation, Writing - original draft. **Moritz J. Maier:** Conceptualization, Writing - review & editing. **Valeria Pagliaro:** Formal analysis, Funding acquisition, Data curation, Writing - original draft. **Kira Deutsch:** Formal analysis,

Funding acquisition, Data curation, Writing - original draft. **Justin Hudak:** Conceptualization, Writing - review & editing. **Florian G. Metzger:** Conceptualization, Writing - review & editing. **Andreas J. Fallgatter:** Conceptualization, Writing - review & editing. **Ann-Christine Ehlis:** Conceptualization, Writing - review & editing.

Acknowledgments

The authors would like to thank Ramona Taeglich and Betti Schopp for their excellent work and their valuable support with the measurements. Furthermore, we would like to thank Dr. Annette Denzinger and Dr. Stefan Fischer for their counseling on animal handling and keeping.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.nicl.2020.102219.

References

Åhs, F., Gingnell, M., Furmark, T., Fredrikson, M., 2017. Within-session effect of repeated stress exposure on extinction circuitry function in social anxiety disorder. Psychiatry Res. Neuroimag. 261, 85–90. https://doi.org/10.1016/j.pscychresns.2017.01.009.

Amano, T., Unal, C.T., Paré, D., 2010. Synaptic correlates of fear extinction in the amygdala. Nat. Neurosci. 13, 489.

American Psychiatric Association, 2013. Diagnostic and Statistical Manual of Mental disorders: DSM-5, 5th ed. American Psychiatric Association, Washington, D.C. ed.

Arntz, A., Lavy, E., van den Berg, G., van Rijsoort, S., 1993. Negative beliefs of spider phobics: a psychometric evaluation of the spider phobia beliefs questionnaire. Adv. Behav. Res. Ther., Phobia: Etiological, Cognit. Physiol. Aspects 15, 257–277. https://doi.org/10.1016/0146-6402(93)90012-Q.

Barlow, D.H., 2004. Anxiety and Its Disorders, Second Edition: The Nature and Treatment of Anxiety and Panic, 2 New edition. Guilford Publications, New York, NY ed.

Blakey, S.M., Abramowitz, J.S., 2016. The effects of safety behaviors during exposure therapy for anxiety: critical analysis from an inhibitory learning perspective. Clin. Psychol. Rev. 49, 1–15. https://doi.org/10.1016/j.cpr.2016.07.002.

Blasi, G., Goldberg, T.E., Weickert, T., Das, S., Kohn, P., Zoltick, B., Bertolino, A., Callicott, J.H., Weinberger, D.R., Mattay, V.S., 2006. Brain regions underlying response inhibition and interference monitoring and suppression. Eur. J. Neurosci. 23, 1658–1664. https://doi.org/10.1111/j.1460-9568.2006.04680.x.

Brigadoi, S., Ceccherini, L., Cutini, S., Scarpa, F., Scatturin, P., Selb, J., Gagnon, L., Boas, D.A., Cooper, R.J., 2014. Motion artifacts in functional near-infrared spectroscopy: a comparison of motion correction techniques applied to real cognitive data. Neuroimage 85, 181–191. https://doi.org/10.1016/j.neuroimage.2013.04.082.

Brooks, S.J., Stein, D.J., 2015. A systematic review of the neural bases of psychotherapy for anxiety and related disorders. Dialog. Clin. Neurosci. 17, 261–279.

Carpenter, J.K., Andrews, L.A., Witcraft, S.M., Powers, M.B., Smits, J.A., Hofmann, S.G., 2018. Cognitive behavioral therapy for anxiety and related disorders: a meta-analysis of randomized placebo-controlled trials. Depress. Anxiety 35, 502–514.

Cieslik, E.C., Mueller, V.I., Eickhoff, C.R., Langner, R., Eickhoff, S.B., 2015. Three key regions for supervisory attentional control: evidence from neuroimaging meta-analyses. Neurosci. Biobehav. Rev. 48, 22–34. https://doi.org/10.1016/j.neubiorev.2014.11.003.

Clark, D.A., Beck, A.T., 2010. Cognitive theory and therapy of anxiety and depression: convergence with neurobiological findings. Trends Cogn. Sci. 14, 418–424.

Craske, M.G., 2015. Optimizing exposure therapy for anxiety disorders: an inhibitory learning and inhibitory regulation approach. Verhaltenstherapie 25, 134–143.

Craske, M.G., Kircanski, K., Zelikowsky, M., Mystkowski, J., Chowdhury, N., Baker, A., 2008. Optimizing inhibitory learning during exposure therapy. Behav. Res. Ther. 46, 5–27. https://doi.org/10.1016/j.brat.2007.10.003.

Craske, M.G., Treanor, M., Conway, C.C., Zbozinek, T., Vervliet, B., 2014. Maximizing exposure therapy: an inhibitory learning approach. Behav. Res. Ther. 58, 10–23.

Cutuli, D., 2014. Cognitive reappraisal and expressive suppression strategies role in the emotion regulation: an overview on their modulatory effects and neural correlates. Front. Syst. Neurosci. 8, 175. https://doi.org/10.3389/fnsys.2014.00175. –175.

Cui, X., Bray, S., Reiss, A.L., 2010. Functional near infrared spectroscopy (NIRS) signal improvement based on negative correlation between oxygenated and deoxygenated hemoglobin dynamics. Neuroimage 49, 3039–3046. https://doi.org/10.1016/j.neuroimage.2009.11.050.

Davidson, R.J., Tomarken, A.J., 1989. Laterality and emotion: an electrophysiological approach. Handb. Neuropsychol. 3, 419–441.

De Silva, P., Rachman, S., 1984. Does escape behaviour strengthen agoraphobic avoidance? A preliminary study. Behav. Res. Ther. 22, 87–91.

Deacon, B.J., Sy, J.T., Lickel, J.J., Nelson, E.A., 2010. Does the judicious use of safety behaviors improve the efficacy and acceptability of exposure therapy for claustrophobic fear? J. Behav. Ther. Exp. Psychiatry 41, 71–80.

Deppermann, S., Notzon, S., Kroczek, A., Rosenbaum, D., Haeussinger, F.B., Diemer, J., Domschke, K., Fallgatter, A.J., Ehlis, A.-C., Zwanzger, P., 2016. Functional co-activation within the prefrontal cortex supports the maintenance of behavioural performance in fear-relevant situations before an iTBS modulated virtual reality challenge in participants with spider phobia. Behav. Brain Res. https://doi.org/10.1016/j.bbr.2016.03.028.

Deppermann, S., Vennewald, N., Diemer, J., Sickinger, S., Haeussinger, F.B., Dresler, T., Notzon, S., Laeger, I., Arolt, V., Ehlis, A.-C., Fallgatter, A.J., Zwanzger, P., 2017. Neurobiological and clinical effects of fNIRS-controlled rTMS in patients with panic disorder/agoraphobia during cognitive-behavioural therapy. NeuroImage Clin 16, 668–677. https://doi.org/10.1016/j.nicl.2017.09.013.

Duval, E.R., Javanbakht, A., Liberzon, I., 2015. Neural circuits in anxiety and stress disorders: a focused review. Ther. Clin. Risk Manag. 11, 115–126. https://doi.org/10.2147/TCRM.S48528.

Etkin, A., Büchel, C., Gross, J.J., 2015. The neural bases of emotion regulation. Nat. Rev. Neurosci. 16, 693–700. https://doi.org/10.1038/nrn4044.

Etkin, A., Wager, T.D., 2007. Functional neuroimaging of anxiety: a meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia. Am. J. Psychiatry 164, 1476–1488. https://doi.org/10.1176/appi.ajp.2007.07030504.

Etten, M.L.V., Taylor, S., 1998. Comparative efficacy of treatments for post-traumatic stress disorder: a meta-analysis. Clin. Psychol. Psychother. 5, 126–144. https://doi.org/10.1002/(SICI)1099-0879(199809)5:3<126::AID-CPP153>3.0.CO;2-H.

Feske, U., Chambless, D.L., 1995. Cognitive behavioral versus exposure only treatment for social phobia: a meta-analysis. Behav. Ther. 26, 695–720. https://doi.org/10.1016/S0005-7894(05)80040-1.

Foa, E.B., Kozak, M.J., 1986. Emotional processing of fear: exposure to corrective information. Psychol. Bull. 99, 20–35.

Goldin, P.R., McRae, K., Ramel, W., Gross, J.J., 2008. The neural bases of emotion regulation: reappraisal and suppression of negative emotion. Biol. Psychiatry, Stress, Anxiety, Post-Traumatic Stress Disord. 63, 577–586. https://doi.org/10.1016/j.biopsych.2007.05.031.

Goossens, L., Sunaert, S., Peeters, R., Griez, E.J., Schruers, K.R., 2007. Amygdala hyperfunction in phobic fear normalizes after exposure. Biol. Psychiatry 62, 1119–1125.

Gould, R.A., Buckminster, S., Pollack, M.H., Otto, M.W., Massachusetts, L.Y., 1997. Cognitive-Behavioral and pharmacological treatment for social phobia: a meta-analysis. Clin. Psychol. Sci. Pract. 4, 291–306. https://doi.org/10.1111/j.1468-2850.1997.tb00123.x.

Haeussinger, F., Dresler, T., Heinzel, S., Schecklmann, M., Fallgatter, A.J., Ehlis, A.-C., 2014. Reconstructing functional near-infrared spectroscopy (fNIRS) signals impaired by extra-cranial confounds: an easy-to-use filter method. Neuroimage 95, 69–79. https://doi.org/10.1016/j.neuroimage.2014.02.035.

Haeussinger, F.B., Heinzel, S., Hahn, T., Schecklmann, M., Ehlis, A.-C., Fallgatter, A.J., 2011. Simulation of near-infrared light absorption considering individual head and prefrontal cortex anatomy: implications for optical neuroimaging. PLoS ONE 6, e26377. https://doi.org/10.1371/journal.pone.0026377.

Hariri, A.R., Bookheimer, S.Y., Mazziotta, J.C., 2000. Modulating emotional responses: effects of a neocortical network on the limbic system. [Miscellaneous Article]. Neuroreport 11, 43–48.

Hermann, A., Schäfer, A., Walter, B., Stark, R., Vaitl, D., Schienle, A., 2009. Emotion regulation in spider phobia: role of the medial prefrontal cortex. Soc. Cogn. Affect. Neurosci. 4, 257–267. https://doi.org/10.1093/scan/nsp013.

Hermann, A., Schäfer, A., Walter, B., Stark, R., Vaitl, D., Schienle, A., 2007. Diminished medial prefrontal cortex activity in blood-injection-injury phobia. Biol. Psychol. 75, 124–130.

Herrmann, M.J., Katzorke, A., Busch, Y., Gromer, D., Polak, T., Pauli, P., Deckert, J., 2017. Medial prefrontal cortex stimulation accelerates therapy response of exposure therapy in acrophobia. Brain Stimulat 10, 291–297.

Hofmann, S.G., Asnaani, A., Vonk, I.J.J., Sawyer, A.T., Fang, A., 2012. The efficacy of cognitive behavioral therapy: a review of meta-analyses. Cogn. Ther. Res. 36, 427–440. https://doi.org/10.1007/s10608-012-9476-1.

Hood, H.K., Antony, M.M., Koerner, N., Monson, C.M., 2010. Effects of safety behaviors on fear reduction during exposure. Behav. Res. Ther. 48, 1161–1169. https://doi.org/10.1016/j.brat.2010.08.006.

Hornberger, M., Bertoux, M., 2015. Right lateral prefrontal cortex—specificity for inhibition or strategy use? Brain 138, 833–835. https://doi.org/10.1093/brain/awv027.

Hung, Y., Gaillard, S.L., Yarmak, P., Arsalidou, M., 2018. Dissociations of cognitive inhibition, response inhibition, and emotional interference: voxelwise ale meta-analyses of fMRI studies. Hum. Brain Mapp. 39, 4065–4082. https://doi.org/10.1002/hbm.24232.

Ipser, J.C., Singh, L., Stein, D.J., 2013. Meta-analysis of functional brain imaging in specific phobia. Psychiatry Clin. Neurosci. 67, 311–322. https://doi.org/10.1111/pcn.12055.

Jasper, H., 1958. Report of the committee on methods of clinical examination in electroencephalography. Electroencephalogr. Clin. Neurophysiol. 10, 370–375. https://doi.org/10.1016/0013-4694(58)90053-1.

Johanson, A., Risberg, J., Tucker, D.M., Gustafson, L., 2006. Changes in frontal lobe activity with cognitive therapy for spider phobia. Appl. Neuropsychol. 13, 34–41. https://doi.org/10.1207/s15324826an1301_5.

Kelly, A.C., Garavan, H., 2004. Human functional neuroimaging of brain changes associated with practice. Cereb. Cortex 15, 1089–1102.

Klorman, R., Weerts, T.C., Hastings, J.E., Melamed, B.G., Lang, P.J., 1974. Psychometric description of some specific-fear questionnaires. Behav. Ther. 5, 401–409. https://doi.org/10.1016/S0005-7894(74)80008-0.

Kohn, N., Eickhoff, S.B., Scheller, M., Laird, A.R., Fox, P.T., Habel, U., 2014. Neural network of cognitive emotion regulation — An ALE meta-analysis and MACM analysis. Neuroimage 87, 345–355. https://doi.org/10.1016/j.neuroimage.2013.11.001.

Landowska, A., Roberts, D., Eachus, P., Barrett, A., 2018. Within-and between-session prefrontal cortex response to virtual reality exposure therapy for acrophobia. Front. Hum. Neurosci. 12.

Maier, M.J., Rosenbaum, D., Haeussinger, F.B., Brüne, M., Enzi, B., Plewnia, C., Fallgatter, A.J., Ehlis, A.-C., 2018. Forgiveness and cognitive control - Provoking revenge via theta-burst-stimulation of the DLPFC. Neuroimage 183, 769–775. https://doi.org/10.1016/j.neuroimage.2018.08.065.

Maier, M.J., Rosenbaum, D., Haeussinger, F.B., Brüne, M., Fallgatter, A.J., Ehlis, A.-.C., 2019. Disinhibited Revenge – An fNIRS study on forgiveness and cognitive control. Front. Behav. Neurosci. 13, 223. https://doi.org/10.3389/fnbeh.2019.00223.

Maren, S., Quirk, G.J., 2004. Neuronal signalling of fear memory. Nat. Rev. Neurosci. 5, 844.

McSweeney, F.K., Swindell, S., 2002. Common processes may contribute to extinction and habituation. J. Gen. Psychol. 129, 364–400.

Messina, I., Sambin, M., Palmieri, A., Viviani, R., 2013. Neural correlates of psychotherapy in anxiety and depression: a meta-analysis. PLoS ONE 8, e74657. https://doi.org/10.1371/journal.pone.0074657.

Meulders, A., Van Daele, T., Volders, S., Vlaeyen, J.W., 2016. The use of safety-seeking behavior in exposure-based treatments for fear and anxiety: benefit or burden? A meta-analytic review. Clin. Psychol. Rev. 45, 144–156.

Michałowski, J.M., Matuszewski, J., Droździel, D., Koziejowski, W., Rynkiewicz, A., Jednoróg, K., Marchewka, A., 2017. Neural response patterns in spider, blood-injection-injury and social fearful individuals: new insights from a simultaneous EEG/ECG–FMRI study. Brain Imaging Behav 11, 829–845. https://doi.org/10.1007/s11682-016-9557-y.

Milosevic, I., Radomsky, A.S., 2008. Safety behaviour does not necessarily interfere with exposure therapy. Behav. Res. Ther. 46, 1111–1118.

Münsterkötter, A.L., Notzon, S., Redlich, R., Grotegerd, D., Dohm, K., Arolt, V., Kugel, H., Zwanzger, P., Dannlowski, U., 2015. Spider or no spider? Neural correlates of sustained and phasic fear in spider phobia. depress. Anxiety 32, 656–663. https://doi.org/10.1002/da.22382.

Muris, P., Merckelbach, H., 1996. A comparison of two spider fear questionnaires. J. Behav. Ther. Exp. Psychiatry 27, 241–244. https://doi.org/10.1016/S0005-7916(96)00022-5.

Myers, K.M., Davis, M., 2007. Mechanisms of fear extinction. Mol. Psychiatry 12, 120.

Ocklenburg, S., Güntürkün, O., Beste, C., 2011. Lateralized neural mechanisms underlying the modulation of response inhibition processes. Neuroimage 55, 1771–1778. https://doi.org/10.1016/j.neuroimage.2011.01.035.

Oliver, N.S., Page, A.C., 2008. Effects of internal and external distraction and focus during exposure to blood-injury-injection stimuli. J. Anxiety Disord. 22, 283–291.

Paquette, V., Lévesque, J., Mensour, B., Leroux, J.-M., Beaudoin, G., Bourgouin, P., Beauregard, M., 2003. "Change the mind and you change the brain": effects of cognitive-behavioral therapy on the neural correlates of spider phobia. Neuroimage 18, 401–409. https://doi.org/10.1016/S1053-8119(02)00030-7.

Parrish, C.L., Radomsky, A.S., Dugas, M.J., 2008. Anxiety-control strategies: is there room for neutralization in successful exposure treatment? Clin. Psychol. Rev. 28, 1400–1412. https://doi.org/10.1016/j.cpr.2008.07.007.

Patel, R., Spreng, R.N., Shin, L.M., Girard, T.A., 2012. Neurocircuitry models of posttraumatic stress disorder and beyond: a meta-analysis of functional neuroimaging studies. Neurosci. Biobehav. Rev. 36, 2130–2142. https://doi.org/10.1016/j.neubiorev.2012.06.003.

Petersen, S.E., Van Mier, H., Fiez, J.A., Raichle, M.E., 1998. The effects of practice on the functional anatomy of task performance. Proc. Natl. Acad. Sci. 95, 853–860.

Podină, I.R., Koster, E.H., Philippot, P., Dethier, V., David, D.O., 2013. Optimal attentional focus during exposure in specific phobia: a meta-analysis. Clin. Psychol. Rev. 33, 1172–1183.

Quinn, J.J., Fanselow, M.S., 2006. Defenses and memories: functional neural circuitry of fear and conditional responding. Fear and Learning: From Basic Processes to Clinical Implications. American Psychological Association, Washington, DC, US, pp. 55–74. https://doi.org/10.1037/11474-003.

Rachman, S., Robinson, S., Lopatka, C., 1987. Is incomplete fear-reduction followed by a return of fear? Behav. Res. Ther.

Raij, T., Nummenmaa, A., Marin, M.-F., Porter, D., Furtak, S., Setsompop, K., Milad, M.R., 2018. Prefrontal cortex stimulation enhances fear extinction memory in humans. Biol. Psychiatry 84, 129–137. https://doi.org/10.1016/j.biopsych.2017.10.022.

Rentz, T.O., Powers, M.B., Smits, J.A., Cougle, J.R., Telch, M.J., 2003. Active-imaginal exposure: examination of a new behavioral treatment for cynophobia (dog phobia). Behav. Res. Ther. 41, 1337–1353.

Rosenbaum, D., Blum, L., Schweizer, P., Fallgatter, A.J., Herrmann, M.J., Ehlis, A.-C., Metzger, F.G., 2018a. Comparison of speed versus complexity effects on the hemodynamic response of the trail making test in block designs. Neurophotonics 5, 045007. https://doi.org/10.1117/1.NPh.5.4.045007.

Rosenbaum, D., Hilsendegen, P., Thomas, M., Haeussinger, F.B., Metzger, F.G., Nuerk, H.-C., Fallgatter, A.J., Nieratschker, V., Ehlis, A.-C., 2018b. Cortical hemodynamic changes during the trier social stress test: an fNIRS study. Neuroimage 171, 107–115. https://doi.org/10.1016/j.neuroimage.2017.12.061.

Rosenbaum, D., Hilsendegen, P., Thomas, M., Haeussinger, F.B., Nuerk, H.-.C., Fallgatter, A.J., Nieratschker, V., Ehlis, A.-.C., Metzger, F.G., 2018c. Disrupted prefrontal functional connectivity during post-stress adaption in high ruminators. Sci. Rep. 8, 15588. https://doi.org/10.1038/s41598-018-33777-1.

Rosenbaum, D., Maier, M.J., Hudak, J., Metzger, F.G., Wells, A., Fallgatter, A.J., Ehlis, A.-C., 2018d. Neurophysiological correlates of the attention training technique: a component study. NeuroImage Clin 19, 1018–1024. https://doi.org/10.1016/j.nicl.2018.06.021.

Rosenbaum, D., Thomas, M., Hilsendegen, P., Metzger, F.G., Haeussinger, F.B., Nuerk, H.-C., Fallgatter, A.J., Nieratschker, V., Ehlis, A.-C., 2018e. Stress-related dysfunction of the right inferior frontal cortex in high ruminators: an fNIRS study. NeuroImage Clin 18, 510–517. https://doi.org/10.1016/j.nicl.2018.02.022.

Rutherford, H.J., Lindell, A.K., 2011. Thriving and surviving: approach and avoidance motivation and lateralization. Emot. Rev. 3, 333–343.

Sankoh, A.J., Huque, M.F., Dubey, S.D., 1997. Some comments on frequently used multiple endpoint adjustment methods in clinical trials. Stat. Med. 16, 2529–2542. https://doi.org/10.1002/(SICI)1097-0258(19971130)16:22<2529::AID-SIM692>3.0.CO;2-J.

Schienle, A., Schäfer, A., Hermann, A., Rohrmann, S., Vaitl, D., 2007. Symptom provocation and reduction in patients suffering from spider phobia. Eur. Arch. Psychiatry Clin. Neurosci. 257, 486–493. https://doi.org/10.1007/s00406-007-0754-y.

Schienle, A., Schäfer, A., Stark, R., Vaitl, D., 2009. Long-term effects of cognitive behavior therapy on brain activation in spider phobia. Psychiatry Res. Neuroimaging 172, 99–102. https://doi.org/10.1016/j.pscychresns.2008.11.005.

Schweckendiek, J., Klucken, T., Merz, C.J., Tabbert, K., Walter, B., Ambach, W., Vaitl, D., Stark, R., 2011. Weaving the (neuronal) web: fear learning in spider phobia. Neuroimage 54, 681–688.

Singh, A.K., Okamoto, M., Dan, H., Jurcak, V., Dan, I., 2005. Spatial registration of multichannel multi-subject fNIRS data to MNI space without MRI. Neuroimage 27, 842–851. https://doi.org/10.1016/j.neuroimage.2005.05.019.

Sloan, T., Telch, M.J., 2002. The effects of safety-seeking behavior and guided threat reappraisal on fear reduction during exposure: an experimental investigation. Behav. Res. Ther. 40, 235–251.

Soravia, L.M., Orosz, A., Schwab, S., Nakataki, M., Wiest, R., Federspiel, A., 2016. CBT reduces CBF: cognitive-behavioral therapy reduces cerebral blood flow in fear-relevant brain regions in spider phobia. Brain Behav. 6. https://doi.org/10.1002/brb3.510.

Sotres-Bayon, F., Bush, D.E., LeDoux, J.E., 2004. Emotional perseveration: an update on prefrontal-amygdala interactions in fear extinction. Learn. Mem. 11, 525–535.

Sotres-Bayon, F., Cain, C.K., LeDoux, J.E., 2006. Brain mechanisms of fear extinction: historical perspectives on the contribution of prefrontal cortex. Biol. Psychiatry 60, 329–336.

Spielberg, J.M., Stewart, J.L., Levin, R.L., Miller, G.A., Heller, W., 2008. Prefrontal cortex, emotion, and approach/withdrawal motivation. Soc. Personal. Psychol. Compass 2, 135–153. https://doi.org/10.1111/j.1751-9004.2007.00064.x.

Straube, T., Mentzel, H.-J., Miltner, W.H.R., 2007. Waiting for spiders: brain activation during anticipatory anxiety in spider phobics. Neuroimage 37, 1427–1436. https://doi.org/10.1016/j.neuroimage.2007.06.023.

Strigo, I.A., Simmons, A.N., Matthews, S.C., Craig, A.D., 2010. The relationship between amygdala activation and passive exposure time to an aversive cue during a continuous performance task. PLoS ONE 5, e15093. https://doi.org/10.1371/journal.pone.0015093.

Sy, J.T., Dixon, L.J., Lickel, J.J., Nelson, E.A., Deacon, B.J., 2011. Failure to replicate the deleterious effects of safety behaviors in exposure therapy. Behav. Res. Ther. 49, 305–314.

Tsuzuki, D., Dan, I., 2014. Spatial registration for functional near-infrared spectroscopy: from channel position on the scalp to cortical location in individual and group analyses. NeuroImage, Celebrating 20 Years of Functional Near Infrared Spectroscopy (fNIRS) 85, 92–103. https://doi.org/10.1016/j.neuroimage.2013.07.025.

Tsuzuki, D., Jurcak, V., Singh, A.K., Okamoto, M., Watanabe, E., Dan, I., 2007. Virtual spatial registration of stand-alone fNIRS data to MNI space. Neuroimage 34, 1506–1518. https://doi.org/10.1016/j.neuroimage.2006.10.043.

Wendt, J., Lotze, M., Weike, A.I., Hosten, N., Hamm, A.O., 2008. Brain activation and defensive response mobilization during sustained exposure to phobia-related and other affective pictures in spider phobia. Psychophysiology 45, 205–215.

Wittchen, H.-.U., Wunderlich, U., Gruschwitz, S., Zaudig, M., 1997. SKID I. Strukturiertes Klinisches Interview für DSM-IV. Achse I: Psychische Störungen. Interviewheft und Beurteilungsheft. Eine deutschsprachige, Erweiterte Bearb. d. Amerikanischen Originalversion Des SKID I. Hogrefe, Göttingen.

Wolitzky-Taylor, K.B., Horowitz, J.D., Powers, M.B., Telch, M.J., 2008. Psychological approaches in the treatment of specific phobias: a meta-analysis. Clin. Psychol. Rev. 28, 1021–1037. https://doi.org/10.1016/j.cpr.2008.02.007.

Zhang, X., Noah, J.A., Hirsch, J., 2016. Separation of the global and local components in functional near-infrared spectroscopy signals using principal component spatial filtering. Neurophotonics 3, 015004. https://doi.org/10.1117/1.NPh.3.1.015004.

Zilverstand, A., Sorger, B., Kaemingk, A., Goebel, R., 2017. Quantitative representations of an exaggerated anxiety response in the brain of female spider phobics—a parametric fMRI study. Hum. Brain Mapp. 38, 3025–3038.