

Does caffeine facilitate exposure therapy for specific phobia? A randomized clinical trial

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Zusammenfassung: Does caffeine facilitate exposure therapy for specific phobia? A randomized clinical trial

Hintergrund: Die Erforschung des optimalen Angstlevels für die Exposition ist im Hinblick auf die Optimierung der Effektivität der Expositionstherapie von großer Bedeutung. Ziel der vorliegenden Studie war es, den Einfluss des anxiogenen Effekts von Koffein auf die Effektivität einer Expositionsbehandlung zu untersuchen. Methode: 31 SpinnenphobikerInnen durchliefen eine kombinierte Virtuelle Realitäts-/in vivo-Expositionsbehandlung. Den ProbandInnen der Experimentalgruppe wurde hierbei eine Stunde vor der Behandlung 200 mg Koffein, den ProbandInnen der Kontrollgruppe ein Placebo verabreicht. Ergebnisse: Die ProbandInnen beider Gruppen profitierten von unserer Behandlung. Die Angst vor Spinnen war noch drei Monate nach der Behandlung effektiv vermindert. Entgegen unserer Hypothesen führte die Einnahme von Koffein vor der Exposition in virtueller Realität im Vergleich zur Einnahme eines Placebos nicht zu einem größeren Behandlungserfolg. Schlussfolgerung: Die Kombination von VR- und in vivo-Elementen im Rahmen einer Expositionsbehandlung ist effektiv bei der Behandlung von Spinnenphobie. Die Verabreichung von Koffein vor der Behandlung schien in unserer Stichprobe jedoch nicht zu einem verbesserten Behandlungsergebnis zu führen.

Schlüsselwörter: Expositionstherapie, Koffein, Placebo, virtuelle Realität, Spinnenphobie

Abstract: Does caffeine facilitate exposure therapy for specific phobia? A randomized clinical trial

Objectives: Investigating the optimal level of fear for exposure therapy is important to enhance treatment effects. With caffeine having been shown to have an anxiogenic effect, the aim of the present study was to investigate the impact of caffeine administration pre-treatment on the therapy effect. Method: Thirty-one spider-phobic participants were assigned to either a caffeine (C: 200 mg caffeine, one hour pre-exposure) or a placebo group (P) and underwent a combined virtual reality (VR) and in vivo treatment protocol. Results: Participants in both groups benefitted from our treatment. Fear of spiders was effectively attenuated up to three months post-treatment. Importantly and in contrast to our hypothesis, caffeine intake compared to placebo prior to VR exposure did not lead to an increased treatment effect. Conclusion: Combining VR with an in vivo treatment protocol is effective in treating spider phobia. Caffeine administration pre-treatment did not seem to enhance treatment effects in our sample.

Keywords: exposure therapy, caffeine, placebo, virtual reality, spider phobia, skin conductance level

Introduction

Exposure-based intervention has become the preferred method in the treatment of specific phobias. It has proven to be efficacious, but it still has some major deficiencies, such as high relapse rates: In some cases, return of fear (ROF) rates of up to 62 % have been reported (Mystkowski, Craske, Echiverri, & Labus, 2006). There have been several approaches to prevent or at least reduce relapses in anxiety disorders. Some of these methods include exposure in multiple contexts (Shiban, Pauli, & Mühlberger, 2013; Shiban, Schelhorn, Pauli, & Mühlberger, 2015), exposure with a reminder cue from the extinction context (Culver, Stoyanova, & Craske, 2011) or pharmacological interventions, e.g. administrations of propranolol (a beta-blocker) prior to or directly after fear reactivation, in order to disrupt memory reconsolidation (Kindt, Soeter, & Vervliet, 2009).

There are various theories attempting to explain the mechanisms underlying exposure therapy (for an overview, please see Shiban, 2017). One of the most prominent ones is the emotional processing theory (EPT) by Foa and Kozak (1986). According to EPT, the mental representation of fear takes the form of a fear network containing different elements: information about the feared stimuli, the meaning of the stimuli and the possible responses, e.g., physiological reactions. As these elements are interconnected, the activation of one element results in the activation of the whole system (Foa & McLean, 2016). According to EPT, activation of the fear structure (observable as a heightened fear reaction) during exposure enables the incorporation of new information into the fear network. Incompatible information has the potential to change the fear network. Thus, fear activation is essential for the success of exposure therapy. There is no consistent empirical evidence as to how important fear activation is for successful exposure therapy. A review by Craske et al. (2008) shows some variance: some report positive effects of high fear activation on therapy success (Foa, Riggs, Massie, & Yarczower, 1995; Lang, Melamed, & Hart, 1970), while others detect no or even negative effects of high initial fear activation (Kamphuis & Telch, 2000; Telch et al., 2004). In their updated version of EPT, Foa et al. (2006) address the problem of their theory by postulating a 'sufficient' fear activation level for the efficacy of exposure therapy. Furthermore, they consider excessive levels of fear activation to be unfavourable, since these high levels impair the cognitive capacity for learning.

To investigate the optimal level of fear for exposure therapy, different levels of fear have to be evoked, so that treatment effects can be compared. Caffeine – besides its well-known effects on arousal, vigilance and reaction time (Nehlig, Daval, & Debry, 1992; Smit & Rogers, 2000) – has an anxiogenic effect: caffeine boosts fear activation in patients suffering from various types of anxiety disorders, such as social phobia (den Boer, 2000) or panic disorder (Vilarim, Rocha Araujo, & Nardi, 2011), and increases the probability of panic attacks in patients with anxiety disorders (Nardi et al., 2009). Therefore, caffeine could be suitable for enhancing arousal and fear.

Caffeine is a widely used stimulant (Ogeil & Phillips, 2015; Stohs & Badmaev, 2016). Caffeine has an impact on noradrenergic and dopaminergic activity (Garrett & Griffiths, 1997; Nehlig et al., 1992). Several of the alerting effects of caffeine might be associated to the impact of methylxanthine on serotonergic neurons (Nehlig et al., 1992). Caffeine has been shown to stimulate locomotor activity (Nehlig et al., 1992; Waldeck, 1975). The effect caffeine has on memory, learning, performance and coordination rather reflect the impact of methylxanthine on arousal, vigilance and fatigue (Nehlig et al., 1992). The effects of caffeine on anxiety and sleep depend on the individual's sensitivity to methylxanthine (Nehlig et al., 1992). The majority of the effects of caffeine result from a blockade of adenosine receptors (please see Fredholm, Bättig, Holmén, Nehlig, & Zwartau, 1999). Adenosine is thought to be involved in the aetiology of anxiety (Correa & Font, 2008).

Virtual reality (VR) is a promising tool that can be used to simulate the complexity of the real-world experiences in a laboratory environment and can activate fear networks in fearful participants, as demonstrated in self-reports and physiological measures (Mühlberger, Weik, Pauli, & Wiedemann, 2006; Shiban, Brütting, Pauli, & Mühlberger, 2015; Shiban et al., 2013). Thus, phobia related stimuli could be presented and experimentally controlled in the virtual environment. Garcia-Palacios, Hoffman, See, Tsai, and Botella (2001) reported that VR induces ecologically valid emotions in a standardized environment, and that it is well accepted by patients. Moreover, exposure in VR has proven to be an effective therapeutic treatment for phobias (Powers & Emmelkamp, 2008).

The aim of the present study is to investigate the effect of caffeine administration on the treatment outcome using a combined VR exposure and in vivo treatment protocol. The arousal and level of fear activation was manipulated by administering 200 mg^[1] of caffeine (we assumed that this amount would have an anxiety-inducing effect but would not cause panic attacks or excessive anxiety, which might impair corrective learning) or placebo. Caffeine intake was postulated to lead to increased treatment effects compared to placebo.

Materials and Methods

Participants

Forty-five^[2] volunteers were recruited through advertisements in local newspapers. A phone screening was used to evaluate inclusion and exclusion criteria. Exclusion criteria were pregnancy, current involvement in psycho- or pharmacotherapy, high caffeine consumption (> 4 cups/day) and/or tobacco consumption (> 20 cigarettes/day), and caffeine or lactose intolerance. During the phone screening, participants were asked if they were afraid of spiders and – if so – to indicate

on a scale ranging from 0 (= “no fear”) to 100 (= “maximum fear”) how pronounced this fear was. Only participants with a score of 60 or above were included in the study. Another inclusion criterion was age ≥ 18 years. During the phone screening, participants were instructed not to consume any drinks or food containing caffeine within 48 hours prior to the exposure session. In addition, they agreed not to consume alcohol within 24 hours prior to the exposure. Since nicotine might have an impact on the anxiogenic effects of caffeine (Kayir & Uzbay, 2006), participants were told not to smoke 24 hours prior to the exposure. In order to ensure that the saliva samples were not distorted, participants were asked not to eat or to drink 30 minutes prior to the session. During session 1 (diagnostics), participants were screened for mental disorders with the help of the structured clinical interview for the DSM-IV (SCID-I; Wittchen, Wunderlich, Gruschwitz, & Zaudig, 1997). Participants were excluded if a mental disorder other than spider phobia was the main diagnosis or if it was expected to interfere with the treatment outcome.

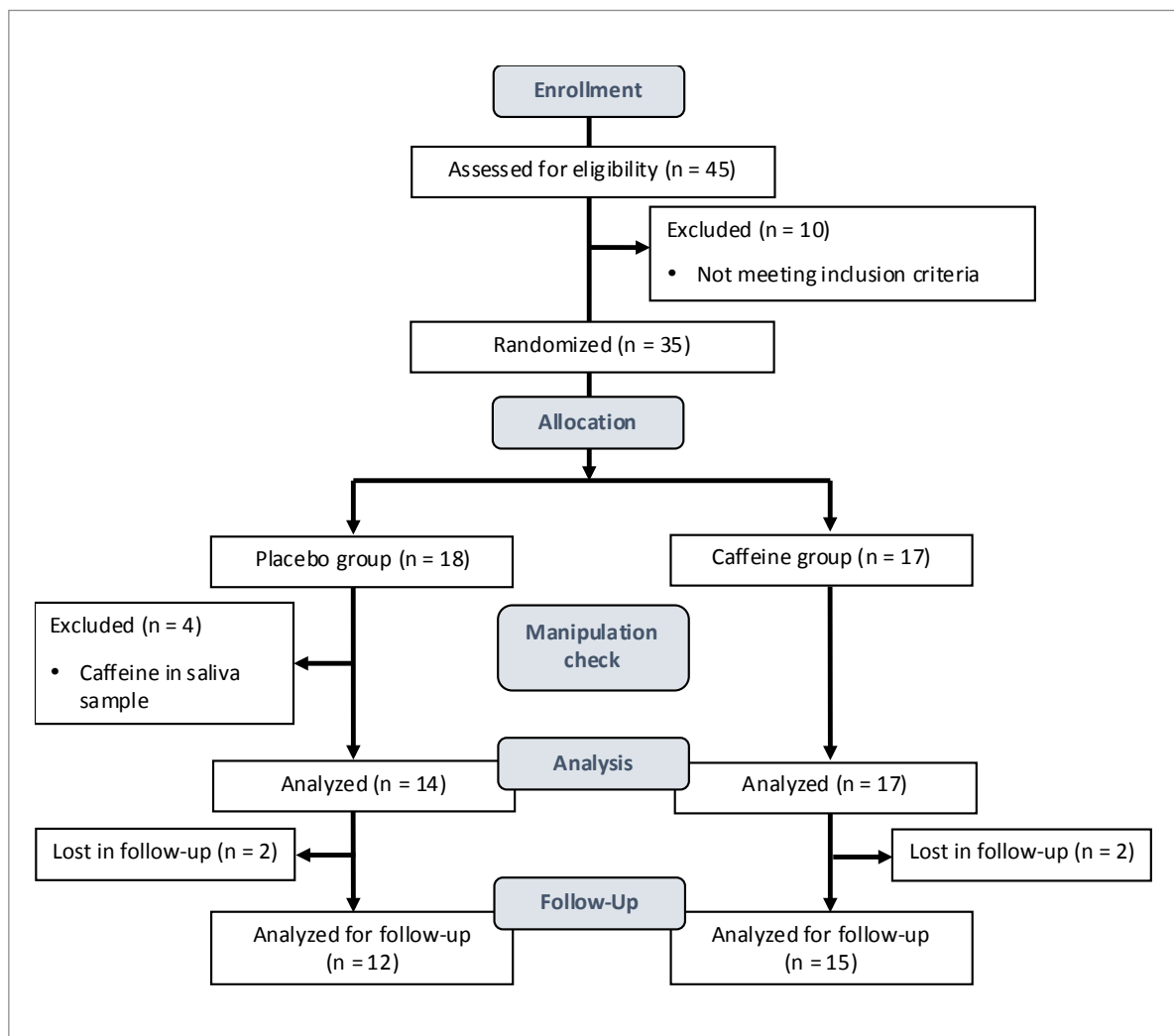


Figure 1

10 participants were excluded after the phone screening or session 1 (diagnostics) for not meeting the inclusion criteria (1 × caffeine intolerance, 1 × panic disorder, 1 × intake of beta blockers, 4 × currently undergoing psychotherapeutic treatment, 1 × delusions, 1 × hypertension, 1 × no spider phobia) and another four because caffeine was detected in their saliva samples (please see Figure 1 for a detailed description of the dropouts in each phase). Thus, 31 participants (placebo group: $n = 14$; caffeine group: $n = 17$) were included in the data analysis.

The participants were mostly female (100% female in the caffeine group, 85.7% female in the placebo group). Participants in the caffeine group were aged between 18 and 67 years ($M = 33.00$, $SD = 14.41$), participants in the placebo group were aged between 22 and 40 years ($M = 31.36$, $SD = 6.92$). However, there were no differences between the two groups regarding these and other fear related variables (see Table 1 for initial group differences).

<i>SCID-I Diagnosis</i>		Group	
		Placebo	Caffeine
SCID-I Diagnosis (only selected)		<i>n</i> (%)	<i>n</i> (%)
History of Major Depression		2 (6.5%)	2 (6.5%)
Agoraphobia		1 (3.2%)	1 (3.2%)
Social Phobia		0	0
Arachnophobia		14 (45.2%)	17 (54.8%)
Other specific Phobias:	Flying	0	1 (3.2%)
	Height	3 (9.7%)	1 (3.2%)
	Doves	0	1 (3.2%)
	Others	0	1 (3.2%)
Obsession		1 (3.2%)	0

Note. n = size of each group. Only diagnoses that occurred at least once were included in the table. Percentage (%) refers to the whole sample size of $N = 45$.

Table 1

Study design

Participants meeting the inclusion criteria were randomly assigned (simple randomization 1-1) to the two groups (caffeine vs. placebo) in a double blind design. The experiment included four exposure sessions within two weeks and a follow-up meeting three months after the last of the four exposure sessions. G*Power 3.1.7 software (Heinrich-Heine-University Düsseldorf, Germany) was used to calculate the sample size. The medical ethics committee of the University of Würzburg approved this study.

Procedure

The study protocol comprised four sessions within two weeks plus a follow-up assessment three months later.

Session 1 (diagnostics): After filling in written informed consent and completing the SCID-I interview, the first Behavioral Avoidance Test (BAT) took place. Participants were informed about the nature of their fear, and the exposure rationale was explained. The exposure rationale included the recommendation to watch the spiders carefully during the virtual reality exposure therapy (VRET), not to perform avoidance behaviour including avoidance thoughts during the VRET, and to concentrate on body sensations provoked by fear, as well as on catastrophic thoughts.

Session 2 (VRET session): First, the saliva samples were collected. Then, a virtual room without spiders was presented to the participants for two minutes in order to get used to the VR equipment. Afterwards, the participants received either a placebo or caffeine tablet, depending on the group. Both groups underwent a controlled waiting condition for one hour (watching part of a documentary film on impressionism), after which the second saliva sample was taken in the same manner as the first one, before VRET began. VRET was conducted in a graded manner with 10 levels (T1 – T10). It started with a scene involving only one spider sitting on the opposite wall of the room wiggling its legs and continuing with more spiders crawling around (up to 4 spiders), which also moved closer and closer to the participant (see Figure 2), whereby the participant was immobile during all of the exposure sessions. VRET ended with the exposure to the first scene once again. Each of the 10 scenes lasted three minutes, and fear ratings were requested at the beginning (5 seconds after spider presentation) and at the end of each scene (15 seconds before the session ended). Thus, we collected 20 fear ratings per participant.

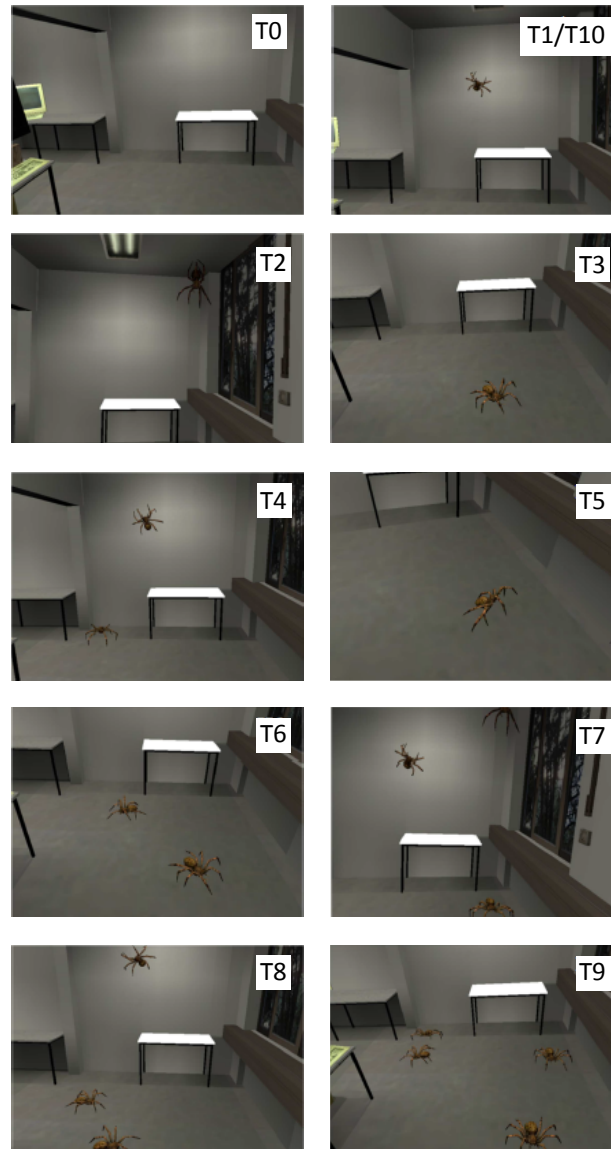


Figure 2. Levels of exposure during VRET. Levels of exposure from T0 to T10 are shown from left to right, with T0 = Familiarization phase (before placebo or caffeine ingestion). Scenes T1 and T10 are identical to measure reduction of fear within the Virtual Reality Exposure Therapy (VRET).

Figure 2

Session 3 (Spontaneous Recovery Test): 24 hours after the VRET session, participants were subjected to the virtual spider scenario again. They were exposed to the same scene they had seen the previous day in T1 (one spider sitting on the opposite wall of the room wiggling its legs). Exposure lasted three minutes and was followed by the second BAT.

Session 4 (in vivo exposure): One week after the third session, the participants were invited to complete an in vivo exposure session with a real tarantula. The session lasted until the participant was able to touch the spider without experiencing a great amount of fear, i.e. reduction of fear ratings by at least 50%. The in vivo session was conducted to facilitate generalization of the treatment effect from the VR to the real world.

Follow-up: Three months after the last exposure session, the participants filled in the Fear of Spiders Questionnaire (FSQ; Szymanski & O'Donohue, 1995) questionnaire and the self-constructed 7-item follow-up questionnaire, which assesses current avoidance behaviour and perceived restriction in daily life due to the fear of spiders.

Virtual Reality Scenarios

The immersive VR environment was generated using the Steam Source® engine (Valve Corporation, Bellevue, Washington, USA). Additional 3D elements were designed and compiled with Softimage XSI Modtool 5 and Softimage XSI 6 software (Softimage Co.; Montreal, Quebec, Canada). We used "Cybersession" software (VTplus GmbH, Würzburg, Germany, www.vtplus.eu) running on a Windows PC (Pentium 4, 3.20 GHz, 1 GB RAM, Intel 82865G Graphics Controller) to control the VR environment during the experiment. The virtual environment was displayed on a Z800 3D Visor head-mounted display (eMagin, NY, USA). The participant's head position was monitored via the Patriot electromagnetic tracking device (Polhemus Corporation, Colchester, Vermont, USA), which adjusts the field of view in response to head movements. The tracker was attached to headphones (Sennheiser HD 215, Sennheiser electronic GmbH, Germany), which were used to deliver instructions and information during the experiment.

Measures

For the diagnosis of spider phobia and the comorbid disorders we used the structured clinical interview for the DSM-IV (SCID-I; Wittchen et al., 1997). The structured interview was conducted either by a graduate psychologist with four years of postgraduate psychotherapy training, or by a psychology graduate student with extensive SCID-I training. All interviews were recorded on video, and in case of uncertainty, a licensed psychotherapist was consulted to confirm diagnosis.

Psychometric assessment of fear of spiders was evaluated using the German version (Rinck et al., 2002) of the FSQ (Szymanski & O'Donohue, 1995). It consists of 18 items containing statements relevant to spider phobia, such as, "If I met a spider right now, I'd leave the room". The answers range from 0 ("I do not agree at all") to 6 ("I completely agree"). The translated FSQ demonstrates a very high internal consistency, Cronbachs $\alpha = .97$, and a high retest reliability, $r_{tt} = .95$ (Rinck et al., 2002).

To measure long-term changes regarding fear of spiders, we developed a 7-item follow-up questionnaire (available from the authors upon request). Five items assess the diagnostic criteria of specific phobias, e.g. fear of spiders ("How high would you rate your actual fear of spiders?"), avoidance of spiders ("How much do you avoid contact with spiders?"), and perceived restriction in daily life due to fear of spiders ("How restricted is your daily life because of your fear of spiders?").

The BAT is a measure of fear in patients with phobias, often used to evaluate the efficacy of exposure therapy (see Shiban, Schelhorn, et al., 2015). For our BAT, we placed a spider (female *Grammostola rosea*, approximately 8 cm long including front legs and cephalothorax) into a transparent plastic box (7x14x10 cm) with a closed lid on a slide 3 m away from the participant's chair. The participant was instructed to enter the room, sit down on the chair, and then slowly pull the box with the spider towards him- or herself as close as possible using a crank. The distance between the participant and the box was used as the dependent variable for the BAT. The participants were informed that the BAT was a measure of their fear of spiders and not part of the treatment. During the test, the experimenter stayed out of the patient's field of vision in order to minimize any potential impact of his or her presence.

Fear ratings, ranging from 0 "no fear" to 10 "maximum fear", were used to assess the participants' perceived level of fear during different stages of the experiment. These ratings were given verbally by the participants to the examiner upon receiving acoustic instructions over headphones during the VR exposure.

The participants' caffeine level was measured using saliva samples (two per participant) - approximately 1.5 ml - collected through a straw into a small airtight tube (SaliCaps, IBL International GmbH, Hamburg). For this manipulation check, a *t*-test showed a significant difference between the two groups (caffeine vs. placebo), $t(29) = -11.1$, $p < .001$. The caffeine group ($M = 2.08$, $SD = .70$) showed a significantly higher concentration of caffeine (mg/litre saliva) than the placebo group ($M = 0.00$, $SD = 0.00$).

Skin conductance level (SCL) was measured using the mobile multichannel recording system "Varioport" (Becker Meditech: Karlsruhe, Germany) on the non-dominant hand, with Ag/AgCl

miniature electrodes (10 mm diameter of electrode area) attached to the thenar muscle. Data were stored on a personal computer with a sampling frequency of 512 Hz. The recording was controlled using “Variograph” software (Becker Meditech: Karlsruhe, Germany). SCL in microsiemens (μS) was recorded continuously during VRET and the spontaneous recovery test (SRT). The analysis was conducted with Brain Vision Analyzer 1.0 software (Brain Products GmbH, Munich, Germany).

Data reduction and statistical analysis

Physiological data were reduced with Brain Vision Analyzer 2.0 software (Brain Products GmbH, Munich, Germany) and further analysis was performed in SPSS 21.0 (IBM Corp., Armonk, NY).

The baseline for the SCL was set at average SCL during the 60 s, in the middle of the first pre-exposure scenario (exposure to a virtual room with no spider). This individual baseline was subtracted from the average levels of SCL recorded during the first and last 15 seconds of each of the 10 exposure trials and of the SRT.

Saliva samples were analysed for caffeine as a manipulation check. For the caffeine group, saliva samples were analysed for a significant increase in caffeine concentration from pre to post caffeine intake. Participants from the placebo group were excluded if caffeine was detected in their saliva samples.

For the process analysis of the VRET, fear ratings and SCL data were subjected to repeated-measures analysis of variance (ANOVA) with the within-subject factors trial (exposure trial 1 to exposure trial 10) and time (beginning of exposure trial vs. end of exposure trial) and the between-subjects factor group (C vs. P).

For the SRT, the return of fear was evaluated with a repeated-measures ANOVA 24 hours after the VRET session with the within-subject factor time (for verbal ratings: last fear rating during the last VRET trial vs. first fear rating during the SRT; for SCL: last 15 s during the last VRET trial vs. first 15 s during the SRT), and the between-subjects factor group (C vs. P). For procedure and selection of time intervals, see also Shiban et al. (2013).

With the BAT we intended to examine whether the reactivation of fear prior to VRET would affect fear behaviour after the SRT. We conducted a repeated-measures ANOVA with the within-subject factor time (BAT 1 in session 1 vs. BAT 2 in session 3) and the between-subjects factor group (caffeine group vs. placebo group).

For the in vivo exposure session, the protocol was not standardized. Each participant was able to decide when he or she wanted to proceed to the next level. Exposure levels included looking at the living spider in the transparent box, touching the lid of the box, touching the box without lid, touching the spider with a pen, touching the spider at the leg with a bare hand, and letting the spider crawl over the hand. The therapist acted as a role model at each level showing the expected approach to the spider. We only examined the first and the last fear rating of each participant during the session.

For the three-month follow-up assessment, questionnaires were sent out by post. There were 4 dropouts out of 31 participants who did not send back the questionnaires. Group differences in the self-constructed follow-up questionnaire were examined with *t*-tests. Participants were asked to rate to which extent they avoided contact with spiders on a scale ranging from 0 "not at all" to 10 "maximum avoidance".

In additional analyses of trial and time, follow-up *t*-tests were performed. The Greenhouse-Geisser correction was applied whenever the assumption of sphericity was violated. Partial η^2 (η_p^2) scores and Cohen's d_z were used as indices of effect size. The significance level was set at $p = .05$.

Results

Process Analysis of VRET

Fear ratings

The results regarding the fear ratings are based on the data of 30 participants (placebo group: $n = 13$; caffeine group: $n = 17$). Figure 3 depicts the decrease in fear ratings within some of the exposure trials. Furthermore, fear ratings slightly decreased over time. An ANOVA on the fear ratings during the VRET confirmed these changes in fear, as indicated by significant main effects of time, $F(1, 28) = 20.53, p < .001, \eta_p^2 = .42$, trial, $F(4.62, 129.41) = 17.84, p < .001, \eta_p^2 = .39$, and a significant interaction of Time x Trial, $F(9, 252) = 7.05, p < .001, \eta_p^2 = .20$. There was neither a significant main effect of group nor significant interactions of Trial x Group, Time x Group and Time x Trial x Group, $ps > .05$.

Follow-up *t*-tests revealed that the decrease in fear was not significant within exposure trials 1 and 10 (for both $p > .05$), suggesting that no fear reduction took place within these two trials, but did indeed take place within trials 2 to 9 (for all $p < .05$). Furthermore, a significant habituation effect within the whole VRET can be detected by comparing the first and the last fear rating within the VRET, $t(29) = 4.72, p < .001, d_z = 0.86$.

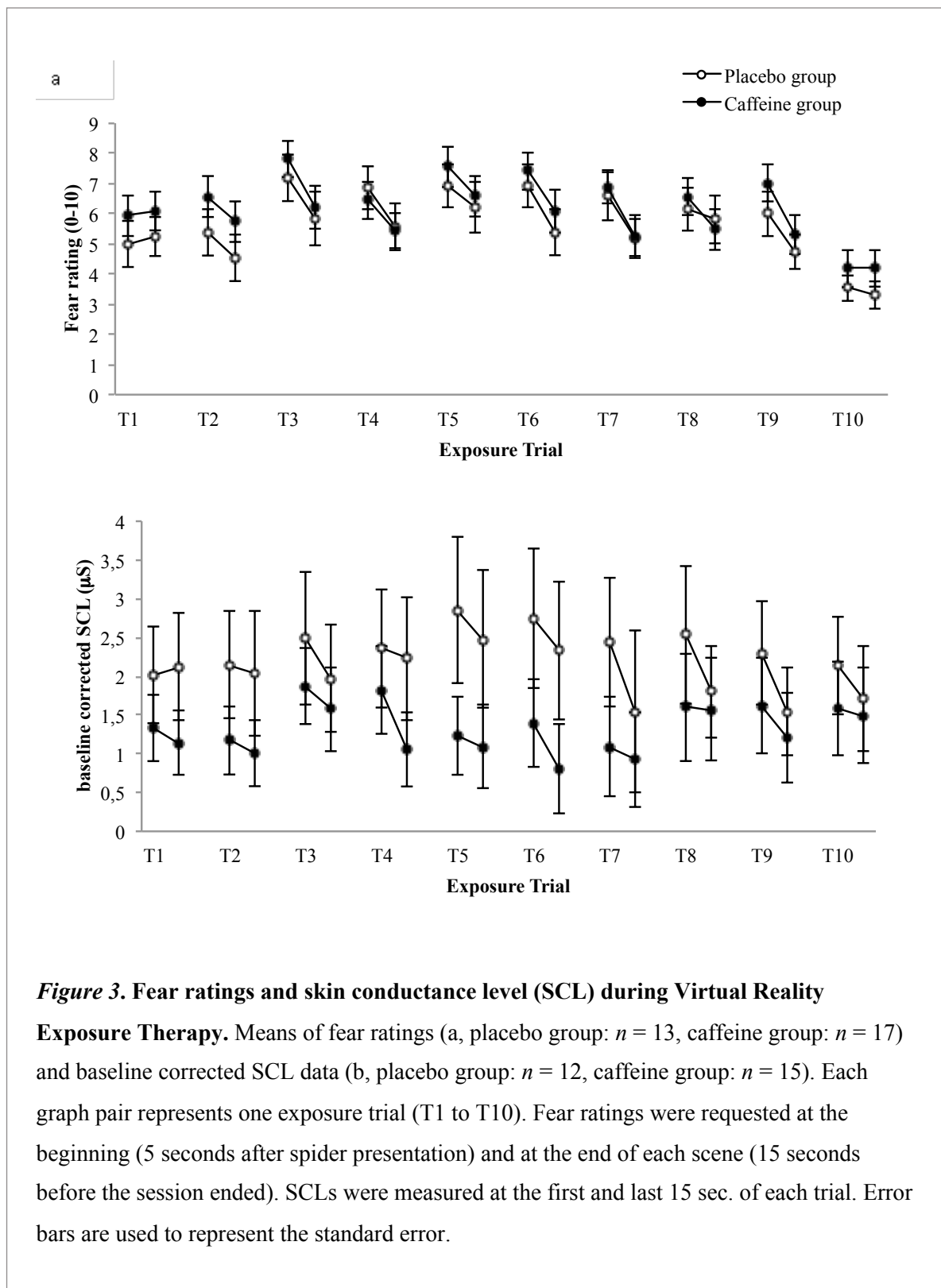


Figure 3

Skin conductance level (SCL)

Due to recording errors, reliable SCL data were not available for four of the participants. Thus, the results regarding the SCL are based on the data of 27 participants (placebo group: $n = 12$; caffeine group: $n = 15$). Figure 3 illustrates that the SCL differs between trials for both groups. For the placebo group, the SCL increased between the first five exposure trials until it decreased again. For the caffeine group, the SCL remained fairly constant during the trials. However, the SCL decreased within the exposure trials for both groups. An ANOVA on the SCL confirmed a significant main effect of time, $F(1, 25) = 24.46$, $p < .001$, $\eta_p^2 = .49$. No further main or interaction effects were found. A follow-up comparison between the first 15 seconds of the first trial and the last 15 seconds of the last trial did not detect a habituation effect, $p > .05$.

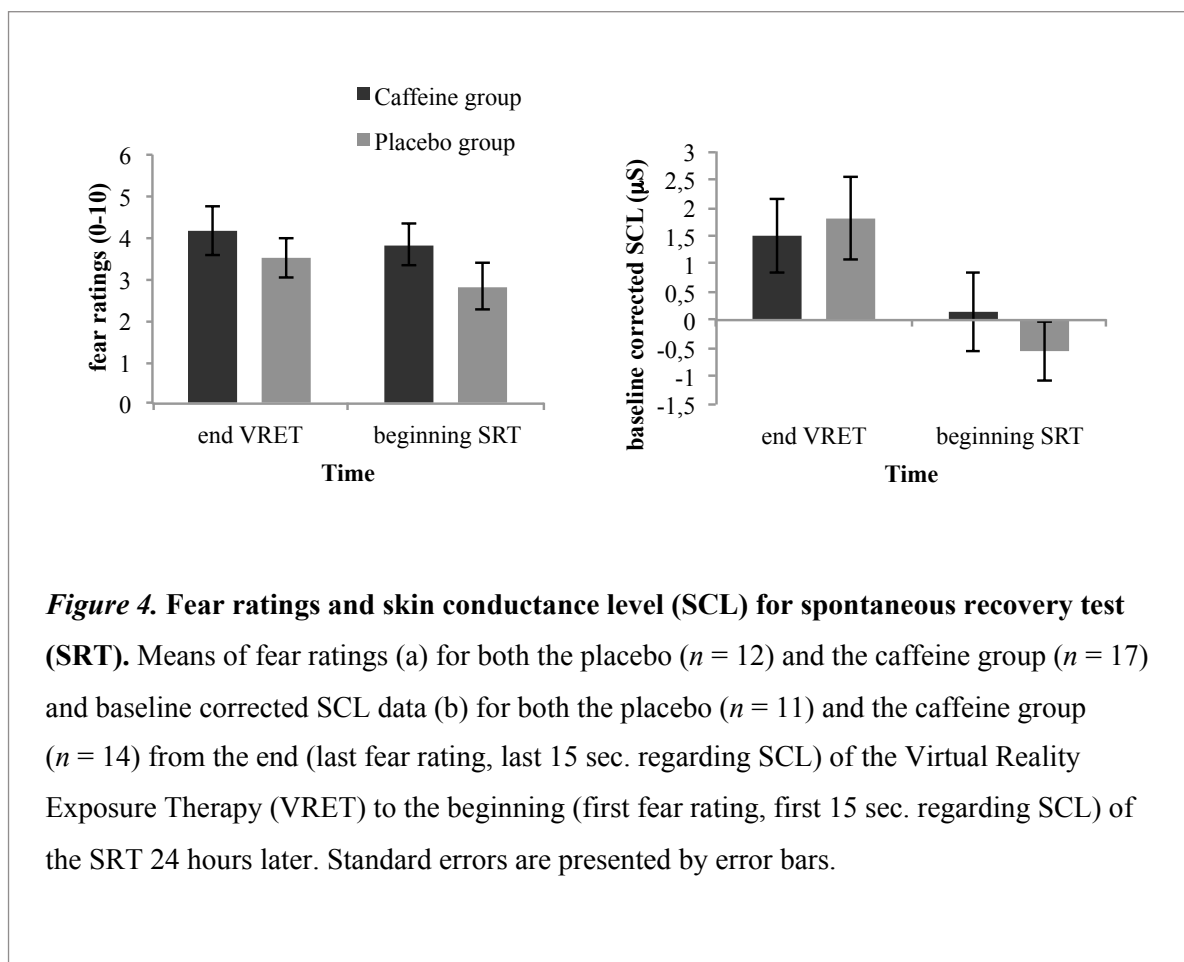
Spontaneous Recovery

Figure 4

Fear ratings

The results regarding the fear ratings are based on the data of 29 participants (placebo group: $n = 12$; caffeine group: $n = 17$). As Figure 4 depicts, there was no return of fear when comparing the last rating of the last exposure trial on day 2 (T10) to the first rating of the SRT (day 3). Fear did not recover for both groups. An ANOVA on the fear ratings showed no significant main or interaction effects, $ps > .05$.

Skin conductance level (SCL)

Due to recording errors, reliable SCL data were not available for four of the participants. Thus, the results regarding the SCL are based on the data of 25 participants (placebo group: $n = 11$; caffeine group: $n = 14$). The SCL decreased in both groups within the 24 hours from the end of the VRET until the beginning of the SRT (Figure 4), as indicated by an ANOVA that showed only a significant main effect of time, $F(1, 23) = 13.44$, $p = .001$, $\eta_p^2 = .37$. There was neither a significant main effect of group nor a significant Time \times Group interaction, $ps > .05$.

*Behavioral Avoidance Test (BAT)****Fear development during Behavioral Avoidance Tests***

	Session 1		Session 3	
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>
Caffeine group	127.50	96.99	46.88	71.25
Placebo group	106.92	111.23	11.54	41.60

Note. Means and standard deviations of the distance (in cm) between the participant and the live tarantula assessed before treatment (session 1) and after the spontaneous recovery test (session 3) for the caffeine ($n = 16$) and the placebo group ($n = 13$) are given

Table 2

The results regarding the BAT are based on the data of 29 participants (placebo group: $n = 13$; caffeine group: $n = 16$). As seen in Table 2, the distance between the participants and the living spider was much higher before than after the VRET for both groups, which was confirmed by an ANOVA that revealed a main effect of time, $F(1, 27) = 25.88$, $p < .001$, $\eta_p^2 = .49$. There was neither a significant main effect of group nor a significant Time \times Group interaction, $ps > .05$.

In vivo exposure session

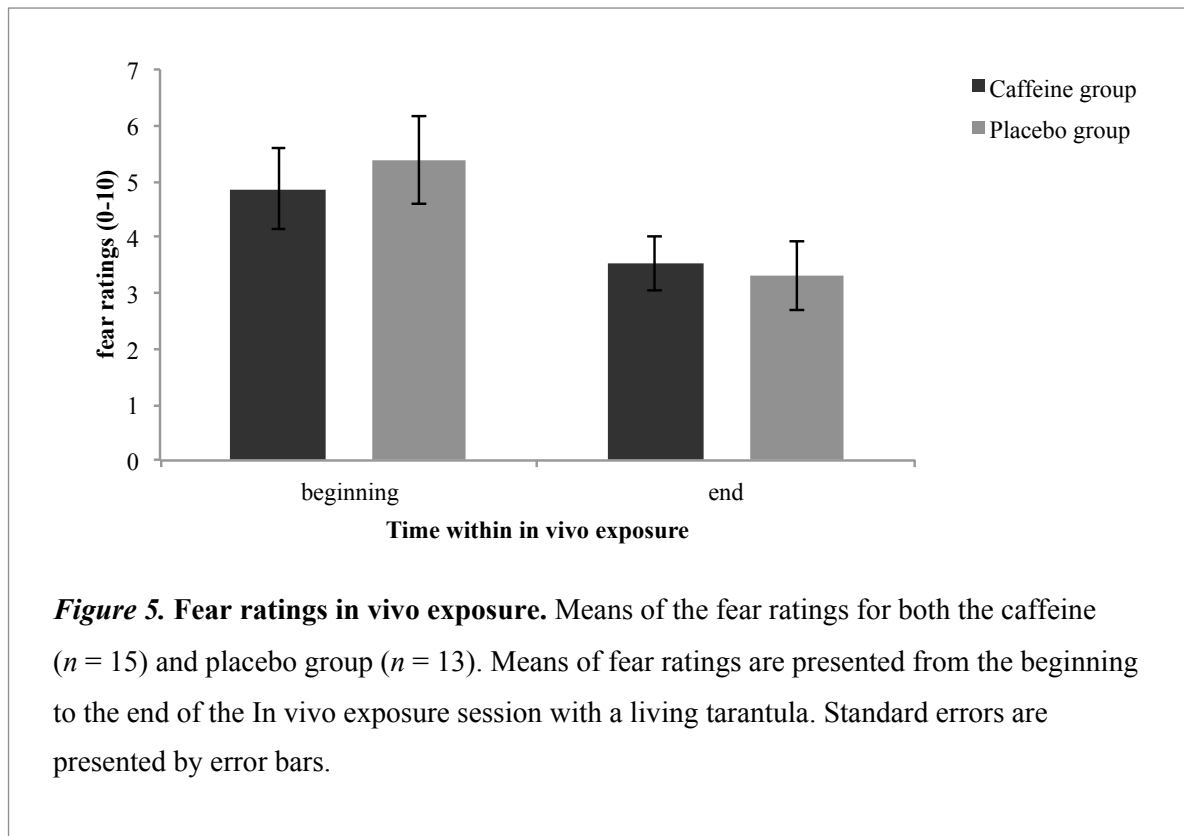


Figure 5

Fear ratings

The results regarding the fear ratings for the in vivo exposure are based on the data of 28 participants (placebo group: $n = 13$; caffeine group: $n = 15$). Fear ratings decreased considerably from the first to the last rating, as indicated by an ANOVA that confirmed only a significant main effect of time, $F(1, 26) = 9.65$, $p = .005$, $\eta_p^2 = .27$ (Figure 5). There was neither a significant main effect of group nor a significant Time \times Group interaction, $ps > .05$. The session lasted on average 25.18 minutes ($SD = 10.84$) and the groups did not show any differences in duration ($p > .05$).

Three Month Follow-Up

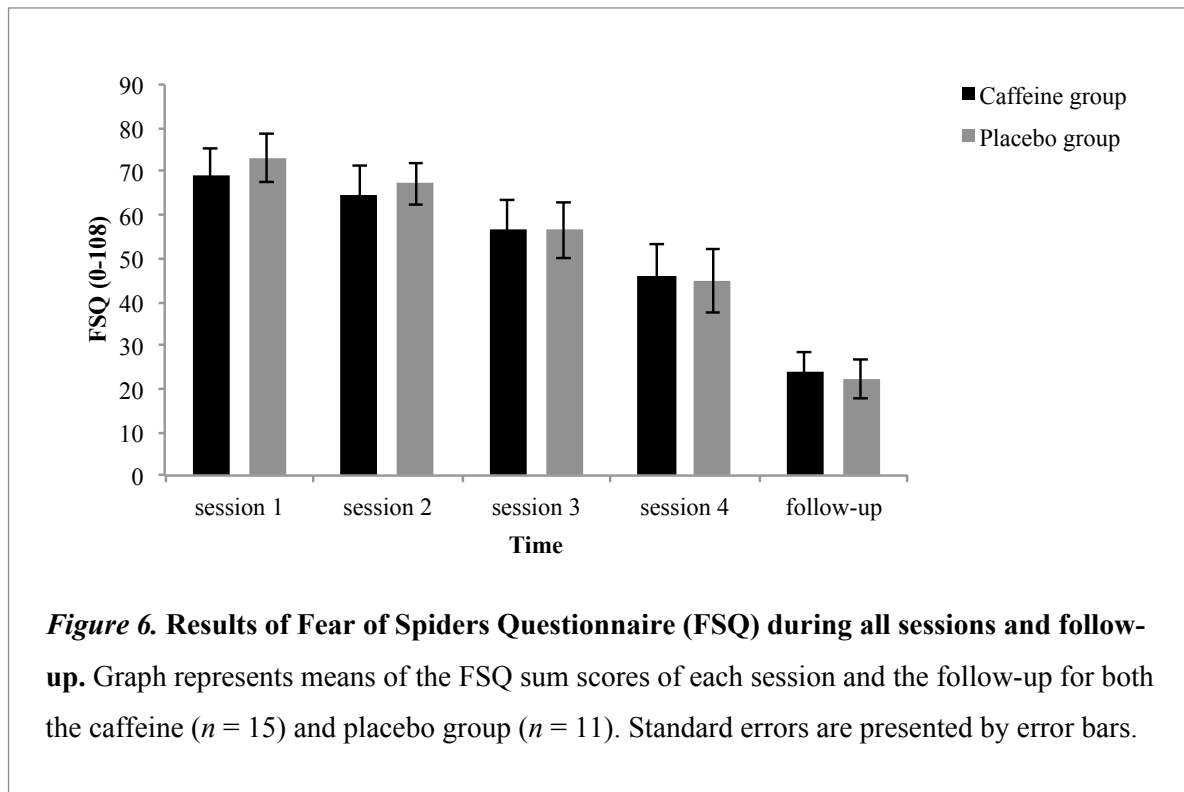


Figure 6

Fear ratings

The results regarding these fear ratings are based on the data of 26 participants (placebo group: $n = 11$; caffeine group: $n = 15$). Figure 6 depicts that both groups experienced a significant decrease in their fear of spiders, as assessed with the FSQ. An ANOVA revealed a significant main effect of time, $F(2.72, 65.36) = 44.64, p < .001, \eta_p^2 = .65$. There was neither a significant main effect of group nor a significant Time \times Group interaction, $ps > .05$.

There were low levels of self-reported avoidance in both groups at the follow up (caffeine group: $n = 15, M = 3.27, SD = 2.43$; placebo group: $n = 12, M = 3.00, SD = 2.22$), but groups did not differ ($p = .77$).

Discussion

The aim of this study was to evaluate the impact of caffeine administration pre-treatment on the effects of exposure in anxiety disorders. For this purpose, we assigned spider-phobic participants to either a caffeine or a placebo group and administered a combined VR and in vivo

treatment. Participants in both groups benefitted immensely from the treatment. Fear of spiders was effectively attenuated up to three months post-treatment. Importantly and in contrast to our hypothesis, caffeine did not lead to an increased treatment effect in the caffeine group when compared to the placebo group.

During the *VRET*, the caffeine group showed marginally higher fear ratings than the placebo group. The fear ratings decreased within and between exposure trials, but did not differ between groups. The SCL differed marginally for both groups within the *VRET* and decreased within in vivo exposure trials. During the *VRET*, the placebo group demonstrated on average higher SCL than the caffeine group. In the placebo group, the SCL increased during the first five exposure trials until it decreased again. In contrast, in the caffeine group the SCL remained fairly constant during the exposure trials. One possible reason for not detecting a decrease in SCL could be the well-documented high inter-individual differences in fear responses on the physiological level.

For the *SRT*, we observed no return of fear in any of the groups, as determined by the fear ratings and SCL measurements. In the *BAT*, the distance between the participants and the living spider was much smaller in both groups after the *VRET*, indicating less avoidance. Based on these results, we believe that both groups benefitted equally from the *VRET*, and that caffeine did not enhance the treatment effect at the *SRT*.

For the *in vivo exposure session*, fear ratings decreased considerably for both groups from the first rating to the last one. The groups did not show any differences in duration of the in vivo session. Results indicate a relatively quick (about 26 minutes) and strong decrease in fear within the in vivo exposure. All participants touched the box without the lid, touched the spider, or even had it crawling across their hands at the end of this session.

At the *three-month follow-up*, both groups experienced a significant decrease in their fear of spiders (assessed via the *FSQ*). Levels of self-reported avoidance were also low in both groups. As avoidance is an important symptom in the *DSM-IV* criteria for specific phobia, we concluded that participants of both groups demonstrated clinical improvement after treatment, which remained stable up to 3 months after the *VRET*. A combined *VR* and in vivo treatment protocol seems to be effective in treating arachnophobia. However, caffeine administration pre-treatment did not seem to enhance treatment effects in our sample.

According to the *EPT* (Foa & Kozak, 1986), the activation of a fear network as well as the variables of within- and between-session-habituation are essential for a successful exposure therapy. However, in a recent update of the *EPT* by Foa, Huppert, and Cahill (2006) the variance regarding current research on exposure therapy is discussed. Some find positive effects for high fear activation, while others suggest just the opposite. In our study, caffeine was expected to intensify

the fear activation and therefore result in a more immersive exposure experience, but the caffeine group showed only marginally higher fear and no amplified treatment effect compared to the placebo group. One possible reason for this could be the mismatch between expectancy and outcome. Caffeine is supposed to maintain a constant readiness to display fear in response to aversive stimuli over the course of the exposure procedure, instead of initiating a gradual fear reduction, as predicted from a habituation-based model of exposure therapy (Craske, Treanor, Conway, Zbozinek, & Vervliet, 2014). Thus, it hinders the experience of expectancy violation for the patients throughout the course of exposure therapy. Another possible reason for our failure to demonstrate enhanced treatment effects following caffeine administration could be that our participants with a considerable daily caffeine consumption (on average 2-3 cups of coffee per day) were habituated to the effect of caffeine. Thus, expectancy violation could not be maintained during exposure, and no benefits in treatment outcome were observed when the groups were compared.

In a previous study with caffeine, Mystkowski, Mineka, Vernon, and Zinbarg (2003) treated people who suffered from spider phobia in a one-session exposure-based therapy and follow-up one week later. Participants were assigned to one of four groups and received either a placebo (P) or caffeine (C) at the time of treatment and at the follow-up sessions: CC, PP, CP, and PC. Mystkowski et al. (2003) reported that in people with phobias, incongruent drug states (caffeine vs. placebo) during both treatment and follow-up sessions provoked a higher reoccurrence of fear than those with congruent drug states. The authors showed that context similarity could be efficacious, because caffeine as (internal) context in the same context can enhance treatment and test effects. Thus, further research with caffeine focusing on context similarity could yield additional information.

There are several limitations to the current study. First, the sample size might have been too small to identify between-group differences. Second, the study lacks a phobic waiting list-control group. Third, 200 mg of caffeine might not have been enough to elicit anxiety in the phobic participants. Thus, the present study would have benefitted from a preliminary study investigating the effects of different doses of caffeine. Fourth, the caffeine dose administered was 200 mg regardless of the participant's height and weight. Choosing a caffeine concentration according to the participant's body mass index might have been preferable. Fifth, we should have assessed potential influencing factors like sleeping habits, alcohol consumption, height and weight in order to control for differences between the two groups regarding these variables.

In conclusion, a combined VR and in vivo treatment protocol seems to be effective in treating spider phobia. Caffeine administration pre-treatment did not seem to enhance treatment effects. For further research, we suggest using a higher dose of caffeine to evaluate the impact of caffeine administration pre-treatment on effects of exposure treatment in anxiety disorders.

Disclosure Statement

Andreas Mühlberger and Paul Pauli are stakeholder of a commercial company that develops virtual environment research systems. All other authors have no potential conflicts of interest.

Author note

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Annotations

[1] The amount of 200 mg of caffeine equals approximately two to three cups of coffee (Childs et al., 2008).

[2] Sample size of $N = 30$ is based on an expected effect size of 0.25 similar to a study we conducted where we had a slightly stronger effect size of 0.33 in the most relevant parameter (Group x Time interaction in the test phase, see Shiban et al. (2013)).

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