Journal of Traumatic Stress
xxxx 2019, *00,* 1–11

ISTSS International Society for Traumatic Stress Studies

Nocturnal Olfactory Stimulation for Improvement of Sleep Quality in Patients With Posttraumatic Stress Disorder: A Randomized Exploratory Intervention Trial

Laura Schäfer,[1] Julia Schellong,[1] Antje Hähner,[2] Kerstin Weidner,[1] Karl-Bernd Hüttenbrink,[3] Sebastian Trautmann,[4] Thomas Hummel,[2] and Ilona Croy[1]

[1]Department of Psychotherapy and Psychosomatic Medicine, Technische Universität, Dresden, Germany
[2]Smell and Taste Clinic, Department of Otorhinolaryngology, Technische Universität, Dresden, Germany
[3]Department of Otorhinolaryngology, University of Cologne, Germany
[4]Institute of Clinical Psychology and Psychotherapy, Technische Universität, Dresden, Germany

Posttraumatic stress disorder (PTSD) is characterized by sleep impairment and nightmares. As pleasant odors presented during sleep affect the emotional tone of dreams without inducing arousal, we investigated whether sleep patterns in PTSD can be improved via nocturnal olfactory stimulation. Participants were 40 inpatients with PTSD ($n = 35$ women; age range: 20–59 years) who completed a randomized, patient-blind, placebo-controlled trial. Baseline measurement for 5 consecutive nights was followed by a 5-night experimental intervention or placebo trial. During the intervention, patients received nocturnal stimulation with a pleasant odor (odor condition) or clean air (placebo condition) via an olfactometer that delivered inspiration-triggered stimuli in a nasal tube or via an odorized nasal clip. After each night, the patients completed standardized questionnaires that assessed sleep parameters and dream content. Each night, sleep efficiency, sleep onset latency, and wakefulness after sleep onset were monitored with a motion biosensor. Baseline assessment revealed that PTSD severity was associated with poorer sleep outcomes. An interaction effect showed that nocturnal odorization affected dream intensity. Post hoc tests revealed an improvement in the group that used the nasal clip as compared to baseline, $d = 0.68$. No negative effects were observed after odorization with the nasal clip. Considering the limited sample size, the study indicates that nocturnal olfactory stimulation may serve as a low-cost concomitant intervention to improve sleep quality in PTSD.

The majority of patients with posttraumatic stress disorder (PTSD) complain about troubled sleep (Ohayon & Shapiro, 2000), with distressing dreams reported more frequently by PTSD patients than by patients who suffer from any other psychological disorder (Ross, William, Sullivan, & Caroff, 1989). Sleep disturbances in PTSD correlate with onset, severity, and exacerbation of the disorder, as well as with poorer physical and mental health functioning (Clum, Nishith, & Resick, 2001; Germain, Buysse, Shear, Fayyad, & Austin, 2004).

Psychotherapeutic interventions that focus on PTSD psychopathology alleviate the symptomatology of the disorder (for a review, see Bisson et al., 2007) sleep outcomes often see less improvement (Spoormaker & Montgomery, 2008; Zayfert & De Viva, 2004). Cognitive behavioral approaches that target PTSD-related sleep problems, such as imagery rehearsal treatment (IRT), are effective (e.g., Krakow et al., 2001) but effortful. Research has mostly focused on subjective sleep measurements and specific populations, such as veterans (for a review, see Ho, Chan, & Tang, 2016). Controlled studies that consider relaxation and exposure approaches are still missing (Spoormaker & Montgomery, 2008), although integrative interventions exist (Davis & Wright, 2005). Additionally, pharmacological treatment does not reliably ease troubled sleep (for a review, see Nappi, Drummond, & Hall, 2012). Therefore, alternative approaches should be considered.

Olfaction is involved in various features of mental health. It serves as a well-suited paradigm for investigating emotion and memory, especially in the context of PTSD (for a review, see Daniels & Vermetten, 2016). Psychological interventions that use olfactory stimulation may serve as a fruitful approach to influence sleep parameters for reasons. First, olfactory stimulation evokes cortical activation in the sleeper (Stuck, Weitz, Hörmann, Maurer, & Hummel, 2006), but, even at a high concentration, does not lead to sleep arousal (Stuck et al., 2007). Hence, olfactory stimulation may affect sleep without waking

This research was kindly supported by aspiraclip GmbH (Berlin, Germany), which sponsored the nasal clips used in the study.

Correspondence concerning this article should be addressed to Laura Schäfer, Department of Psychotherapy and Psychosomatic Medicine, Technical University, Dresden, Fetscherstr.74, 01307 Dresden, Germany. E-mail: laura.donner@uniklinikum-dresden.de

DOI: 10.1002/jts.22359

the sleeper. Second, in healthy individuals, nocturnal olfactory stimulation leads to better sleep quality and a higher level of vigor in the morning (Goel, Kim, & Lao 2005; Goel & Lao, 2006). Third, research has revealed associations between olfactory stimulation and dream processing, which are dependent on the hedonic quality of the stimuli (Schredl et al., 2009). After receiving pleasant olfactory stimuli (phenyl ethyl alcohol [PEA], which smells of roses), participants reported a more positive emotional tone of dreams, whereas unpleasant olfactory stimuli (hydrogen sulphide, which smells of rotten eggs) were associated with more negative dream emotions (Schredl et al., 2009). As this may be a fruitful approach to alleviate distress due to negatively toned dreams, the authors recommended continuing research on burdened patient groups (Schredl et al., 2009).

In summary, nocturnal olfactory stimulation has the potential to manipulate the emotional tone of dreams without waking the sleeper. The neural base for this effect is grounded in the specific anatomy of the olfactory system. Olfaction is one of the evolutionarily oldest senses, and emotion processing brain structures have emerged out of structures that were originally devoted to olfactory processing (Rowe, Mactrini, & Lui, 2011). The primary olfactory cortex consists of a strongly interlinked fiber network that contains the amygdala (Gottfried, 2006) and hippocampus, which are related to emotional functioning (Janak & Tye, 2015) and several psychopathologies, such as PTSD (Shin, Rauch, & Pitman, 2006). It is therefore not surprising that psychological disorders, such as depression or PTSD, are related to changes in olfactory perception (Croy & Hummel, 2017; Croy et al., 2010). In one study, nocturnal olfactory stimulation was applied in patients with depressive disorder; this did not lead to clear effects on sleep but rather to a positive trend toward an improved feeling of recovery and dream quality (Vitinius et al., 2014). In the current study, we explored the influence of nocturnal pleasant olfactory stimulation on objective and subjective sleep parameters in patients with PTSD. The aims of this study were to (a) replicate the negative association between the severity of psychopathology and sleep variables, (b) examine whether nocturnal olfactory stimulation would lead to improvements in sleep and dream outcomes, and (c) test whether the effect of a nasal clip would be superior compared to a computer-controlled olfactometer.

Method

Participants

The total sample consisted of 54 patients with PTSD ($n = 46$ women, M age = 41.45 years, SD = 9.06, age range 20–59 years;) who were recruited between January 2016 and September 2017 at a particular ward at the Department of Psychotherapy and Psychosomatic Medicine, University Hospital Dresden, Germany. This ward specializes in the treatment of complex PTSD and provides a professional multimodal treatment, including single and group psychotherapeutic sessions, art and movement therapy, and relaxation and imagination programs. Neither sleep nor dream content are systematically targeted in any of these modules, but they might be addressed in individual therapeutic sessions, depending on the needs of the patient. Patients stay in shared rooms of two to three people. In our sample, the average duration of stay lasted 9 weeks ($M = 8.90$ weeks, $SD = 2.09$), and participants were assessed during Weeks 1 and 8 (M = Week 3.02, $SD = 2.20$) of their treatment.

At baseline, criteria for the diagnosis of PTSD per the *International Classification of Diseases* (*ICD-10*; World Health Organization, 1993) were initially noted when case history was taken when patients entered the hospital and were later confirmed using the Structured Clinical Interview for *DSM-IV* (SCID-I; Wittchen, Zaudig, & Fydrich, 1997) during the patient's stay. All patients fulfilled the criteria for PTSD (diagnosis code F43.1 in *ICD-10*); index traumas were interpersonal traumas that mostly occurred during childhood. In addition to fulfilling the criteria for PTSD, several patients also met the criteria of other disorders. There were 21 patients who met the *ICD-10* criteria for a depressive disorder (F32–F33), 14 who also suffered from anxiety disorders (F40–F41), 12 who were also diagnosed with dissociative disorders (F44), 12 with personality disorders (F60), 7 with substance abuse (F10–F19), 5 with somatoform disorders (F45), and 4 with eating disorders (F50). The majority of patients were on medication; psychopharmacological medication was prescribed as follows: Tricyclic antidepressants, which were taken by 8 patients (14.8%), and selective serotonin reuptake inhibitors (SSRIs) and neuroleptics, each of which were taken by 20 patients (37.0%).

Olfactory impairment (anosmia or hyposmia) served as the exclusion criterion and was tested with subjective olfactometry using the Sniffin' Sticks Step II (Burghart, Wedel, Germany) prior to study enrollment. This standardized and well-established procedure assesses an individual's olfactory threshold, odor discrimination, and odor identification ability (TDI) in a forced multiple-choice paradigm (Hummel, Sekinger, Wolf, Pauli, & Kobal, 1997; Hummel, Kobal, Gudziol, & Mackay-Sim, 2007). Patients with a TDI score below the normative score for their age were deemed ineligible for the study. Hence, all participants were normosmic (Sniffin' Sticks Score TDI, $M = 35.73$, $SD = 2.91$). Further exclusion criteria were active and chronic rhinitis with or without polyps, symptomatic acute and chronic upper airway disease, previous head trauma, neurodegenerative disorders, malignant tumors, or previous chemo-radiation (Hummel, Landis, & Rombaux, 2017).

Of the 54 patients who enrolled in the study, 40 patients (M age = 41.69 years, $SD = 9.12$, age range: 24–59 years) completed the trial and were included in statistical analysis of intervention effects (for further details, see Figure 1). Patients in the placebo and odor groups did not differ in terms of age and sex distribution, $t(38) = -1.26$, $p = .215$ for age and $p = .287$ for sex (see Supplementary Tables 1 and 2). Neither age, $t(38) = 0.89$, $p = .381$; nor sex, $p = .294$ (see Supplementary

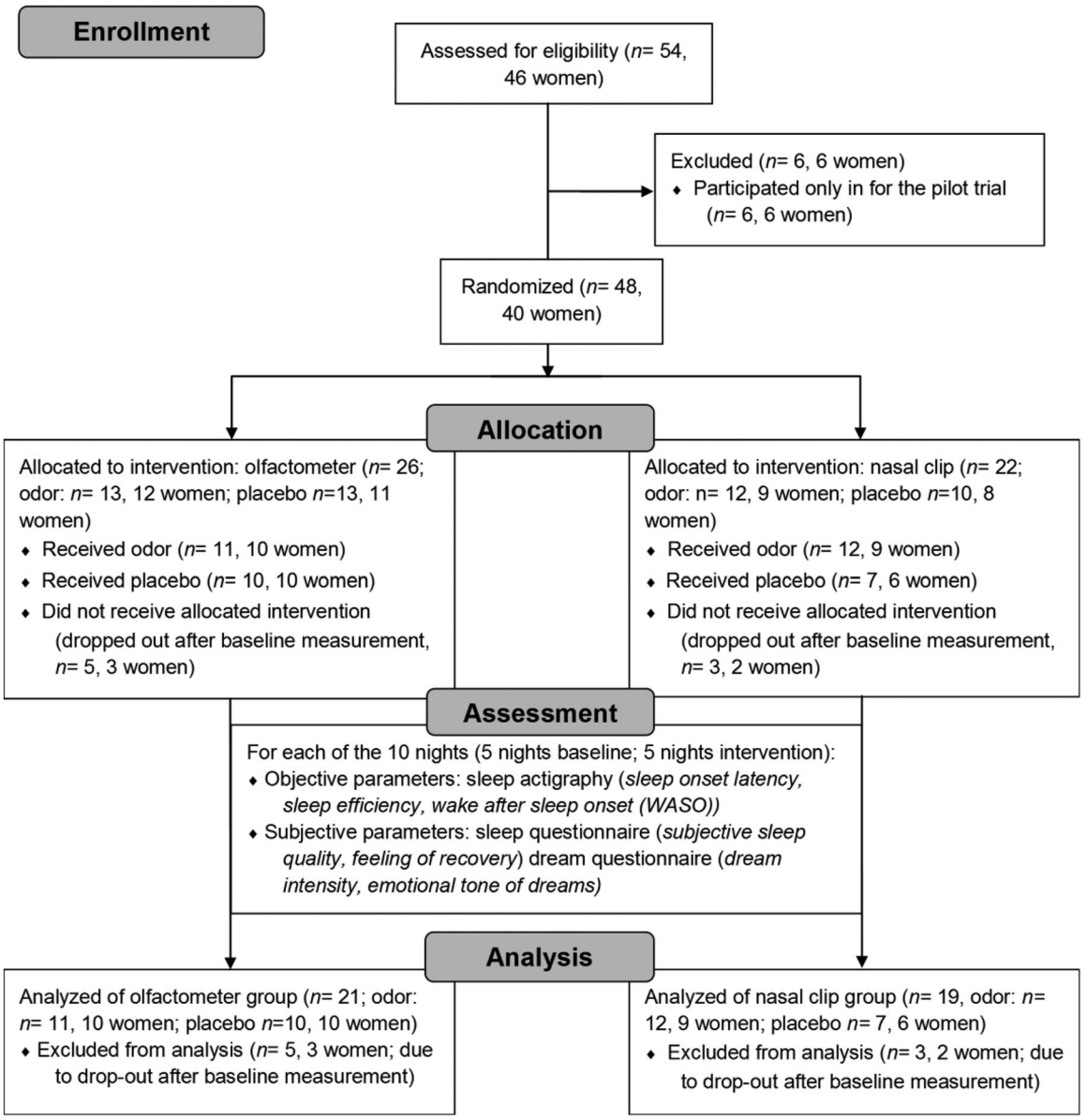

Figure 1. CONSORT 2010 flow diagram of participants in the randomized controlled intervention trial of nocturnal olfactory stimulation, including assessment parameters.

Tables 1 and 2), differences were found between groups in terms of application type. No differences for other sample characteristics were observed, except for SSRI usage and personality disorders—in the placebo group, more participants took SSRIs, $p = .036$, and had been diagnosed with personality disorders, $p = .014$, compared to participants in the odor group (see supplementary Table 2).

Procedure

The study was designed as an exploratory, two-condition, placebo-controlled patient-blind trial. Baseline measurement included 5 consecutive nights. After this was complete, half of the patients were randomly assigned to an intervention condition and the other half to a placebo condition, each for 5 more consecutive nights (see Figure 1). Randomization of participants to odor or placebo condition was restricted by simultaneous assessment of two patients per time. In order to prevent carryover effects and to minimize the risk that patients would discover they were undergoing placebo treatment, we randomized the dyads of patients who were tested at the same time but ensured that simultaneously tested subjects were always in the same condition. Allocation to odor or placebo condition was carried out by the examiner for each dyad of patients, depending on a computer-generated list of a random numbers. Patients were informed about the study via announcements, and all eligible patients were asked individually if they wanted to participate. Before enrollment, the general procedure and requirements were explained, and written informed

Table 1
Mean Values and Standard Deviations of Outcome Variables for Application Type (Olfactometer or Nasal Clip) and Group (Placebo or Odor) for Each Baseline and Intervention Condition

	Baseline								Intervention							
	Placebo				Odor				Placebo				Odor			
	Olfactometer		Nasal Clip		Olfactometer		Nasal Clip		Olfactometer		Nasal Clip		Olfactometer		Nasal Clip	
Parameter	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
Dream intensity[a]	3.46	0.84	3.50	1.05	3.63	0.90	3.99	0.71	3.61	0.81	4.40	0.50	3.75	0.82	3.46	0.61
Emotional tone of dreams[a]	2.38	0.77	2.32	0.91	2.07	0.57	1.83	0.37	2.51	0.80	1.70	0.96	2.28	0.67	2.11	0.46
Subjective sleep quality[b]	2.95	0.64	2.59	0.77	2.60	0.97	2.74	0.52	3.14	0.67	2.67	0.97	2.98	0.78	2.96	0.61
Feeling of recovery[b]	2.27	0.47	2.04	0.79	2.22	0.97	2.03	0.51	2.34	0.68	2.05	0.88	2.15	0.65	2.28	0.53
Sleep onset latency (min)	35.41	17.34	23.08	9.34	34.71	31.71	40.14	22.06	32.85	15.49	40.62	18.35	33.46	24.50	31.31	21.44
Sleep efficiency (%)	84.32	6.47	84.61	6.66	83.19	7.30	81.74	6.61	84.17	3.81	83.45	3.39	83.29	7.99	84.19	5.58
Wake after sleep onset (min)	32.26	14.49	24.67	6.94	34.69	10.02	31.27	11.05	41.72	23.96	29.04	11.14	36.68	8.96	33.84	18.03

Note. $N = 40$. For baseline comparisons, no significant differences were observed, except for the variable "emotional tone of dreams," on which the placebo group ($n = 19$) reported higher scores than odor group ($n = 21$), $U = 84.53$, $p = .029$.
[a]The scales "dream intensity" (higher scores indicate higher emotional intensity of dreams) and "emotional tone of dreams" (higher scores reflect a more positive emotional tone) are rated on a 5-point Likert scale. [b]The scales "subjective sleep quality" and "feeling of recovery" are general sleep factors summing up several items, with higher numbers indicating a better sleep quality, ranging from 1–5.

consent was obtained. A standardized interview was performed to check inclusion and exclusion criteria and, subsequently, normosmia was assessed using the Sniffin' Sticks as described earlier. Patients were then asked how pleasant (on a scale of –5 to +5) they perceived the smell of four different odors, which were available for nocturnal odorization, and asked to identify the odors. For each participant in the odor group, the most pleasantly rated odor was chosen for stimulation during sleep.

The baseline measurement was always performed during a weekday (i.e., Monday–Friday) during which objective sleep data were recorded by a biomotion tracker (Actiwatch 2 devices; Philips Respironics, Herrsching, Germany). Patients were asked to wear the device on their nondominant wrist during the whole trial (day- and nighttime). Participants had to complete a recording protocol and note the duration of time they did not wear the device (if they took it off) as well as the times they went to bed and got up. General sleeping time for inpatients was from 11 p.m. to 6.30 a.m. After each night, within 15 min of awakening, the patients completed the Sleep Questionnaire A (SF-A; Görtelmeyer, 2011) and the Mannheim Dream Questionnaire (MADRE; Schredl, Berres, Klingauf, Schellhaas, & Göritz, 2014) for subjective evaluation of sleep. The intervention phase then took place for 5 more consecutive nights, again from Monday to Friday. Irrespective of the condition, participants were instructed that they may smell a light odor during the night. Objective sleep data were again recorded by the Actiwatch 2 device, and subjective sleep was reported on the SF-A MADRE each morning within 15 min of awakening. In addition, participants were asked if they smelled an odor during the night.

Odor choice was based on the patients' ratings. Four different odors were preselected: PEA (which smells of rose), lavender, orange, and peach (Frey + Lau GmbH; Henstedt-Ulzburg, Germany). Evidence has suggested that rose and peach are perceived as pleasant (Croy, Maboshe, & Hummel, 2013), and lavender (Lehrner, Marwinski, Lehr, Johren, & Deecke, 2005), orange (Lehrner, Eckersberger, Walla, Pötsch, & Decke, 2000; Lehrner et al., 2005), and rose (i.e., PEA; de Almeida, Motta, de Brito Faturi, Catallani, & Leite, 2004) have been reported to be associated with anxiolytic effects. As subjective hedonic evaluation differs strongly between humans (Keller, Zhuang, Chi, Vosshall, & Matsunami, 2007), it was important to select the most pleasant odor for each participant individually. Participants rated the individual pleasantness on a visual analog scale (−5 to +5) and, based on this rating, the most pleasant odor was chosen. The majority of participants preferred orange (43.8%), followed by peach (31.2%), rose (18.7%), and lavender (6.3%). The limited number of men in the sample made gender comparisons difficult, but it is interesting to note that all male participants chose orange as their favored odorant.

During the intervention, the odor (or placebo) was initially delivered by an inspiration-triggered olfactometer. After patients made several complaints about this device, we changed

the odor (or placebo) stimulation for the second half of the patients to a lightweight and noninvasive nasal clip (aspiraclip; aspiraclip GmbH, Berlin, Germany). Both devices were new for application during the night—the olfactometer had been used in one study (Vitinius et al., 2014) and the nasal clip had not been evaluated thus far.

The olfactometer is a device that produces inspiration-triggered air puffs every 30 s for 6 hr (for a detailed explanation, see Vitinius et al., 2014). An oxygen tube connected the patients' nostrils to the machine and a piece of cotton wool that contained the odor (0.25 ml, without odor for the placebo group) was placed in the connection piece between the tube and device. The odorant device was turned on by nursing staff at 11 p.m. and turned off 1 hr before patients awoke in the morning (i.e., 5 a.m.). The advantage of this device is that it minimizes olfactory adaptation by presentation of inspiration-triggered olfactory stimulation in intervals. Information about feasibility and tolerance of the treatment is still insufficient (Vitinius et al., 2014), and more data are required to prove its usefulness in clinical settings. The nasal clip is a light and small (3 mm inner diameter × 10 mm total size) half-ring made out of medical silicone, with two pieces of cotton wool containing the odor (0.25 ml, without odor for the placebo group). Participants placed the nasal clip themselves about 1 cm into the nasal cleft before they went to sleep; each patient practiced the application before measurement began. Although the nasal clip does not hinder adaption, it was applied as an alternative method, as our experiences with the olfactometer showed that six patients complained about the device as a potential source of nocturnal noise and some felt uncomfortable sleeping with the nasal tube. Therefore, the nasal clip seemed to be a less invasive and more practical approach.

Because PTSD can alter olfactory perception, the implementation of pleasant odors in therapeutic treatment to promote relaxation can be challenging (Croy et al., 2010); thus, it is especially important to ensure individual pleasantness. We aimed to do this by presenting a rather weak stimulation of 0.25 ml of the odor. In the placebo condition, the very same devices and procedures were used, but the devices were not filled with odor. The patients may therefore have been aware whether they were in the placebo or odor group. We tried to minimize this risk by (a) telling the patients that the odors were low-concentrated, in order to distract individuals in the placebo group; and (b) never simultaneously testing patients from the same ward who were in different groups. In line with this aim, 32.9% of participants in the placebo group stated that they smelled an odor. However, in total, participants in the placebo group reported smelling significantly fewer odors during the night than those in the odor group, $U = 254.52$; placebo group, $n = 19$, odor group, $n = 21$, $p = .005$.

The ethics committee of the University of Dresden (Code: EK 104032015) approved the conduction of the study in accordance with the World Medical Association´s Declaration of Helsinki. Written informed consent was obtained from all participants.

Measures

PTSD and depression. For assessment of PTSD symptom severity, patients completed the PTSD Checklist for *DSM-5* (PCL-5; Weathers et al., 2013), with an average score of 49 ($M = 48.70$, $SD = 14.47$), which is higher than the cutoff of 33 that indicates clinically meaningful symptom severity (for a detailed overview, see supplementary Table 1). Depressive symptomatology was measured using the German version of the Beck Depression Inventory–II (BDI-II; Hautzinger, Keller, & Kühner, 2006), on which the average score was in the range of severe depression (cutoff of greater than 29; $M = 30.74$, $SD = 11.90$; for a detailed overview, see supplementary Table 1).

Sleep actigraphy. The Actiwatch 2 device records reliable and valid measurements of sleep, such as sleep onset latency, sleep efficiency, wake after sleep onset (WASO), and frequency of awakenings (Alsaadi et al., 2014; Kawada, 2015; Lauderdale et al., 2014). According to the device's manual, sleep onset latency depicts the number of minutes between the start of the rest interval and the first epoch of scored sleep. Sleep efficiency reflects the proportion of sleep relative to rest time (i.e., sleep time divided by the number of minutes in the rest interval) and is given as a percentage. The WASO measure is the number of minutes of wake detected by the Actiware software after the participant has initially fallen asleep (Philips Healthcare, 2009). As WASO and frequency of awakenings were strongly correlated, $r = .65$, $p < .001$, frequency of awakenings was excluded in the analysis in order to reduce the number of tested variables.

Sleep questionnaire. Although there are specific instruments available for measuring subjective sleep quality related to PTSD (e.g., Germain, Hall, Krakow, Shear, & Buysse, 2005), we decided to use the SF-A (Görtelmeyer, 2011) to get results comparable to those reported in previous studies (Vitinius et al., 2014). The SF-A contains 25 items about sleep behavior and sleep experience of the previous night, which respondents rate on Likert scales of different formats. The items are summarized into general sleep factors. We focused on the following sleep factor scales: Subjective Sleep Quality and Feeling of Recovery After Sleep. Higher numbers indicate better sleep quality, with a range from 1 to 5. These scales serve as reliable measurements of self-reported sleep quality, with demonstrated Cronbach's alpha values of .89 for Subjective Sleep Quality and .91 for Feeling of Recovery (Görtelmeyer, 2011). The subscale Psychosomatic Symptoms During Sleep has been shown to have insufficient internal consistency (Görtelmeyer, 2011) and was therefore excluded from analysis. We did not analyze the subscales that reflect daily mood states before sleep onset so as to focus on direct sleep outcomes.

Dream questionnaire. Dream quality was assessed with an adapted version of MADRE (Schredl et al., 2014). Previous

evaluation of the questionnaire has shown acceptable test–retest reliability for the scales, rs = .59–.79 (Schredl et al., 2014); Cronbach's alpha values were not reported. The first seven questions of the original questionnaire were modified in order to refer to the previous night. The other questions deal with certain dream characteristics, such as lucid, creative, or childhood dreaming, and were therefore left out as this was not the focus of our research, and we were aiming to minimize the time it would take for participants to complete the daily questionnaires. For the analysis, we focused on the two questions about general dream experience: dream intensity (higher scores indicate higher emotional intensity of dreams) and emotional tone of dreams (higher scores reflect a more positive emotional tone), both of which are rated on a 5-point Likert scale. The other questions focus on dream remembrance and nightmare experience and were not analyzed. The nightmare experience questions were excluded from the analysis as the events were too seldom reported to give a secure base for analysis (44.9% of patients reported nightmares at baseline and 36.3% reported nightmares during the intervention stage).

Data Analysis

A power analysis conducted with G*power (Version 3.1.9.2; Faul, Erdfelder, Lang, & Buchner, 2007) for a repeated measurement analysis of variance (ANOVA) with two within-subject factors and two groups revealed that a sample size of 34 (17 per group) would be sufficient to detect effects with at least medium effect size ($f = 0.25$) at an alpha level of .05 and a power of 1-beta = 0.8 with an assumed intercorrelation of 0.5 between measurements. In order to allow exploratory analysis of the effect of different odor application forms, we continued study enrollment until we had 40 participants.

Baseline. In order to assess associations between sleep parameters and PTSD symptom severity, correlation coefficients were calculated based on the mean values of the respective baseline scores (i.e., mean value of the 5 days of measurement). The same analysis was used to test the coherence between sleep actigraphy as an objective measurement and questionnaire ratings. The parameters of dream intensity, emotional tone of dreams, sleep onset latency, and sleep efficiency were not normally distributed; they were tested by visual inspection and confirmed with Kolmogorov–Smirnov–Analysis, $p < .05$. For the purpose of consistency, Spearman´s correlation coefficients were used for all analyses (significance level of $p < .05$; for details, see Supplementary Table 3).

Intervention. In order to test whether the groups (placebo vs. odor, and olfactometer vs. nasal clip) differed beforehand in predictor and outcome variables, t tests, Mann–Whitney tests, and likelihood ratios were calculated (see Supplementary Tables 1 and 2). No significant differences were found except for emotional tone of dreams—the placebo group ($n = 19$) reported higher emotional tone of dreams than the odor group ($n = 21$) in baseline condition, $U = 84.53$, $p = .029$. A generalized linear mixed (GLM) model was used to test the effect of the intervention. Therefore, each participant who had completed the intervention ($n = 40$) served as an individual, each day (5 consecutive nights), and time (baseline vs. intervention) served as repeated measurement.

Case-wise deletion was used in order to handle missing data. For the dream questionnaire, missing values of 1.8% in baseline and 3.3% in the intervention condition were observed. For the sleep questionnaire, 0.8% missing values were reported for each (baseline and intervention) condition. The sleep actigraphy measures contained 0.5% missing values in baseline and 1.0% missing values in intervention condition. Robust covariances and Satterwheight approximation were used in order to handle potential violations of the model.

Each of the aforementioned outcome variables (see Figure 1) was used as the target in an individual analysis. In each analysis, the following fixed effects were included: time (baseline vs. intervention), group (placebo vs. odor), and application type (olfactometer vs. nasal clip). The Time x Group interaction and the Time x Group x Application Type interaction were modeled. Post hoc t tests were performed as pairwise comparisons in order to specifically test the effect of placebo versus odor or intervention versus baseline. Effect sizes of post hoc tests were calculated using Cohen's d. Due to the exploratory character of the study, we did not adjust for multiple testing. This approach minimizes the risk of Type II error (false negative) on the cost of maximizing Type I error (false positive).

Results

Baseline Assessment: Sleep Characteristics in Patients With PTSD

Significant associations emerged between psychopathological symptom severity and sleep (see Supplementary Figure 1). For the dream questionnaire, the emotional tone of dreams was negatively associated with PTSD symptoms, $r = -.46$, $p = .005$. Intensity of dreams was not associated with the psychopathology score. For the sleep questionnaire outcomes, PTSD symptoms were negatively associated with subjective sleep quality, $r = -.43$, $p = .007$, and feeling of recovery, $r = -.54$, $p = .001$, which indicates a lower subjective sleep quality reported by patients with higher symptom severity. For objective sleep quality, no associations between PTSD psychopathology and objective sleep parameters were found. An overview of all correlations is reported in supplementary Table 3.

Baseline Assessment: Association Between Objective and Subjective Sleep Parameters

For WASO, moderate significant associations between sleep actigraphy and questionnaire parameters were found. The objective sleep quality was positively associated with dream

intensity, $r = .35$, $p = .020$, and negatively associated with subjective sleep quality, $r = -.30$, $p = .044$. No other significant associations between objective and subjective sleep parameters were observed.

Effects of Intervention

Figure 2 depicts changes between baseline and intervention across groups and application types, plotted by each individual assessment. In addition, the mean and standard deviation values for all outcome variables for each factor (group, time, and application type) are presented in Table 1 in order to give a detailed overview.

Dream questionnaire. For dream intensity, a Time x Group interaction was found, $F(1, 111) = 7.08$, $p = .009$, which was, however, based on the placebo group that worsened during intervention as compared to baseline, $t(68) = 2.8$, $p = .006$, $d = 0.51$, whereas the odor group remained constant. Nevertheless, a specific effect of the applicator type was observed: Time x Group x Application, $F(3, 42) = 3.55$, $p = .007$. Post hoc tests revealed that patients who used the nasal clip and received an odor reported less dream intensity in intervention compared to baseline, $t(230) = -2.53$; $p = .012$, $d = 0.68$, whereas patients who used the nasal clip and received placebo treatment reported more dream intensity compared to baseline, $t(55) = 3.25$, $p = .002$, $d = 0.87$. For the emotional tone of dreams, no significant interactions were observed (see the Supplementary Materials for further results).

Sleep questionnaire. For sleep questionnaire outcomes, no significant interactions were found. See the Supplementary Materials for further results.

Sleep actigraphy. For sleep efficiency, a Time x Group interaction was observed, $F(1, 103) = 4.61$, $p = .034$. This effect was based on worsening of sleep efficiency during intervention in the placebo group, $t(301) = -2.26$, $p = .025$, $d = 0.50$), whereas no effect was found in the odor group. No significant three-way interactions were observed (see Supplementary Materials for further results). For sleep onset latency, no significant interactions were observed (see Supplementary Materials for further results). No negative effects toward negative effects were observed after nocturnal odorization.

Discussion

The present study revealed a correlation between PTSD severity and troubled sleep and found a positive effect of nocturnal odorization on dream intensity. Both effects are discussed in the following paragraphs.

In line with what has been reported with other studies (for a review, see Harvey, Jones, & Schmidt, 2003; Pillai & Delahanty, 2012) and our hypothesis, baseline measurement showed that PTSD symptom severity was negatively associated with subjective sleep quality and the feeling of recovery. Higher symptom severity concurred with more negatively toned dreams, which reflects emotional regulation of daytime distress and mood (Nielsen & Carr, 2016; Schredl & Hofmann, 2003).

In contrast, objective sleep parameters were not related to psychopathology. This finding emphasizes the importance of subjective sleep evaluation in PTSD, as this can be affected by subjective misperception of sleep quality, such as an underestimation of sleep quality (Harvey et al., 2003) or subjectively perceived greater amount of wake time compared to sleep time because of a higher frequency of awakenings (e. g., van Liempt, 2012). The baseline associations between objective and subjective sleep parameters support this idea: Subjective sleep outcomes were related only to WASO but not to other objective outcomes, such as sleep efficiency. Nocturnal wake time seemed to affect subjective sleep evaluation irrespective of actual sleep efficiency.

Nocturnal odorization improved negative dream intensity in PTSD. No adverse effect of the odorization was found. As the study was powered to detect medium effects, potential smaller effects were not observable due to the sample size. It would, therefore, be interesting to replicate the present study with a larger sample in order to explore whether odorization might be superior to a placebo group in other outcomes. Our data did not reveal significant results in relation to improved emotional tone of dreams, feeling of recovery, or sleep onset latency (see Supplementary Materials). Given that these results were nonsignificant, they should be confirmed by future research to support the conclusion that the positive effects pleasant odors have on sleep outcomes (e. g., Goel et al., 2005) transfer to patients with PTSD.

These results must be interpreted with caution, as the exploratory character of this study implied several specifics, such as testing two different odor devices, whereas only one had been tested for usability before, as well as a rather liberal report of results that were uncorrected for multiple testing. Another limitation relates to the placebo condition. Expectation effects cannot be excluded as the placebo group reported a significantly lower perception of smell during the night and may therefore have had fewer expectations. Furthermore, therapeutic treatment might have biased the results of the intervention due to reconsolidation processes at night. However, this effect is assumed to have affected the placebo condition to the same extent as the odor condition.

Our main finding of an improvement of dream characteristics is in line with previous results (Schredl et al., 2009) and suggests alleviating effects of pleasant odorization on negative dream tone. As dream intensity correlated highly with the negative emotional tone of dreams, the odorization-dependent reduction of dream intensity is assumed to reflect reduced distress. However, it has to be considered that the dream variables were based on single items, thus limiting interpretability due to unknown reliability and validity.

In line with the results reported by Vitinius et al. (2014), we observed no significant effect regarding increased feelings

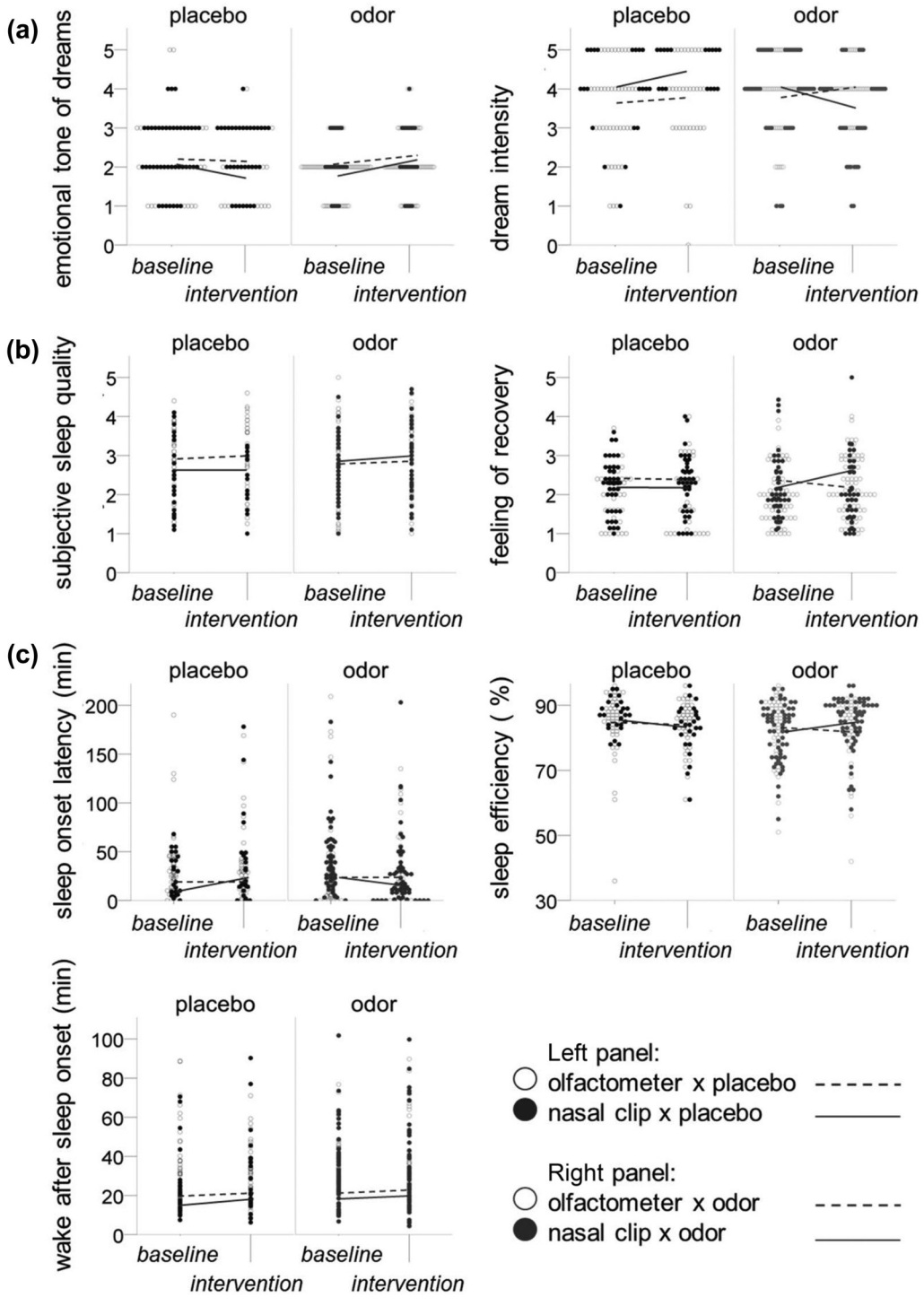

Figure 2. Intervention: Each assessment (each night, each participant) is plotted for each baseline and intervention condition for (A) dream questionnaire, (B) sleep questionnaire, and (C) sleep actigraphy. The respective mean values are connected via line graphs. A significant interaction indicating a positive effect of odorization via the nasal clip was observed for dream intensity.

of recovery after odorization (see Supplementary Materials). Regarding the objective sleep outcomes, no substantial results were found. The lack of significance might have been due to the limited statistical power available and, therefore, should be replicated in a larger sample. If this effect proves to be stable, it could be interpreted in the context of the relaxant effect of odorants. Such an effect has previously been reported for lavender (Goel et al., 2005); however, the majority of our subjects chose

orange as their preferred odor. To the best of our knowledge, thus far, orange has not been investigated for improvement of sleep, but the odor is associated with relaxant effects in the wake state (Lehrner et al., 2000, 2005). Alternatively, shortened sleep onset latency may be based on a distraction effect. Rumination processes in PTSD can be mediated by sleep problems (Borders, Rothman, & McAndrew, 2014) and rumination hinders sleep onset (Zoccola, Dickerson, & Lam, 2009). Thus, an attentional shift from internal rumination processes to the external pleasant olfactory stimulation of the odor might have led to shorter sleep onset duration. This effect may not be specific for the odorization but could reflect a more general effect of distraction by environmental stimulation. We found that, across both the odor and placebo groups, WASO was not affected in the intervention condition. This matches aforementioned results (Stuck et al., 2007) that demonstrated olfactory exposure did not show an arousal effect on sleep.

Regarding objective sleep quality, it has to be noted that actigraphy itself does not replace polysomnographic measures. However, it is a useful device for measuring objective sleep parameters and has applications in clinical studies (e.g., Pati, Kar, Soni, Roy, & Choudhary, 2007). Nevertheless, validation studies are still missing and need to be conducted in future trials.

The comparison between the forms of odor application suggests that the nasal clip is better suited to support positive sleep experience. It was better tolerated, perceived as less distracting, and was superior in terms of sleep outcome. The disadvantage of this method lies in a potential adaption to the odors. To overcome this issue, pulsatile room odorization might also be considered; this application method was not possible in the present study due to the inpatient setting of shared rooms.

Taken together, the present results suggest that patients with PTSD suffering from disturbed sleep may benefit from olfactory intervention. Controlled studies evaluating olfactory intervention effects on sleep outcomes have been scarce thus far (Vitinius et al., 2014; Goel et al., 2005; Goel & Lao, 2006). Therefore, our placebo-controlled patient-blind trial adds to the present understanding of odorization treatment on sleep and may serve as an approach for investigating healthy and patient populations. It is still an open question as to whether the specific odor characteristic itself induces aromatherapeutic effects (pharmacological hypothesis) or whether the odor treatment is effective due to expectation beliefs (psychological hypothesis; for a review, see Herz, 2009). Nevertheless, especially in view of the targeted population of focus in this study, the results seem promising for future trials. Impaired sleep and PTSD are accompanied by long-term adverse correlates, such as heightened mortality or medical care costs (Dew et al., 2003; Marshall, Jorm, Grayson, & Toole, 2000). Sleep problems can predict as well as maintain the disorder (van Liempt, 2012), which is why development of appropriate and economical treatment approaches is required. In sum, our exploratory results suggest that exposure to pleasant odors is a potentially fruitful addition to conventional treatment of sleep disorders in PTSD. It improved negative dream intensity and did not lead to negative side effects in our study. Replication of these results within a larger sample and investigation of long-term implementation effects are warranted.

References

Alsaadi, S. M., Mcauley, J. H., Hush, J. M., Bartlett, D. J., Mckeough, Z. M., Grunstein, R. R., … Maher, C. G. (2014). Assessing sleep disturbance in low back pain: The validity of portable instruments. *PLoS One*, *9*(4), e95824. https://doi.org/0.1371/journal.pone.0095824

Bisson, J. I., Ehlers, A., Matthews, R., Pilling, S., Richards, D., & Turner, S. (2007). Psychological treatments for chronic posttraumatic stress disorder: Systematic review and meta-analysis. *British Journal of Psychiatry*, *190*, 97–104. https://doi.org/10.1192/bjp.bp.106.021402

Borders, A., Rothman, D. J., & McAndrew, L. (2014). Sleep problems may mediate associations between rumination and PTSD and depressive symptoms among OIF/OEF veterans. *Psychological Trauma: Theory, Research, Practice, and Policy*, *7*, 76–84. https://doi.org/10.1037/a0036937

Croy, I., & Hummel, T. (2016). Olfaction as a marker for depression. *Journal of Neurology*, *264*, 631–638. https://doi.org/10.1007/s00415-016-8227-8

Croy, I., Maboshe, W., & Hummel, T. (2013). Habituation effects of pleasant and unpleasant odors. *International Journal of Psychophysiology*, *88*, 104–108. https://doi.org/10.1016/j.ijpsycho.2013.02.005

Croy, I., Schellong, J., Gerber, J., Joraschky, P., Iannilli, E., & Hummel, T. (2010). Women with a history of childhood maltreatment exhibit more activation in association areas following non-traumatic olfactory stimuli: a fMRI study. *PLoS One*, *5*(2), e9362. https://doi.org/10.1371/journal.pone.0009362

Clum, G. A., Nishith, P., & Resick, P. A. (2001). Trauma-related sleep disturbance and self-reported physical health symptoms in treatment-seeking female rape victims. *Journal of Nervous and Mental Disease*, *189*, 618–622.

Daniels, J. K., & Vermetten, E. (2016). Odor-induced recall of emotional memories in PTSD: Review and new paradigm for research. *Experimental Neurology*, *284*, 168–180. https://doi.org/10.1016/j.expneurol.2016.08.001

Davis, J. L., & Wright, D. C. (2005). Case series utilizing exposure, relaxation, and rescripting therapy: Impact on nightmares, sleep quality, and psychological distress. *Behavioral Sleep Medicine*, *3*, 151–157. https://doi.org/10.1207/s15402010bsm0303_3

de Almeida, R. N., Motta, S. C., de Brito Faturi, C., Catallani, B., & Leite, J. R. (2004). Anxiolytic-like effects of rose oil inhalation on the elevated plus-maze test in rats. *Pharmacology Biochemistry and Behavior*, *77*, 361–364. https://doi.org/10.1016/j.pbb.2003.11.004

Dew, M. A., Hoch, C. C., Buysse, D. J., Monk, T. H., Begley, A. E., Houck, P. R., … Reynolds, C. F. (2003). Healthy older adults' sleep predicts all-cause mortality at 4 to 19 years of follow-up. *Psychosomatic Medicine*, *65*, 63–73. https://doi.org/10.1097/01.PSY.0000039756.23250.7C

Faul, F., Erdfelder, E., Lang, A. G., & Buchner, A. (2007). G* Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior research methods*, *39*, 175–191. https://doi.org/10.3758/BF03193146

Germain, A., Buysse, D. J., Shear, M. K., Fayyad, R., & Austin, C. (2004). Clinical correlates of poor sleep quality in posttraumatic stress disorder. *Journal of Traumatic Stress*, *17*, 477–484. https://doi.org/10.1007/s10960-004-5796-6

Germain, A., Hall, M., Krakow, B., Shear, M. K., & Buysse, D. J. (2005). A brief sleep scale for posttraumatic stress disorder: Pittsburgh Sleep Quality Index Addendum for PTSD. *Journal of Anxiety Disorders*, *19*, 233–244. https://doi.org/10.1016/j.janxdis.2004.02.001

Goel, N., Kim, H., & Lao, R. P. (2005). An olfactory stimulus modifies nighttime sleep in young men and women. *Chronobiology International*, *22*, 889–904. https://doi.org/10.1080/07420520500263276

Goel, N., & Lao, R. P. (2006). Sleep changes vary by odor perception in young adults. *Biological Psychology*, *71*, 341–349. https://doi.org/10.1016/j.biopsycho.2005.07.004

Görtelmeyer, R. (2011). *SFA/R und SFB/R Schlaffragebogen A und B. Revidierte Fassung. Handanweisung* [SFA/R and SFB/R Sleep questionnaire A and B. Revised version. Manual]. Göttingen, Germany: Hogrefe.

Gottfried, J. A. (2006). Smell: Central nervous processing. *Advances in Otorhinolaryngology*, *63*, 44–69. https://doi.org/10.1159/000093750

Harvey, A. G., Jones, C., & Schmidt, D. A. (2003). Sleep and posttraumatic stress disorder: A review. *Clinical Psychology Review*, *23*, 377–407. https://doi.org/7358(03)00032-1

Hautzinger, M., Keller, F., & Kühner, C. (2006). *Das Beck Depressionsinventar II. Deutsche Bearbeitung und Handbuch zum BDI II* [Beck Depression Inventory II. German adaptation and manual for the BDI-II]. Frankfurt, Germany: Harcourt Test Services.

Herz, R. S. (2009). Aromatherapy facts and fictions: A scientific analysis of olfactory effects on mood, physiology and behavior. *International Journal of Neuroscience*, *119*, 263–290. https://doi.org/10.1080/00207450802333953

Ho, F. Y., Chan, C. S., & Tang, K. N. (2016). Cognitive behavioral therapy for sleep disturbances in treating posttraumatic stress disorder symptoms: A meta-analysis of randomized controlled trials. *Clinical Psychological Review*, *43*, 90–102. https://doi.org/10.1016/j.cpr.2015.09.005

Hummel, T., Kobal, G., Gudziol, & Mackay-Sim, A. (2007). Normative data for the "Sniffin' Sticks" including tests of odor identification, odor discrimination, and olfactory thresholds: an upgrade based on a group of more than 3,000 subjects. *European Archieves of Otorhinolaryngology*, *264*, 237–243. https://doi.org/10.1007/s00405-006-0173-0

Hummel T., Landis, B. N., & Rombaux, P. (2017). Disrupted odor perception. In A. Buettner, (Ed.), *Handbook of odor* (pp. 653–673). Heidelberg, Germany: Springer.

Hummel, T., Sekinger, B., Wolf, S. R., Pauli, E., & Kobal, G. (1997). "Sniffin' sticks:" Olfactory performance assessed by the combined testing of odor identification, odor discrimination and olfactory threshold. *Chemical Senses*, *22*(1), 39–52. https://doi.org/10.1093/chemse/22.1.39

Janak, P. H., & Tye, K. M. (2015). From circuits to behavior in the amygdala. *Nature*, *517*, 284–292. https://doi.org/10.1038/nature14188

Kawada, T. (2015). Sleep evaluation by actigraphy. *Journals of Gerontology Series B: Psychological Sciences and Social Science*s, *71*, 115–116. https://doi.org/10.1093/geronb/gbu219

Keller, A., Zhuang, H., Qiuyi, C., Vosshall, L. B., & Matsunami, H. (2007). Genetic variation in a human odor receptor alters human olfactory perception. *Nature*, *449*, 468–473. https://doi.org/10.1038/nature06162

Krakow, B., Hollifield, M., Johnston, L., Koss, M., Schrader, R., Warner, T. D., … Cutchen, L. (2001). Imagery rehearsal therapy for chronic nightmares in sexual assault survivors with posttraumatic stress disorder: A randomized controlled trial. *JAMA*, *286*, 537–545. https://doi.org/10.1001/jama.286.5.537

Lauderdale, D. S., Schumm, L. P., Kurina, L. M., Mcclintock, M., Thisted, R. A., Chen, J., & Waite, L. (2014). Assessment of sleep in the National Social Life, Health, and Aging Project. *Journals of Gerontology Series B: Psychological Sciences and Social Sciences*, *69*, 125–133. https://doi.org/10.1093/geronb/gbu092

Lehrner, J., Eckersberger, C., Walla, P., Pötsch, G., & Deecke, L. (2000). Ambient odor of orange in a dental office reduces anxiety and improves mood in female patients. *Physiology and Behavior*, *71*, 83–86. https://doi.org/10.1016/S0031-9384(00)00308-5

Lehrner, J., Marwinski, G., Lehr, S., Johren, P., & Deecke, L. (2005). Ambient odors of orange and lavender reduce anxiety and improve mood in a dental office. *Physiology and Behavior*, *86*, 92–95. https://doi.org/10.1016/j.physbeh.2005.06.031

Marshall, R. P., Jorm, A. F., Grayson, D. A., & O'Toole, B. I. (2000). Medical-care costs associated with posttraumatic stress disorder in Vietnam veterans. *Australian and New Zealand Journal of Psychiatry*, *34*, 954–962. https://doi.org/10.1080/000486700269

Nappi, C. M., Drummond, S. P. A., & Hall, J. M. H. (2012). Neuropharmacology treating nightmares and insomnia in posttraumatic stress disorder: A review of current evidence. *Neuropharmacology*, *62*, 576–585. https://doi.org/10.1016/j.neuropharm.2011.02.029

Nielsen, T., & Carr, M. (2017). Nightmares and nightmare function. In M. H. Kryger, T. Roth, & W. C. Dement (Eds.), *Principles and practice of sleep medicine* (6th ed. pp. 546–554.e5). Philadelphia, PA: Elsevier.

Ohayon, M. M., & Shapiro, C. M. (2000). Sleep disturbances and psychiatric disorders associated with posttraumatic stress disorder in the general population. *Comprehensive Psychiatry*, *41*, 469–478. https://doi.org/10.1053/comp.2000.16568

Pati, A. K., Parganiha, A., Kar, A., Soni, R., Roy, S., & Choudhary, V. (2007). Alterations of the characteristics of the circadian rest-activity rhythm of cancer in-patients. *Chronobiology international*, *24*, 1179–1197. https://doi.org/10.1080/07420520701800868

Pillai, V., & Delahanty, D. L. (2012). Sleep perception among individuals with posttraumatic stress disorder. *Sleep*, *35*, 897–898. https://doi.org/10.5665/sleep.1940

Philips Healthcare. (2009). *Equivalence of activity recordings and derived sleep statistics*. Retrieved from http://www.actigraphy.com/assets/AWDataEquivalenceReport_0309_final-e69f789615144b7e1b8a3b3959e94556fee79f5ec67e2f02edea641c427524c3.pdf

Ross, R. J., William, A. B., Sullivan, K. A., & Caroff, S. N. (1989). Sleep disturbance as the hallmark of posttraumatic stress disorder. *American Journal of Psychiatry*, *146*, 697–707. https://doi.org/10.1176/ajp.146.6.697

Rowe T. B., Macrini, T. E., & Luo, Z. (2011). Fossil evidence on origin of the mammalian brain. *Science*, *332*, 955–957. https://doi.org/10.1126/science.1203117

Schredl, M., Atanasova, D., Hörmann, K., Maurer, J. T., Hummel, T., & Stuck, B. A. (2009). Information processing during sleep: The effect of olfactory stimuli on dream content and dream emotions. *Journal of Sleep Research*, *18*, 285–290. https://doi.org/10.1111/j.1365-2869.2009.00737.x

Schredl, M., Berres, S., Klingauf, A., Schellhaas, S., & Göritz, A. S. (2014). The Mannheim Dream questionnaire (MADRE): Retest reliability, age and gender effects. *International Journal of Dream Research*, *7*, 141–147. https://doi.org/10.11588/ijodr.2014.2.16675

Schredl, M., & Hofmann, F. (2003). Continuity between waking activities and dream activities. *Consciousness and Cognition*, *12*, 298–308. https://doi.org/10.1016/S1053-8100(02)00072-7

Shin, L. M., Rauch, S. L., & Pitman, R. K. (2006). Amygdala, medial prefrontal cortex, and hippocampal function in PTSD. *Annals of the New York Academy of Sciences*, *1071*, 67–79. https://doi.org/10.1196/annals.1364.007

Spoormaker, V. I., & Montgomery, P. (2008). Disturbed sleep in post-traumatic stress disorder: Secondary symptom or core feature*? Sleep Medicine Reviews*, *12*, 169–184. https://doi.org/10.1016/j.smrv.2007.08.008

Stuck, B. A, Stieber, K., Frey, S., Freiburg, C., Hörmann, K., Maurer, J. T., & Hummel, T. (2007). Arousal responses to olfactory or trigeminal

stimulation during sleep. *Sleep*, *30*, 506–510. https://doi.org/10.1093/sleep/30.4.506

Stuck, B. A., Weitz, H., Hörmann, K., Maurer, J. T., & Hummel, T. (2006). Chemosensory event-related potentials during sleep: A pilot study. *Neuroscience Letters*, *406*, 222–226. https://doi.org/10.1016/j.neulet.2006.07.068

van Liempt, S. (2012). *Sleep disturbances and post-traumatic stress disorder; A perpetual circle*? (Doctoral dissertation). University Medical Center Utrecht, Utrecht, the Netherlands.

Vitinius, F., Hellmich, M., Matthies, A., Bornkessel, F., Burghart, H., Albus, C., … Vent, J. (2014). Feasibility of an interval, inspiration-triggered nocturnal odorant application by a novel device: A patient-blinded, randomised crossover, pilot trial on mood and sleep quality of depressed female inpatients. *European Archives of Otorhinolaryngology*, *271*, 2443–2454. https://doi.org/10.1007/s00405-013-2873-6

Weathers, F. W., Litz, B. T., Keane, T. M., Palmieri, P. A., Marx, B. P., & Schnurr, P. P. (2013). *The PTSD Checklist for DSM-5 (PCL-5)*. Retrieved from the National Center for PTSD at http://www.ptsd.va.gov/professional/assessment/adult-sr/ptsd-checklist.asp

Wittchen, H. -U., Zaudig, M., & Fydrich, T. (1997). *SKID Strukturiertes Klinisches Interview für DSM-IV. Achse I und* II [Structured clinical interview for *DSM-IV*. Axis I and II]. Göttingen, Germany: Hogrefe.

World Health Organization. (1992). *International Classification of Disease (10th version)*. Geneva: World Health Organization.

Zayfert, C., & De Viva, J. C. (2004). Residual insomnia following cognitive behavioral therapy for PTSD. *Journal of Traumatic Stress*, *17*, 69–73. https://doi.org/10.1023/B:JOTS.0000014679.31799.e7

Zoccola, P. M., Dickerson, S. S., & Lam, S. (2009). Rumination predicts longer sleep onset latency after an acute psychosocial stressor. *Psychosomatic Medicine*, *71*, 771–775. https://doi.org/10.1097/PSY.0b013e3181ae58e8