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Investigating the Putative Impact of Odors Purported to Have Beneficial Effects on Sleep: Neural and Perceptual Processes

Rochelle Ackerley¹ · Ilona Croy² · Håkan Olausson³ · Gaby Badre⁴

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Abstract

Introduction Olfaction has an important role in physiological and affective processes, as well as the potential to have profound effects on activities such as sleep and learning. We investigated two commercially manufactured odors (“Deep Sleep” and “Oriental,” from This Works) purported to promote sleep, compared with control odor, where we aimed to explore whether neural and behavioral differences existed after odor inhalation.

Methods In a neuroimaging study, 30 healthy participants were exposed to the odors via an olfactometer during functional magnetic resonance imaging (fMRI). In a further behavioral study using 12 chronic insomniacs, we investigated whether the commercial odors showed effects on sleep during a double-blind, randomized home evaluation.

Results In the neuroimaging, the odors were related to activation of olfactory-relevant areas, such as the orbitofrontal cortex, and we found positive connectivity between the piriform cortex and the hippocampus, amygdala, insula, and middle cingulate cortex. Deep Sleep specifically activated the superior temporal gyrus, whereas Oriental activated the caudate. Further, these commercial odors showed some beneficial impact on sleep.

Conclusions The perceptual and neural impacts of the commercial odors showed that olfactory stimulation can potentially aid sleep and modify affective processes in a number of ways.

Implications The present work opens up opportunities for further investigations into how different odors may lead to specific behavioral and physiological modifications, such as their impact on sleep and well-being, which may provide non-pharmacological alternative approaches.

Keywords Smell · Olfaction · Affect · Emotion · Well-being · Sleep

Introduction

For a long time, fragranced substances (odors, aromas, scents, perfumes) have been used for mental, psychological, physiological, and even spiritual purposes to address disorders and aid well-being, through aromatherapy. Olfaction is the most basic and evocative of our senses (Herz 2004), where there is a strong association between odor and emotion, and olfaction

can have a profound impact on memories and learning (Wilson 2010; Rihm et al. 2014; Arzi et al. 2014). Further, odors can modify neural processes during sleep (e.g., Perl et al. 2016), which opens up opportunities to affect sleep beneficially through olfaction. Hence, it is of interest to explore non-pharmacological approaches and strategies to address health issues associated with modern-day stressors, which can adversely affect sleep and well-being (e.g., the impact of overusing mobile phones; Munezawa et al. 2011; Thomée et al. 2011).

Specific ingredients commonly used in commercial odorants targeting sleep and well-being (e.g., lavender, patchouli) have been found to induce central relaxant and sedative effects (Haze et al. 2002; Ito and Ito 2011; El Alaoui et al. 2017). However, the process through which an odor produces affective responses is relatively unknown, but it is hypothesized to be via the amygdala, through the absorption of pharmacologically active components of an odor and/or its perceptual associations (Fisler and Pilkington 2012). Odors can nevertheless have profound effects, where studies have reported that

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pleasant odor inhalation may have positive psychophysiological impacts (Liljenquist et al. 2010; Haehner et al. 2017). Conversely, it has been found that people who are intolerant of volatile chemicals (e.g., in multiple chemosensitivities) generally suffer from sleep disturbances and health complaints (Baldwin et al. 2004; Persson et al. 2008). Previous works have demonstrated that odors, especially lavender, can aid sleep and well-being in patients having clinical interventions (e.g., Lytle et al. 2014; Muz and Taşçı 2017; Ayik and Özden 2018). A majority of studies in aromatherapy research have used anecdotal and subjective evidence, where objective investigations are relatively few (Fisler and Pilkington 2012). Only a handful of studies have systematically looked at the effects of pleasant odors on sleep quality in healthy humans (e.g., Hardy et al. 1995; Sano et al. 1998; Tanaka et al. 2002) and have found some beneficial impact, yet we know little about the exact relationship between odors and their neural, behavioral, and perceptual effects.

Understanding the mechanisms of odor neuronal processing and perception is important in comprehending the influence of odors on the brain. It is of interest to further explore these processes in humans by comparing neural and perceptual findings, which we explore presently in our two studies. There is a direct connection from olfactory neurons to limbic and memory areas (Gottfried 2006) and the limbic system (including the amygdala) regulates emotions and behaviors (LeDoux 2012). A behavioral response can be elicited directly by a particular odorant, which may also be linked to the memory of that odorant (Soudry et al. 2011; Billot et al. 2017). This route may be used as a way to impact emotions and behavior profoundly and thus may aid in beneficial outcomes, such as restful sleep.

It is debated whether different odors elicit specific patterns of activation in the brain, as humans differ not only in the memories they relate to different odors but also on the level of the expression of olfactory receptor neurons (Verbeurgt et al. 2014; Croy et al. 2015b). However, there is some evidence that olfactory processing is organized according to the affective perception an odor elicits (for a review, see Zou et al. 2016). For example, Anderson et al. (2003) found that the pleasantness of an odor was processed in spatially separate areas of the orbitofrontal cortex (OFC), which plays a large role in emotional processing. They also showed that an unpleasant odor activated the hippocampus, known for its role in memory. Another area of interest in odor processing is the hypothalamus. Oxytocin is produced in the hypothalamus and it is known to be a “social” hormone promoting sleep, well-being, and relaxation (Carter 2014). Oxytocin is released by tactile stimulation (e.g., massage) (Uvnäs-Moberg et al. 2015) and may also be released by olfactory cues (see Croy et al. (2015b) for potential positive effects and Wyatt (2015) for controversies in the area). Hence, it is of interest to specifically look at any impact of odors on the hypothalamus.

Further, odors can act as excitatory sexual input (Verhaeghe et al. 2013; Bendas et al. 2018), where differences between the sexes may exist.

The present study aimed at evaluating the influence of commercially manufactured odors on cortical brain processes and to assess whether these odors correspondingly produced effects on sleep. Two commercially manufactured complex odors, reported to be pleasant and have positive sensory impacts on sleep and relaxation, were selected and compared with a control odor. One odor (“Deep Sleep”) is claimed to aid in falling asleep faster, sleeping better, and waking feeling more refreshed. The other commercial odor (“Oriental”) is not currently on the market but is being formulated to have similar benefits to Deep Sleep. We hypothesized that all the odors would produce activity in primary olfactory areas and that the complex commercial odors, aimed at promoting sleep and relaxation, should have additional impact on emotionally relevant brain areas and be rated more positively. From the neuroimaging and behavioral studies, we aimed to identify preliminary markers for assessing the wider impact of odors on the brain and sleep, respectively.

Material and Methods

Two separate experiments were conducted as follows: (1) a comprehensive spatio-functional study using functional magnetic resonance imaging (fMRI) and (2) a small, exploratory behavioral study in order to investigate whether there is any psycho-physiological impact of the presence of an odor during sleep. Informed consent was obtained from all individual participants included in the study, where they all gave their written consent (details per study below) and were remunerated for their participation. The project was approved by the relevant local ethical committees (in Gothenburg and Dresden) and was conducted in accordance with the Declaration of Helsinki. Different groups of participants were used so not to habituate any of the participants to the odors and because each study was conducted in a place due to the availability of the experimental resources. Further, healthy participants were used in the fMRI study to investigate the typical neuronal responses to the commercial odors, whereas in the behavioral study, we wanted to test a clinical angle, where it was more pertinent to use mild–moderate insomniacs to gain differences in the results and see a larger effect (i.e., we knew that the insomniac group already had sleeping issues, to test the efficacy of the odors). In both studies, two commercially manufactured mixtures of odors containing ingredients claiming to improve sleep (see <https://www.thisworks.com/why-this-works-2/clinical-studies>) were tested, namely Deep Sleep (containing lavender, vetivert, chamomile, patchouli,

and ho wood; full ingredients' list from the manufacturer: water, polysorbate 20, Parfum, *Lavandula angustifolia* (lavender) oil, *Pogostemon cablin* (patchouli) oil, *Cinnamomum camphora* (Ho Wood) oil, *Vetiveria zizanoides* (vetivert) oil, *Ormenis Multicaulis* (wild chamomile) flower extract, linalool, diazolidinyl urea, geraniol, limonene, iodopropynyl butylcarbamate and Oriental (containing patchouli, ylang ylang, and olibanum frankincense; full ingredients' list unavailable, due to the odor not being on the market) (from This Works, London, UK). These were compared with a control odor (synthetic lavender in the behavioral study (containing water, PEG-40 hydrogenated castor oil, Parfum (fragrance), sodium benzoate, potassium sorbate, linalool, disodium EDTA, citric acid, limonene, coumarin, eugenol, geraniol) and phenylethyl alcohol (PEA) in the fMRI study). In the fMRI study, PEA was used as it is commonly used in olfaction neuroimaging (e.g., Hummel et al. 2010; Sezille et al. 2013) and provided a well-validated control for brain activation in olfactory areas, for better comparison with the activity produced from the commercial odors. In the behavioral study, we wanted to test the effect of different odors contrasted to a baseline (no odor), where the control was used in a different way as a comparative common odorant. Synthetic lavender was chosen due to its similarity in character to the commercial odors, yet it was a single, pure odorant rather than a complex, multi-fragranced odor.

fMRI Odor Study

Thirty participants were tested (15 females, 15 males; mean age 24 years \pm 3 SD). All of them exhibited normal olfactory function regarding threshold, discrimination, and identification as controlled with Sniffin' Sticks test (Burghardt, Germany) (Hummel et al. 1997) using a cut-off of 32 points (Hummel et al. 2007). The fMRI measurement of the blood oxygenation level-dependent (BOLD) signal was performed with a 3-T scanner (Sonata; Siemens, Erlangen, Germany). Three different odors were presented individually to both nostrils during scanning. The same two odors as used in the behavioral study, Deep Sleep and Oriental, were tested, and compared with the control odor PEA.

In order to ensure a subjective iso-intense odor perception, a pretest with various dilutions per odor was conducted in a sample of 15 different participants. Each of the odors was presented three times in a randomized order and the participants rated the odorants' intensity. The averaged ratings per odor were compared with each other with a *t* test and iso-intense odor dilutions were chosen for the fMRI presentation. Based on the pretest results, a dilution of 6.25% (made in 1,2-propanediol) was chosen for Deep Sleep and Oriental, and a dilution of 100% for the control odor in order to achieve iso-intense perception.

fMRI Procedure

Each odor was presented in two runs, where the order was pseudo-randomized (e.g., Deep Sleep-Oriental-PEA followed by a block Deep Sleep-PEA-Oriental). Hence, a total of six runs of odor presentation in on-off (inspiration/exhalation) blocks were performed. Each run consisted of continuous odor presentation for 10 s, followed by a baseline of at least 17 s during which clean air was presented. The exact number of inhalations per run of a single odor depended on the participant's own breathing frequency, but this was \sim 10 (over at least 27 s). The three individual odors, as well as the clean air, were applied by a computer-controlled olfactometer with respiratory feedback that enabled synchronization between in breathing and odor presentation, which ensured constancy in the airflow, without any odor-correlated changes due to odor concentration changes (cf. Sezille et al. 2013). The airflow rate was set to 2 l/min. During the baseline periods, clean air was presented at the same airflow rate. The tubes containing the odors were positioned directly in the scanner and were connected to the participant's nose via a 2-mm tube of 1-m length, which enabled direct and fast stimulus presentation. Odors were presented intranasally, on the right side, using an anatomically formed nosepiece and the participants were given instructions to remain calm and breathe normally.

After each run, the participants were asked to verbally rate the intensity of the odor on a scale from 0 (not intense at all) to 5 (very intense). A total of 150 volumes per run were acquired by means of a 38 axial-slice matrix (TR 3000 ms/TE 40 ms, FA 90; matrix = 348×348). Following the fMRI sessions, a T1-weighted image was acquired in the sagittal direction by using a T1-MPR sequence (TR 1890 ms/TE 3.24 ms; matrix = 238×348): This scan was run to allow individualized brain normalization in the later statistical analysis.

fMRI Analyses

Intensity ratings were analyzed using SPSS 22 (IBM, Armonk, NY). The main effect of odor type (3 levels: Deep Sleep, Oriental, PEA) and repetition (2 levels: run 1, run 2), as well as the interaction effect, was tested in a repeated-measures ANOVA. Post hoc tests were computed as *t* tests for dependent measurements and were Bonferroni corrected for multiple comparisons. Gender effects were investigated (added as a factor), due to the power given through the high number of participants and the equal gender balance.

Neural data analyses of the $2 \times 2 \times 2$ mm³ functional images were performed with SPM 12 software (Statistical Parametric Mapping; Wellcome Department of Imaging Neuroscience, Institute of Neurology at University College London (UCL, UK)), implemented in Matlab (version R2015b; The MathWorks, Natick, MA), following spatial pre-processing with the same software (spatial filtering:

high-pass filter = 128 Hz, registering, realignment, coregistration between functional and structural images, normalization using segmentation procedure, smoothing by means of $6 \times 6 \times 6 \text{ mm}^3$ FWHM Gaussian kernel). Motion regressors from the realignment procedure were included in the generation of t maps for each individual, in order to account for potential head movement. A whole-brain analysis was conducted using the default settings applied in SPM ($p < 0.001$, uncorrected). Multiple comparison correction was only applied in this conventional way, and although this may be less stringent than other approaches, it is an accepted level in olfactory fMRI analyses, which are complicated due to a reduced signal-to-noise level (Moessnang and Freiherr 2013).

SPM matrices reflecting the differences between odor and baseline (on-off) were calculated for each fragrance block, based on the general linear modeling approach. As the odors were not perceived as iso-intense (as per the pretest) in the scanner, all activations were corrected for the individual intensity rating at the group level by adding the individual intensity ratings as regressors of no interest in the analysis. Analyses were based on t tests with a global height threshold $p < 0.001$ for the overall olfactory activation. All activation coordinates are presented in MNI (Montreal Neurological Institute) space. As we were looking for a possible oxytocin release, it was specifically checked whether the odors would be related to enhanced hypothalamic activation. For this purpose, a region-of-interest (ROI) sphere of 6 mm^3 was created around the hypothalamic peak activation observed in a previous odor study (3 0 -8; MNI space, Wallrabenstein et al. 2015) and a threshold of $p < 0.01$ (uncorrected) was applied. The more liberal threshold was used, as the ROI analysis minimizes the possibility of false-positive responses; however, interpretation should nevertheless be considered with respect to this level.

As outlined in the “Introduction,” consistent and distinguishable neural activity for an individual odor is unlikely; however, the odors produced different results in the behavioral study. In order to capture potential differential neural effects of the odors, we performed a connectivity analysis to focus on the temporal correlation of neural responses. The preprocessed data were analyzed with the connectivity toolbox in SPM (nitrc.org/projects/conn). The primary olfactory cortex (piriform cortex) was used as a seed and functional connectivity was computed over each block, as a linear regression between the seed and the rest of the brain with the CONN toolbox, which performs voxel-seed correlations by estimating temporal correlation maps (Whitfield-Gabrieli and Nieto-Castanon 2012). The piriform cortex was defined according to the criteria described by Zelano et al. (2005), using MRIcron (Maldjian et al. 2003). The analysis focused on the right piriform cortex, reflecting the ipsilateral olfactory processing from right-sided odor presentation. An FDR-corrected statistical threshold of 0.05 was used.

Behavioral Odor Study

The behavioral study was designed as a first step into probing perceptual effects of these same odors on sleep. A power analysis (using a power and effect size calculator from Ramakrishnan and Holleran on biomath.info) and comparison with similar previous work (Lewith et al. 2005) revealed that for $> 80\%$ power, at least 9 participants should be included for perceptual responses and 12 for actigraphy. We recruited a total of 12 participants (8 females, 4 males; mean age 43 years \pm 12 SD) with chronic mild–moderate insomnia (Insomnia Severity Index; Morin et al. 2011; 17 ± 2 SD) entered a double-blind 3-week period home evaluation study assessing the efficacy of the two commercial odors, compared with a control. Insomniacs were used as they represented a group requiring aid in sleeping, which the commercial odors were meant to target. Chronic insomnia was defined as difficulties in falling asleep and/or maintaining sleep for several nights a week (> 3 days) for more than 3 months and having feelings of not being refreshed when waking up in the morning. The level of insomnia was assessed in a European-recognized sleep laboratory (SDS Kliniken, Gothenburg, Sweden), by a certified expert in sleep medicine. If the participants were on medication upon entering the study, this was continued throughout the trial period. If on any medication, the participants should not have changed it 4 weeks prior to commencing the study; otherwise, they had to be healthy. The inclusion criteria were as follows: a normal (self-reported) sense of smell, insomnia for > 3 months, difficulties falling asleep and/or maintaining sleep, and having no fragrance sensitivity. The exclusion criteria were the presence of illnesses or newly discovered problems (< 6 months), for example, sleep apnea, untreated metabolic disorders, psychiatric disorders, or high blood pressure. Participants were selected by advertising at the sleep clinics and through leaflets on boards.

Behavioral Study Procedure

The three odors (Deep Sleep, Oriental, control) were randomly assigned in a counter-balanced order. Participants slept the first three nights as usual, and for the proceeding four nights, they sprayed the first randomized odor on their pillowcase before bedtime, evaluating their experiences at the end of the period. Following a few “washing” nights (new pillowcase) without an odor, they slept four nights with a second odor, and the same procedure continued with the third odor. Adherence to this and regularity in the participants’ sleep–wake scheme was controlled by actigraphy, which detected their movements (e.g., time-to-bed).

The experimental measures included self-report questionnaires and movement (actigraphy) data. For the subjective reports, participants filled out the daily sleep diary, which also included reports on their daytime behavior and sleep

perception, with free comments about their night's sleep. They were also able to note if there were any environmental changes of importance (e.g., severe meteorological occurrences, moving house). On awakening, they noted their "sleep quality" on a visual analog scale (VAS; with the end-anchors "very good" and "very bad"), as well as on the Karolinska Sleepiness Scale (KSS, Akerstedt and Gillberg (1990); 1, very alert; 9, very sleepy). The participants also filled out a questionnaire (Table 1) about their perceptions. Physiological movement data were collected using wrist actigraphy (Actiwatch; Cambridge Neurotechnology Ltd., Cambridge, UK), consisting of an accelerometer watch that was worn continuously during the study. However, data were only recorded from eight participants (6 females and 2 males), as the data from the other participants were not reliable (e.g., gaps in the recordings). Hence, we do not present the actigraphy results, as this part was underpowered.

Behavioral Study Analyses

The odors were coded so that the experiment and analyses were conducted double blind. The data were analyzed in Prism (version 7; GraphPad, San Diego, CA), where the data were tested for normality. Significant differences were sought at $p < 0.05$. Parametric statistics were used to analyze the KSS, and sleep quality measures. For each, an ANOVA was carried out, where post hoc t tests were corrected for multiple comparisons using the false-discovery rate (FDR) two-stage linear step-up procedure of Benjamini et al. (2006). Each odor response was compared with the response at baseline (no odor) and to the three odors. We primarily wanted to investigate whether an odor could aid sleep on various measures, but it was also of interest to compare the effects between the

different odors. Non-parametric statistics were used to analyze the questionnaire data, due to violations of normality. Bonferroni-corrected Wilcoxon tests were used to compare whether each odor deviated from the middle of a questionnaire measure (i.e., the value "5," which represented no difference in the perceptual measure). Gender differences were not investigated due to the unequal number of participants.

Results

fMRI Odor Study

There was a significant effect of odor type on intensity ratings ($F[2,29] = 29.3, p < 0.001$), but no effect of repeated presentation ($F[1,30] = 1.6, p = 0.21$), and no significant interaction effect ($F[2,29] = 1.6, p = 0.20$, Fig. 1). As post hoc tests revealed that both the odors Deep Sleep and Oriental were rated as significantly more intense than the control odor of PEA, intensity ratings were used as a covariate for all further analyses.

The presentation of the odors was related to a clear activation of olfactory-relevant areas, such as the OFC, amygdala, and insula (Fig. 2 and Table 2). Neural response patterns were further found in the middle cingulate. There were no significant differences in neural activation between both presentations of the same odor. Gender effects are stated where found.

Deep Sleep Odor

Deep Sleep vs Control After the correction for differences in intensity ratings, the Deep Sleep odor was related to higher BOLD signal changes in the thalamus and middle frontal

Table 1 Subjective questions on sleep in the behavioral odor study, after experiencing each odor

1. How did you find your sleep with the odor?	1 = convenient	10 = inconvenient
2. How was your sleep quality with the odor, compared to your typical sleep quality?	1 = better	10 = worse
3. Was your insomnia worse or better with the odor?	1 = better	10 = worse
4. Did you experience any problems with the odor?	1 = none	10 = many
5. How did you find maintaining sleep with the odor?	1 = easier	10 = difficult
6. Did you find it easier to get to sleep with the odor?	1 = much	10 = not at all
7. Do you feel safer with the odor?	1 = much	10 = not at all
8. How do you feel in the morning when you woke up?	1 = more rested	10 = more tired
9. Did you experience dreams with the odor, as compared to your typical sleep?	1 = much more	10 = much less
10. What was the content of your dreams like?	1 = pleasant	10 = unpleasant
11. After waking up with the odor, how did you experience daytime?	1 = drowsy	10 = alert
12. After waking up with the odor, did you experience any troubles?	1 = No difficulty, 2 = Headache, 3 = Darkness, 4 = Dizziness, 5 = Nausea, 6 = Fatigue, 7 = Other	
13. Did you feel that the odor effect decreased after...?	1 = 1 day, 2 = 2 days, 3 = 3 days, 4 = It did not last throughout the test period, 5 = No effect from the beginning	
14. At the end of the test: Do you prefer sleeping with the...?	1 = 1st odor, 2 = 2nd odor, 3 = 3rd odor, 4 = No odor	

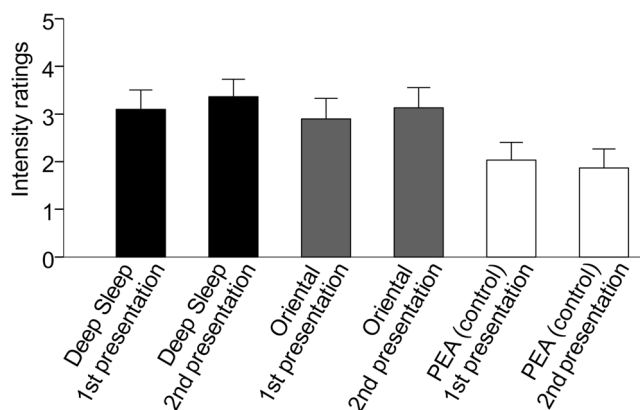


Fig. 1 Intensity ratings within the scanner. Significant effects of odor were observed, but no effect of repetition. The error bars indicate the 95% confidence intervals

gyrus (Fig. 3 and Table 3). No other brain areas were significantly enhanced for Deep Sleep, compared with the control odor.

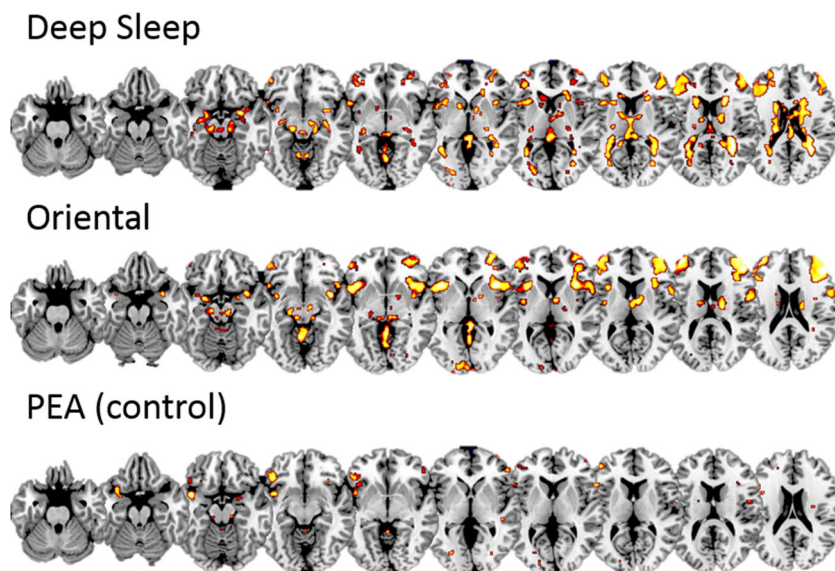
Deep Sleep vs Oriental After the correction for differences in intensity ratings, the Deep Sleep odor was related to a higher BOLD signal change in the right superior temporal gyrus.

For the focused hypothalamic activation, Deep Sleep activated this region in women ($t = 2.5$, $p = 0.007$, $k = 4$), but not in men (Fig. 3).

Oriental Odor

Oriental vs Control After the correction for differences in intensity ratings, the Oriental odor was related to enhanced BOLD signal changes in the right and left caudate, and a cluster which bordered the right thalamus (Fig. 4). None of the primary or secondary olfactory projection areas, and none

Fig. 2 Comparison of the neural activation following the “deep sleep,” “oriental,” and control (PEA) odor. The activations vs. baseline are adjusted for intensity effects and presented in a standardized template with a height threshold of $p < 0.001$, uncorrected



of the trigeminal projection areas, proved to be significantly enhanced for Oriental compared with the control odor.

Oriental vs Deep Sleep There was no enhanced activation in Oriental odor compared with Deep Sleep. Focusing on hypothalamic activity, Oriental activated this region significantly in men ($t = 2.6$, $p = 0.005$, $k = 2$) but not in women.

Connectivity Analysis

With each of the odors, the piriform cortex was significantly positively connected to other olfactory and emotionally relevant brain areas, including the hippocampus, anterior insula, and amygdala. The overall connectivity was most widespread and strongest in the control odor (PEA: intensity 170 and 41 nodes; Deep Sleep: intensity 102 and 23 nodes; Oriental: intensity 86 and 18 nodes).

With Deep Sleep, there was a negative connectivity between the piriform cortex and the superior temporal cortex. In Oriental, there was a negative connectivity between the piriform cortex and the posterior cingulate cortex (a node of the default mode network). In the control odor, negative connectivity was detected in the left parietal frontal gyrus (the frontal executive control network) (Fig. 5).

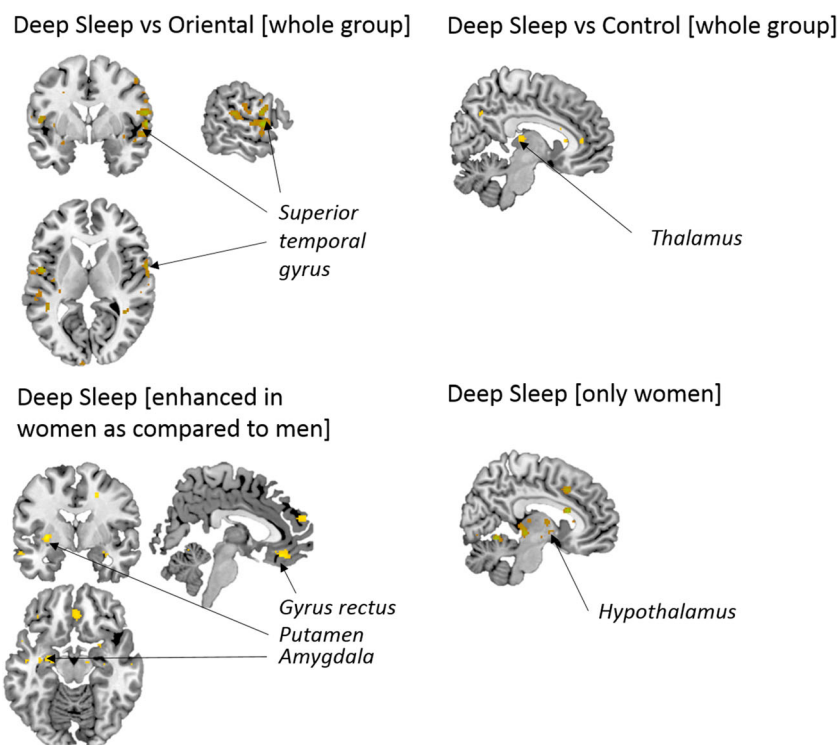
Behavioral Odor Study

For the perceptual measures, significant differences were found in the KSS measure of alertness (ANOVA $F(3,11) = 5.37$, $p = 0.013$), where there was significantly increased alertness on waking after sleeping with the Deep Sleep odor compared with baseline sleep (difference = -1.6 ± 0.6 SEM, $t = 2.86$, $df = 11$, $p = 0.029$). There were no significant differences in the same comparisons of baseline sleep compared with the

Table 2 Activation to olfactory stimulation (on vs off contrasts), $p < 0.001$, uncorrected, cluster extend threshold $k = 20$

Cluster size	<i>T</i>	<i>X</i>	<i>y</i>	<i>z</i>	Brain area
“Deep Sleep” odor					
1945	5.85	39	52	24	Right middle frontal gyrus extending to superior temporal gyrus
1420	5.26	-37	58	14	Left middle frontal gyrus
960	5.38	1	-16	12	Thalamus
564	4.04	35	-48	36	Right inferior parietal lobule
553	4.68	-51	14	-4	Left temporal pole extending to insula
452	5.22	7	18	42	Right middle cingulate cortex
417	4.60	-39	-48	38	Left inferior parietal lobule
189	4.12	-17	-94	0	Left middle occipital gyrus
187	4.62	-23	0	-16	Left amygdala
185	4.43	17	-60	40	Right precuneus
157	4.46	25	2	-16	Right amygdala
131	4.24	-13	-8	16	Left caudate nucleus
102	3.87	-5	-68	44	Left precuneus
102	4.52	21	-22	22	Right caudate nucleus
85	4.47	-15	-20	-10	Thalamus
79	4.22	3	-98	14	Left cuneus
49	4.40	59	-16	24	Right supramarginal gyrus
43	3.59	29	-98	-2	Right inferior occipital gyrus
“Oriental” odor					
472	4.23	-43	20	-6	Left inferior frontal gyrus (p. Orbitalis) extending to insula
360	4.32	19	10	22	Right caudate nucleus
166	4.50	31	-52	22	Left area hOc1 (V1)
149	4.02	-19	-58	38	Left middle occipital gyrus extending to superior parietal gyrus
148	5.19	-27	-74	4	Right area hOc1 (V1)
145	4.18	-23	44	20	Left superior frontal gyrus extending to middle frontal gyrus
141	3.87	-49	34	28	Left middle frontal gyrus
114	3.98	-35	42	6	Left inferior frontal gyrus (p. Triangularis)
42	3.77	3	22	38	Right middle cingulate cortex
40	4.15	13	-6	12	Thalamus
38	3.86	53	26	30	Right inferior frontal gyrus
35	4.10	-19	-22	20	Left caudate nucleus
35	3.73	45	46	24	Right middle frontal gyrus
31	3.68	-45	6	-12	Left temporal pole extending to insula
26	4.10	-1	-8	8	Thalamus
25	3.79	13	12	0	Right caudate nucleus
25	3.62	37	28	-8	Right inferior frontal gyrus (p. Orbitalis) extending to insula
24	3.51	43	8	32	Right inferior frontal gyrus (p. Opercularis)
21	3.79	-27	30	6	Left insula
PEA (control) odor					
293	4.36	51	32	30	Right middle frontal gyrus
191	5.17	1	-44	-4	Cerebellar vermis (4/5)
108	4.33	45	-48	40	Right inferior parietal lobule
95	4.43	47	8	26	Right inferior frontal gyrus (p. Opercularis)
93	4.32	37	62	2	Right middle frontal gyrus
43	3.88	-47	28	38	Left middle frontal gyrus
32	4.28	51	-2	14	Right rolandic operculum
29	3.97	21	-72	10	Right calcarine gyrus
21	3.80	25	2	-16	Right amygdala
20	3.65	43	30	44	Right middle frontal gyrus
20	4.10	45	10	-8	Right insula

Fig. 3 Neural activation following the inhalation of the “deep sleep” odor. The images are adjusted for intensity effects and presented in a standardized template. The threshold level is set to $p < 0.01$ for visualization purposes



Oriental odor (difference = -0.9 ± 0.7 SEM, $t = 1.30$, $df = 11$, $p = 0.241$) or with the control odor (difference = -0.7 ± 0.7 SEM, $t = 0.99$, $df = 11$, $p = 0.359$). In the sleep quality measure, no significant main effects were found (ANOVA $F(3,11) = 0.71$, $p = 0.443$) and hence, significant differences were not explored between the conditions.

In the subjective questionnaire about the use of the odors (Table 1), we found that Oriental was rated as significantly lower (better) than the middle of the scale (i.e., no difference,

value = 5) on a number of questions, where the participants slept better with this odor present (difference = -2 , $W = -28$, $n = 12$, $p = 0.044$; question 1), experienced few problems with this odor (difference = -3 , $W = -24$, $n = 12$, $p = 0.043$; question 4), and found it easier to get to sleep with this odor (difference = -1 , $W = -28$, $n = 12$, $p = 0.016$; question 6), respectively (Fig. 6). There was no clear preference for a particular odor overall, but 75% of participants preferred sleeping with an odor, rather than no odor. In 58% of participants, the impact of the odor lasted at least 1 day. None of the odors affected the participants' dreams and occasional headaches and dry mouths were reported.

Table 3 Activation in contrasts between odors, $p < 0.001$, uncorrected, cluster extend threshold $k = 10$ (n.s., no significant activations)

Cluster size	T	x	y	z	Brain area
“Deep Sleep” vs control					
33	3.95	1	-16	12	Left thalamus
28	3.99	33	36	38	Right middle frontal gyrus
“Deep Sleep” vs “Oriental”					
33	3.98	65	-30	16	Right superior temporal gyrus
19	3.87	-47	-30	28	Left supramarginal gyrus
16	3.60	59	0	16	Right rolandic operculum
13	3.85	61	2	6	Right rolandic operculum
11	3.96	-49	-2	10	Left rolandic operculum
“Oriental” vs control					
15	3.70	21	18	14	Right caudate nucleus
29	3.73	-21	16	16	Left caudate nucleus
“Oriental” vs Deep Sleep					
n.s.					

Oriental vs Control [whole group]

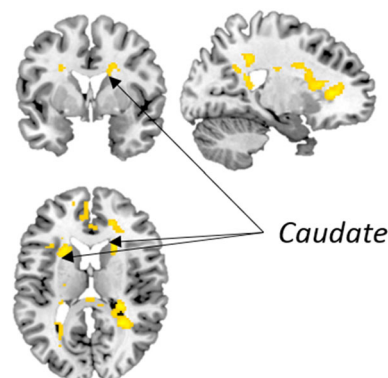
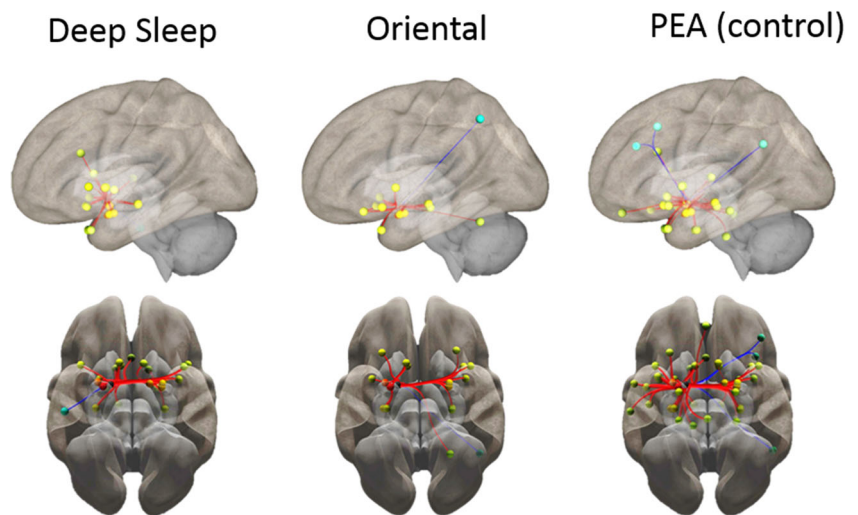


Fig. 4 Neural activation following the inhalation of the “Oriental” odor. The images are adjusted for intensity effects and presented in a standardized template. The threshold level is set to $p < 0.01$ for visualization purposes

Fig. 5 Averaged connectivity results from all of the participants. Positive connectivity is indicated by red lines, and negative connectivity is indicated by blue lines. All results are presented at a threshold of 0.05, FDR-corrected for multiple comparisons



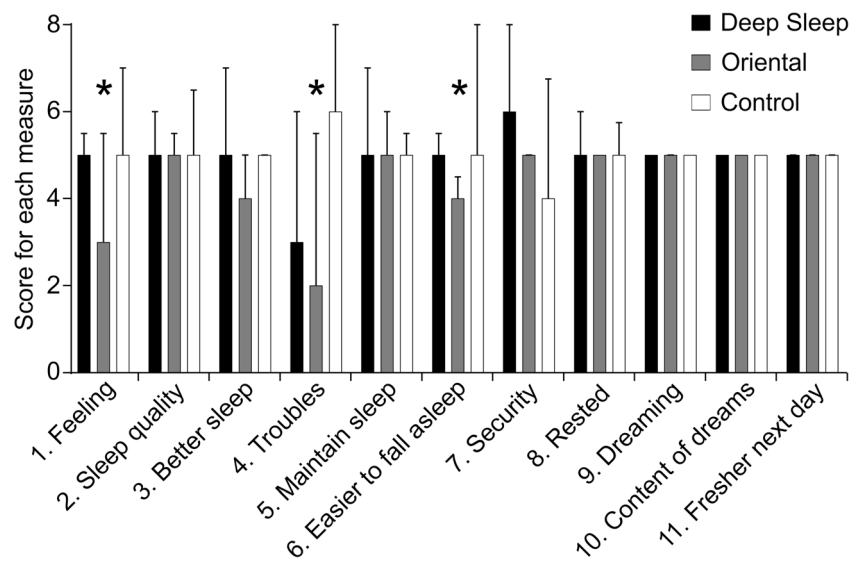
Discussion

We conducted a comprehensive fMRI study and an exploratory behavioral study to investigate the potential for odors claimed to affect sleep to produce neural and perceptual effects. Our investigation was primarily directed at finding possible ways of measuring how aromatherapy can be used to improve everyday life and well-being. We presented putative data to show that specific neural activity occurred during commercial odor inhalation and that these effects could be assessed using a variety of behavioral approaches. In the fMRI study, all the odors produced significant brain activity in olfactory-related areas, including the cingulate cortex that is related to affective processing of odors (Zou et al. 2016) and the complexity of an odor (Sezille et al. 2015). We found further specific activations for each of the commercial odors tested. For example, with Deep Sleep, the superior temporal gyrus was activated, whereas with Oriental we found

additional caudate activity. These additional activations may have occurred for a number of reasons, including the processing of the increased complexity of the commercial odors and the affective consequences of this. However, this interpretation is limited by the possibility that the odors were sniffed with different intensities (although we found a similar inhalation frequency across all the odors) and that the inhalation of the present odors nevertheless produced impacts on neural processing over normal respiration (cf. Koritnik et al. 2009).

The pronounced effect of all the odors on the brain showed that these were well registered within the olfactory system and in further areas, such as the anterior intra-parietal sulcus, which is an area involved in somatosensory integration, likely activated due to stimulation of the trigeminal nerve (cf. Croy et al. 2014). The activation of the middle cingulate cortex that was especially seen with Deep Sleep suggested that the odors evoked emotional responses, which may have influences on behavior (Hadland et al. 2003), although multiple brain areas

Fig. 6 Median scores and interquartile range from questions about sleep (see Table 1). “Oriental” was rated as significantly lower (better sleep experience) for measures 1, 4, and 6



are involved in such affective and motivational processes (LeDoux 2000). The activation of the caudate (Oriental) and the putamen (Deep Sleep) suggested the participation of processes associated with reward or novelty (Báez-Mendoza and Schultz 2013) for the commercial odors, which may relate to the complex nature of the commercial odors and their interpretation. Similarly, Deep Sleep was related to the highest BOLD signal changes in the middle frontal gyrus, an area involved in the top-down modulation of attention (Japee et al. 2015) and Oriental showed higher activation than the control in the caudate, which is an area associated with reward processes (Knutson and Cooper 2005), again likely reflecting the complexity of the commercial odors. As compared with Oriental, Deep Sleep produced stronger activations in the right superior temporal gyrus, an area implicated in social perception and emotion (Narumoto et al. 2001; Zahn et al. 2007). This area was furthermore significantly coupled to the piriform cortex in Deep Sleep, suggesting a direct effect of olfactory areas, stimulated by Deep Sleep on the superior temporal gyrus. Gender-specific effects were observed for the hypothalamus, with enhanced activation in men for Oriental and an enhanced activation in women for Deep Sleep. The result of gender-differentiated hypothalamic activation of odors is in line with previous findings of sex differences in the hypothalamus associated with putative pheromone inhalation (Wallrabenstein et al. 2015), but given the a priori search and activation probability threshold, it would be preferable to conduct further studies into this.

We also found a coupling between the primary olfactory region (piriform cortex) and other olfactory and emotionally relevant brain areas, including the amygdala that is known for its role in emotion (LeDoux 2012), which was the case across all the odor conditions. Overall, the commercial odors seemed to show more widespread neural activity, yet the connectivity between the primary olfactory region and other brain areas was more focused on the commercial odors than with the control odor. These differences likely represent how the more simple control odor differed in its quality and subsequent processing, as compared with the multi-fragranced commercial odors. The increased complexity of the commercial odors likely required further central processing, where the close relationship between olfactory and affective processing (Weber and Heuberger 2008) may entail the recruitment of more emotional and cognitive structures. The higher an odorant's complexity, the more likely it is to be evaluated as pleasant (Kermen et al. 2011) and plant-derived odors are also typically classed as pleasant and can positively affect states such as calmness, alertness, and mood (Weber and Heuberger 2008). The commercial odors we tested presently were both complex and plant based, and although we did not explicitly test their affective qualities, we found that they were well tolerated during the fMRI and behavioral studies. Moreso, in the behavioral study, we found that the majority of participants

preferred sleeping with an odor than without. The pleasantness of an odor may play a role in mediating its effects, including over longer periods, such as during sleep, thus it seems advantageous to both design and test the effects of complex odors.

The presentation of odors for extended time periods leads to their adaptation (Croy et al. 2015a). As there was no effect of repeated odor stimulation, we assumed that the neural effect did not weaken over time in the scanner. Our block design thus appeared to work well, providing a balance between statistical power and the effects of repeated olfactory stimulation. However, the effect of adaptation to odors for longer time periods (e.g., during sleep) should be taken into account, as the neural (and also perceptual) effects may change (Croy et al. 2013), although it is known that odors are processed nevertheless during sleep (e.g., odors can affect dreams; Schredl et al. 2009) and in our behavioral study, 58% of participants found that the impact of the odor lasted at least 1 day. Therefore, the potential mechanisms underlying the effects of odor inhalation at the beginning of sleep may be through such processes, but we cannot assume these are the same over time, due to the perceptual and/or physiological adaptation of odors, and decreased levels of consciousness during sleep. However, it is likely that the effects of odor inhalation can persist and this may be a way to influence health and well-being for more prolonged periods.

In our additional exploratory behavioral study, we investigated whether the two commercial odors and a single fragrance control odor could impact sleep. We found that the commercial odors were rated as having a positive significant impact on sleep, but that such studies may be limited by the variability between subjects. Specifically, we found that Oriental was rated as producing significantly better overt sleep effects (as measured through the questionnaire about how the odors were perceived) and Deep Sleep produced decreased sleepiness on waking (as measured through the alertness on waking in the KSS). Hence, the more complex commercial odors were found to have beneficial effects in the perceptual ratings; however, it is unknown which aspect(s) of these odors led to this finding (e.g., the content and/or hedonics of the odor). Akin to the fMRI findings, it is likely that the multi-fragranced commercial odors may have further impacts, where the active ingredients (e.g., lavender, patchouli, vetiver, chamomile) may alter central processes (Haze et al. 2002; Ito and Ito 2011; El Alaoui et al. 2017). Overall, it was clear that the insomniac participants preferred to sleep with an odor, than without, which may mean that simply having such an odor present may aid sleep and restfulness. Comparable beneficial perceptual effects were found in a similar-sized study on insomniacs testing the effects of lavender odor on sleep (Lewith et al. 2005), but we aimed to explore whether actigraphy may prove a useful measure. However, we were not able to include these data as there was variability in our

actigraphy measures (e.g., missing data due to non-adherence to the protocol) and this part of the study was underpowered, but the current work is a step toward seeing whether such effects are measurable and we believe that a future larger study may yield promising results. An advantage of our approach was that it may be more ecological (e.g., a field study); however, the participant-led method produced increased variability than would be found in more standard approaches (e.g., laboratory testing). Overall, our preliminary findings show the potential for odors to produce both perceptual and behavioral beneficial effects on sleep, which should be investigated further.

Conclusions

We found that a number of brain areas were activated in our fMRI study, where more areas were recruited during inhalation of the commercial odors and there were differences between the areas activated between the odors. The more profound activations for the commercial odors may relate to their increased olfactory complexity compared with the control (e.g., the number and type of ingredients). We cannot comment on the way in which single chemicals may activate the brain as we investigated blends; however, the differential effects may be due to both lower level basic processing of the specific chemicals and/or the individual perception of these. In our exploratory sleep study, using the same commercial odors, we found it was possible to investigate the impact of odorant inhalation during sleep, where the commercial odors showed beneficial effects on the subjective rating of sleep and its quality. Further studies are needed into such mechanisms, but overall, our present results suggest that different odors may relate to specific perceptual and neuronal alterations. The ingredients in the commercial odors have been chosen due to previous findings that such components (e.g., patchouli, lavender) may induce relaxant and sedative effects, which we presently found some evidence for in the brain activations found and in the perceptual responses.

Implications

The present work provides findings about psychological and functional activations of odor inhalation. It opens up opportunities for further investigations into how different odors may lead to specific behavioral and physiological modifications on sleep and their impact on well-being, which may provide non-pharmacological alternatives that may be safer than prescribed drugs and more cost-effective.

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Compliance with Ethical Standards

Conflict of Interest The studies were initiated by the authors and This Works provided the odors and supported the fMRI study financially. Prof. Badre is an independent expert scientific advisor for This Works, but has no financial role or involvement in the company.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study, where they all gave their written consent and were remunerated for their participation.

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