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## AN OLFACTORY STIMULUS MODIFIES NIGHTTIME SLEEP IN YOUNG MEN AND WOMEN

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Aromatherapy is an anecdotal method for modifying sleep and mood. However, whether olfactory exposure to essential oils affects night-time objective sleep remains untested. Previous studies also demonstrate superior olfactory abilities in women. Therefore, this study investigated the effects of an olfactory stimulus on subsequent sleep and assessed gender differences in such effects. Thirty-one young healthy sleepers (16 men and 15 women, aged 18 to 30 yr, mean  $\pm$  SD,  $20.5 \pm 2.4$  yr) completed 3 consecutive overnight sessions in a sleep laboratory: one adaptation, one stimulus, and one control night (the latter 2 nights in counterbalanced order). Subjects received an intermittent presentation (first 2 min of each 10 min interval) of an olfactory (lavender oil) or a control (distilled water) stimulus between 23:10 and 23:40 h. Standard polysomnographic sleep and self-rated sleepiness and mood data were collected. Lavender increased the percentage of deep or slow-wave sleep (SWS) in men and women. All subjects reported higher vigor the morning after lavender exposure, corroborating the restorative SWS increase. Lavender also increased stage 2 (light) sleep, and decreased rapid-eye movement (REM) sleep and the amount of time to reach wake after first falling asleep (wake after sleep onset latency) in women, with opposite effects in men. Thus, lavender serves as a mild sedative and has practical applications as a novel, nonphotic method for promoting deep sleep in young men and women and for producing gender-dependent sleep effects.

**Keywords** Sleep, Mood, Nonphotic, Odor, Aromatherapy, Soporific, Gender differences, Polysomnography, Sleepiness, POMS, Circadian

#### INTRODUCTION

Both biologic and nonbiologic olfactory stimuli modify circadian rhythms (see reviews, Davidson and Menaker, 2003; Mistlberger and Skene, 2004). However, evidence of such direct effects on the sleep-wake cycle—a fundamental circadian rhythm partially controlled by the

Submitted May 9, 2005, Returned for revision June 25, 2005, Accepted July 15, 2005 Address correspondence to Namni Goel, PhD, Department of Psychology, 207 High Street, Judd Hall, Wesleyan University, Middletown, CT 06459, USA. E-mail: ngoel@wesleyan.edu circadian clock—is lacking. Therefore, this study explores the effects of lavender oil, a common odor, on night-time sleep and morning alertness.

Aromatherapy's physiological and psychological effects, produced by pure plant or essential oils, are acknowledged worldwide in folk medicine and health care (Buckle, 2001; Price and Price, 1999; Tisserand, 1988). Aromatherapy claims significant effects on sleep and mood (Price and Price, 1999), although such evidence is predominantly anecdotal, deriving from small trials and case studies (Buckle, 2001; Gyllenhaal et al., 2000). Indeed, the effects of aromatherapy on human sleep remain untested under controlled laboratory conditions.

Olfactory stimuli such as peppermint and pyridine, when presented during sleep, produce physiological responses in young adults, despite a reduced arousal threshold during sleep compared with waking (Badia et al., 1990; Carskadon and Herz, 2004). Several other studies report improved sleep—including decreased time awake, increased total time asleep, and reduced daytime sleepiness—following lavender presentation before and during sleep in elderly and demented subjects (Hardy, 1991; Henry et al., 1994; Hudson, 1996; Wolfe and Herzberg, 1996). Other essential oils have produced similar effects in young and older adults (Connell et al., 2001; Raudenbush et al., 2003; Sano et al., 1998; Svoboda et al., 2002). However, these studies were uncontrolled, had small sample sizes, and used subjective evaluations. Thus, further investigations are necessary to determine the effects of odors on objective sleep.

Beyond sleep, lavender's sedative and calming effects have been noted using various physiological measures during waking. Lavender lowers heart rate and blood pressure (Nagai et al., 2000; Romine et al., 1999) and changes electroencephalographic (EEG) frequency and contingent negative variation (Torii et al., 1988), suggesting increased drowsiness. Lavender also increases beta activity (Diego et al., 1998; Lorig et al., 1990), decreases alpha activity (Masago et al., 2000), and increases theta activity (Klemm et al., 1992; Lorig and Schwartz, 1988). Such findings concur with self-reported relaxing mood states induced by lavender exposure (Diego et al., 1998; Goel and Grasso, 2004; Motomura et al., 2001). In addition, lavender slows reaction times (Karamat et al., 1992; Yagyu, 1994) and reduces performance of cognitive tasks (Ludvigson and Rottman, 1989; but see Diego et al., 1998).

According to the homeostatic function of sleep, sleep represents in part, a recovery period following the cumulative increase in physiological strain during wakefulness (Borbély, 1982). Providing support for this theory, various sensory stimuli or behavioral events experienced before bedtime modify subsequent sleep by increasing deep or slow-wave sleep (SWS). SWS increases following auditory (Cantero et al., 2002; Fruhstorfer et al., 1984, 1988) and visual stimulus exposure (Horne and Walmsley, 1976). Similarly, exercise increases nighttime SWS (*e.g.*, Bunnell et al.,

1983; Horne and Staff, 1983; Horne and Moore, 1985; Youngstedt et al., 1997), as does body warming (Bunnell et al., 1988; Dorsey et al., 1999; Horne and Reid, 1985; Sung and Tochihara, 2000). Thus, lavender odor may share a common mechanism with other sensory stimuli for promoting SWS (García-García et al., 1998).

Gender differences in olfactory performance have been examined widely, in which women generally show superior abilities (see reviews in Brand and Millot, 2001; Velle, 1987). Odors also produce greater physiological responses in women than in men (Becker et al., 1993; Evans et al., 1995; Henkin and Levy, 2001; Levy et al., 1999; Yousem et al., 1999, see Bengtsson et al., 2001; Levy et al., 1997).

This experiment investigated the effects of commercially available lavender oil on subsequent polysomnographic (PSG) sleep in healthy young men and women. We hypothesized that lavender would promote sleep by increasing SWS (in a manner similar to other sensory stimuli) and by shortening sleep onset latency when presented before bedtime. We also predicted that lavender would produce gender-differentiated effects, with larger PSG changes in women. Finally, we predicted that lavender would increase sleepiness and fatigue and decrease vigor at bedtime.

#### MATERIALS AND METHODS

#### **Participants**

Thirty-one subjects, 16 men and 15 women, ages 18 to 30 yr (overall mean age  $\pm$  SD, 20.5  $\pm$  2.4 yr; men: 20.2  $\pm$  2.9 yr; women: 20.8  $\pm$  1.8 yr) participated. Subjects were recruited through local newspaper advertisements and campus postings and were screened by telephone and in-person interviews. These interviews ascertained that all subjects were in good physical and psychological health, were healthy sleepers, were not using central nervous system medications, and had no history of respiratory disease such as chronic asthma or sinus problems. Subjects with extreme morningness or eveningness, assessed by the Morningness-Eveningness Questionnaire (Horne and Ostberg, 1976), were excluded. To test olfactory function, subjects were exposed to several odors and water and asked whether they could detect each. Those with detection difficulties were excluded. This supra-threshold detection approach ensured that each subject had a similar minimal level of olfactory functioning and avoided possible expectancy effects that may emerge with sub-threshold concentrations (Campenni et al., 2004; Torii et al., 1988).

Three women were taking oral contraceptives, and all women had normal menstrual cycles. An equal number of women were in their luteal (n = 6) or follicular (n = 6) menstrual cycle phases. Although smokers were not excluded, only 3 subjects (2 men, 1 woman) had a

history of smoking. Subjects maintained a stable wake-up time and bedtime, documented by sleep logs for 1 wk before study entry. Wesleyan University's Institutional Review Board approved the study, and all procedures conformed to the Declaration of Helsinki and to the ethical and good practice standards for biological rhythm research as advanced by the Journal (Touitou et al., 2004). Subjects received monetary compensation for participation and signed informed consent before study entry.

#### Polysomnographic Recordings

Central and occipital electroencephalographic (EEG), electrooculographic (EOG), and submental electromyographic (EMG) measures were recorded from 24:00 (lights off) to 08:00 h (lights on). During the adaptation night, subjects were screened for sleep pathologies, including apneas, oxygen desaturation, and periodic limb movements by monitoring respiratory effort, nasal airflow, arterial oxygen saturation level, bilateral anterior tibialis EMG, and heart rate (EKG). Sleep records were visually scored in 30 sec epochs according to Rechtschaffen and Kales' (1968) standard scoring criteria by two trained scorers blind to the experimental conditions. Inter-rater reliability for the two scorers was 95.2%. Sleep parameters for the whole night and for the first (24:00 to 04:00 h) and second (04:00 to 08:00 h) half of the stimulus and control nights were analyzed.

#### **Subjective Sleepiness and Mood Questionnaires**

The Stanford Sleepiness Scale (SSS; Hoddes et al., 1973) quantifies the progressive, subjective stages of the sleep-alertness continuum, with a scale from 1 to 7 (1: feeling active, vital, alert, or wide awake; 7: sleep onset soon, lost struggle to remain awake). The SSS has been tested with repeated acute sampling periods (*e.g.*, 15 min).

The Profile of Mood States Questionnaire (POMS; McNair et al., 1992), a 65-item self-report scale, assesses transient affective states in response to various stimuli including olfactory cues (Jacob and McClintock, 2000; Jacob et al., 2001; Schiffman et al., 1995). The POMS has been validated in repeated measures designs (reviewed in Schiffman et al., 1995) and sleep studies (Dollins et al., 1994; Jockovich et al., 2000; Wright et al., 1998). Moreover, it has been tested with repeated acute sampling periods (*e.g.*, 3 min; McNair et al., 1992). Each item is rated on a scale from 0 to 4 (0: not at all; 4: extremely), on each of 6 factors: depression-dejection (Depression), tension-anxiety (Tension), angerhostility (Anger), confusion-bewilderment (Confusion), vigor-activity (Vigor), and fatigue-inertia (Fatigue). The total score for each factor is calculated by adding together the respective set of adjectives corresponding to that factor. The total mood disturbance score (TMD), a global estimate

of affective state, derives from summing the factors together, with vigoractivity weighted negatively.

#### Odor

The olfactory stimulus was commercially available lavender oil (International Fragrance and Technology, Inc., Canton, Georgia, USA). The lavender oil contained a natural lavender base component to which constituents were added; it did not contain solvent materials (verified by gas chromatography). This particular lavender oil was validated externally as a sedative in a previous study of subjects recruited from the same college population; in that study, lavender increased fatigue and confusion and decreased vigor compared with distilled water (Goel and Grasso, 2004). Lavender has been rated as neutral to mildly pleasant on pleasantness scales and is neutral on familiarity, intensity, and irritability scales (Knasko, 1992; Levick et al., 1993; Millot and Brand, 2001; Millot et al., 2002; Royet et al., 2000; Savic and Berglund, 2000; Savic and Gulyas, 2000; Zatorre et al., 1992). Distilled water served as the control.

#### **Procedure**

Subjects slept in a sleep laboratory for 3 consecutive overnight sessions (Figure 1). Each session lasted from approximately 21:00 to 08:00 h. On

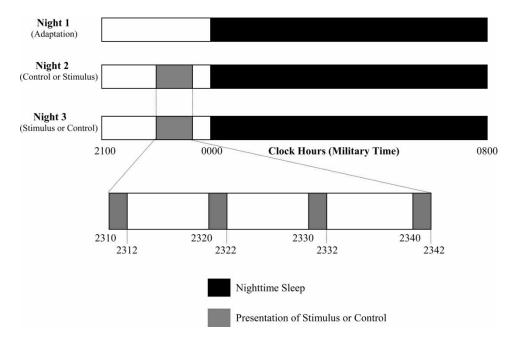


FIGURE 1 Schematic representation of the 3 consecutive night study protocol.

the second and third intervening days, subjects left the laboratory between 08:00 to 21:00 h and engaged in their habitual activities. On these study days, subjects refrained from napping and exercise, and from alcohol or caffeine intake. In addition, subjects were not allowed to wear scented products (*e.g.*, perfume, lotion) or to eat or drink for at least 1 h before test sessions.

Electrode placement for PSG recordings occurred at 21:00 h on all nights. Subjects then engaged in recreational activities until bedtime (24:00 h) on the first night and until 23:10 h on the second and third nights. PSG data were collected from 24:00 to 08:00 h each night. Subjects remained in bed if they awakened before 08:00 h.

The first night served as an adaptation session. During the second and third nights, subjects received either lavender essential oil or distilled water from approximately 23:10 to 23:40 h. Subjects were not told what odors they were receiving, nor were they informed about the odors' intensity, hedonics, or stimulating/sedating properties. They also were not told that one of the vials contained water. The session order was counterbalanced; furthermore, gender was counterbalanced within order assignment. Of the 31 subjects, 16 (9 men, 7 women) received the odor first and 15 (7 men, 8 women) received the control first.

During the experimental session, subjects received lavender oil intermittently between 23:10 and 23:40 h. The stimulus was presented for the first 2 min of each 10 min period (23:10, 23:20, 23:30, and 23:40 h). Subjects held the lavender vial at chest level, and breathed normally and steadily with their eyes closed. The experimenter ensured that subjects remained awake and that no other competing stimuli were present during odor exposure. The control session was identical to the experimental session except that subjects held and smelled a vial containing distilled water. The various components of this experimental procedure, including intermittent odor exposure, the odor administration technique, and use of water as a control have been used previously (Goel and Grasso, 2004; Ilmberger et al., 2001; Kline et al., 2000; Lao et al., 2004). The SSS was administered at 23:50 and 08:00 h on all 3 nights; the POMS was administered at 23:00, 23:12, 23:42, and 08:00 h on the stimulus and control nights. These instruments are designed for repeated measures over short time intervals, as noted above; moreover, any possible repeated administration effects would be observed in both the lavender and control sessions.

#### Statistical Analyses

Repeated measures analyses of variance (ANOVA), with gender and session order as between-subject factors, examined differences in PSG measures and SSS and POMS scores between the two sessions. A companion manuscript in this journal issue reports on the 3-night analyses (including the adaptation night) for these measures, highlighting robust gender differences (Goel et al., 2005). Post-hoc tests, corrected for multiple comparisons, examined significant interactions for all measures. The magnitude of between-group differences in scores was expressed as effect size, d, the standardized difference between means (d=0.3, small; 0.5, medium; 0.8, large; Cohen, 1988). Data are presented as mean  $\pm$  SD; p < 0.05 was considered significant for all statistical analyses.

#### **RESULTS**

#### Polysomnographic (PSG) Sleep

#### Session Order Differences

There were no significant session order (stimulus-control vs. control-stimulus) differences in PSG measures for the whole night, or for the first or second half of the night. Furthermore, there were no significant session order  $\times$  gender interactions for any PSG measure.

#### Session Differences

Across the whole night, lavender significantly increased deep or SWS (stages 3 and 4) %sleep period time (the duration from sleep onset to the end of sleep; SPT) compared with the control ( $F_{1,27}=10.41,\,p<0.005,\,d=0.29$ ; Table 1). Similarly, during the first half of the night, SWS %SPT was significantly higher following lavender exposure (13.3%  $\pm$  7.7% vs. 11.5%  $\pm$  8.5%;  $F_{1,27}=4.79, p<0.05, d=0.22$ ). More specifically, lavender significantly increased SWS duration during the first NREM-REM cycle (NREM sleep followed immediately by rapid eye movement [REM] sleep; 24.5  $\pm$  16.0 vs. 20.4  $\pm$  15.6 min;  $F_{1,27}=4.33,\,p<0.05,\,d=0.26$ ). Although there were no significant session differences in sleep measures for the second half of the night, SWS %SPT showed a trend toward significance in the same direction as that for the first half of the night (0.9%  $\pm$  1.8% vs. 0.4%  $\pm$  0.5%;  $F_{1,27}=3.24,\,p=0.08,\,d=0.40$ ).

#### Session × Gender Differences

Across the whole night, wake after sleep onset (WASO) latency (the time to reach wake after first falling asleep) showed a significant session  $\times$  gender interaction ( $F_{1,10} = 10.07$ , p < 0.01; Table 1): compared with the control, lavender decreased WASO latency in women, while increasing WASO latency in men. WASO latency did not differ significantly between sessions for either gender (men,  $t_8 = 0.38$ , p = 0.71, d = 0.02; women,

**TABLE 1** Mean  $\pm$  SD Whole Night Sleep Measures for the Stimulus and Control Nights

	Stimulus night			Control night		
PSG measure	Men	Women	Total	Men	Women	Total
Total sleep time (TST), min	$453.7 \pm 29.2$	467.9 ± 13.3	$460.6 \pm 23.7$	$451.0 \pm 27.1$	$463.4 \pm 20.7$	$457.0 \pm 24.6$
Sleep period time (SPT), min <sup>a</sup>	$460.8 \pm 23.1$	$471.5 \pm 7.1$	$466.0 \pm 17.8$	$456.6 \pm 26.3$	$469.2 \pm 9.0$	$462.7 \pm 20.6$
Total wake time (TWT), min	$26.1 \pm 29.4$	$9.9 \pm 12.1$	$18.2 \pm 23.9$	$27.9 \pm 25.7$	$14.9 \pm 20.0$	$21.6 \pm 23.7$
Sleep efficiency (SE), %	$94.6 \pm 6.1$	$97.8 \pm 2.6$	$96.1 \pm 5.0$	$94.2 \pm 5.4$	$96.8 \pm 4.2$	$95.5 \pm 5.0$
Sleep maintenance efficiency (SME), %	$98.4 \pm 3.1$	$99.3 \pm 2.3$	$98.8 \pm 2.7$	$98.8 \pm 1.6$	$98.7 \pm 2.8$	$98.8 \pm 2.2$
Sleep onset latency (SOL), min	$18.5 \pm 23.6$	$5.9 \pm 5.3$	$12.4 \pm 18.2$	$22.5 \pm 24.7$	$9.2 \pm 8.4$	$16.0 \pm 19.6$
Wake after sleep onset (WASO), %SPT	$1.7 \pm 3.0$	$0.8 \pm 2.3$	$1.2 \pm 2.7$	$1.2 \pm 1.6$	$1.3 \pm 2.8$	$1.2 \pm 2.2$
WASO, latency, min <sup>b</sup>	$245.3 \pm 112.3$	$94.9 \pm 88.0$	$191.6 \pm 125.4$	$243.3 \pm 113.0$	$186.6 \pm 156.7$	$223.6 \pm 129.2$
Stage 1, %SPT	$2.7 \pm 2.5$	$1.7 \pm 1.6$	$2.2 \pm 2.1$	$2.6 \pm 1.3$	$3.4 \pm 4.4$	$3.0 \pm 3.2$
Stage 1, latency, min	$18.4 \pm 23.6$	$5.9 \pm 5.3$	$12.4 \pm 18.2$	$23.0 \pm 24.6$	$31.4 \pm 84.8$	$27.1 \pm 60.7$
Stage 2, %SPT	$65.6 \pm 5.0$	$66.8 \pm 7.0$	$66.2 \pm 6.0$	$67.9 \pm 4.6$	$64.7 \pm 8.4$	$66.3 \pm 6.8$
Stage 2, latency, min	$23.9 \pm 25.0$	$9.4 \pm 5.3$	$16.9 \pm 19.5$	$25.5 \pm 25.6$	$13.8 \pm 10.8$	$19.8 \pm 20.4$
Slow-wave sleep (SWS; Stages $3 + 4$ ), SPT <sup>c</sup>	$6.8 \pm 3.9$	$7.1 \pm 4.4$	$6.9 \pm 4.1$	$5.6 \pm 3.8$	$5.8 \pm 4.8$	$5.7 \pm 4.2$
SWS (Stages $3 + 4$ ), latency, min	$58.3 \pm 32.1$	$41.9 \pm 13.1$	$50.4 \pm 25.8$	$64.9 \pm 45.9$	$49.0 \pm 19.2$	$57.2 \pm 35.9$
Non-rapid eye movement (NREM), %SPT	$75.2 \pm 5.7$	$75.6 \pm 5.4$	$75.4 \pm 5.5$	$76.2 \pm 6.6$	$73.9 \pm 4.2$	$75.1 \pm 5.6$
Rapid-eye movement (REM), %SPT	$23.2 \pm 5.6$	$23.7 \pm 5.3$	$23.4 \pm 5.4$	$22.6 \pm 6.5$	$24.9 \pm 2.9$	$23.7 \pm 5.1$
REM, latency, min	$114.4 \pm 46.7$	$101.8 \pm 53.4$	$108.3 \pm 49.6$	$128.4 \pm 75.3$	$95.3 \pm 37.3$	$112.4 \pm 61.4$

<sup>&</sup>lt;sup>a</sup>SPT is defined as the duration from sleep onset to the end of sleep.

<sup>&</sup>lt;sup>b</sup>Significant session × gender interaction for the stimulus and control nights (p < 0.01).

<sup>&</sup>lt;sup>c</sup>Significant session effect for the stimulus and control nights (p < 0.005).

 $t_4 = 1.00$ , p = 0.38, d = 0.68), although women showed a significantly shorter WASO latency with lavender ( $F_{1,13} = 6.62$ , p < 0.05; d = 1.44).

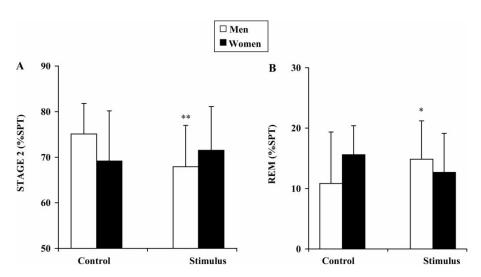
In the first half of the night, stage 2 %SPT showed a significant session × gender interaction ( $F_{1,27} = 14.34$ , p < 0.001): compared with the water control, lavender reduced stage 2 %SPT in men ( $t_{15} = 4.41$ , p < 0.001, d = 0.90; Figure 2A), but not in women ( $t_{14} = 1.22$ , p = 0.24, d = 0.23). REM %SPT also showed a significant session × gender interaction ( $F_{1,27} = 7.25$ , p < 0.05): compared with water, lavender significantly increased REM %SPT in men ( $t_{15} = 2.10$ , p < 0.05, d = 0.54; Figure 2B), but not in women ( $t_{14} = 1.42$ , p = 0.18, d = 0.51). There were no significant interactions in PSG measures in the second half of the night.

#### Subjective Sleepiness and Mood

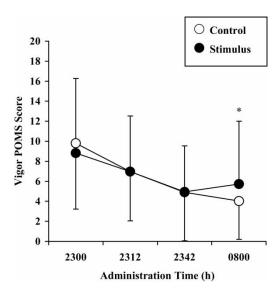
Vigor showed a significant session × time interaction ( $F_{3,66} = 3.93$ , p < 0.05), with higher scores at 08:00 h in the lavender than control session ( $t_{26} = 2.44$ , p < 0.05, d = 0.32; Figure 3). There were no other significant POMS differences. SSS scores did not differ significantly between the lavender and control sessions, between the morning and evening, or between men and women.

#### DISCUSSION

This study demonstrates sleep-promoting effects of lavender odor in young healthy male and female sleepers. Lavender produced small but



**FIGURE 2** Significant session × gender interactions in the first half of the night for (A) Stage 2 %SPT and (B) REM %SPT (mean  $\pm$  SD). Men showed significant differences in these measures between the control and stimulus nights (\* = p < 0.05; \*\* = p < 0.001).



**FIGURE 3** Vigor POMS scores across assessment time points for the stimulus and control nights (mean  $\pm$  SD). \* Significantly greater than the control night, p < 0.05.

significant increases in SWS or deep sleep in all subjects, with higher vigor the morning following exposure. In addition, lavender produced gender-differentiated effects on stage 2 and REM sleep, and WASO latency, underscoring gender as an important variable for future sleep research using young populations.

The predicted SWS increase corroborates previous reports of improved sleep quality following exposure to lavender (Hardy, 1991; Henry et al., 1994; Hudson, 1996; Wolfe and Herzberg, 1996) or other odors (Connell et al., 2001; Raudenbush et al., 2003; Sano et al., 1998; Svoboda et al., 2002). While these earlier studies contained methodological drawbacks, our results demonstrate lavender's sleep-promoting effects using a larger sample and objective sleep measures. Furthermore, the SWS increase, indicating lavender's sedative properties, concurs with lavender-induced reductions in blood pressure and heart rate (Nagai et al., 2000; Romine et al., 1999). In contrast to our prediction, however, lavender did not shorten sleep onset latency. Since all subjects were healthy sleepers, who on average fell asleep approximately 15 min after lights off, the short sleep latencies may have precluded detection of lavender-induced changes.

Lavender likely would substantially affect sleep onset latency, and thus perhaps the circadian timing of sleep, in subjects with initial insomnia or in older adults. Indeed, other mild nonpharmacologic sedatives, such as valerian, show individual differences in effectiveness, with greater responses in habitually poor or irregular sleepers, including the elderly

(Leathwood and Chauffard, 1982). Beyond these groups, lavender also may benefit depressed subjects who characteristically show reductions in SWS, along with other sleep changes (Benca et al., 1992). Certainly, depressed young adults show a heightened ability to discriminate lavender (Goel and Grasso, 2004). Finally, lavender may be used to promote sleep in critically ill or hospitalized patients, two groups that have shown benefit from aromatherapy (Richards et al., 2003; Waldman et al., 1993).

Increases in SWS %SPT were found during the first, but not the second half of the night, and were found predominantly during the first NREM-REM cycle, suggesting that lavender's effects on deep sleep do not persist throughout the night. Given its route of administration, lavender likely is absorbed quickly, exerting immediate but transient effects. Moreover, a lack of morning sleepiness score changes suggests that lavender does not produce "hangover" effects the next day.

The significant session  $\times$  gender interactions for WASO latency, stage 2 %SPT, and REM %SPT may reflect differences in odor abilities between men and women, as supported by other studies (see reviews, Brand and Millot, 2001; Velle, 1987). Specifically, neural activation differences may explain the contrasting changes in these sleep measures observed between men and women. Indeed, odors activate different structures (Savic et al., 2001) or produce greater responses in women (Becker et al., 1993; Evans et al., 1995; Henkin and Levy, 2001; Levy et al., 1999; Yousem et al., 1999) than in men (Levy et al., 1997). There also may be chemical (systemic/non-perceptual) gender differences for lavender, or inhalation and dosing differences, since we did not control breathing rates. In contrast with sleep changes, lavender did not produce genderdifferentiated mood changes, concurring with our earlier study using the same odor and self-rated questionnaire (Goel and Grasso, 2004). Thus, our results suggest that the gender-differentiated sleep responses may be mediated by physiological rather than psychological mechanisms.

Lavender increased vigor the morning following exposure, corroborating the increase in restful deep sleep. By contrast, POMS changes were not detected immediately following exposure at 23:42 h. The absence of such immediate changes, including in vigor and fatigue, contrasts another study in which lavender increased fatigue, anxiety, anger, confusion, and total mood disturbance, and decreased vigor compared with distilled water (Goel and Grasso, 2004). Our results also contrast with studies that found lavender decreased tension/anxiety (Dunn et al., 1995; Itai et al., 2000; Kawai and Noro, 1996; Louis and Kowalski, 2002), improved mood (Dunn et al., 1995; Knasko, 1992), and reduced total mood disturbance (Diego et al., 1998) and stress (Motomura et al., 2001). Such differences may be due to lavender administration time or exposure duration.

Similarly, lavender did not affect subjective sleepiness before bedtime. Other mild sedatives, such as melatonin, also produce changes in objective sleep without SSS changes (Pires et al., 2001; Zhandova et al., 1995; but see Dollins et al., 1994). Our results may seem inconsistent with previous findings indicating immediate physiological, including EEG, changes following lavender exposure (Diego et al., 1998; Klemm et al., 1992). Such discrepant results may reflect the inaccuracy of self-rated evaluations or the possibility that lavender produces physiological changes without awareness by the subjects.

Overall, our findings are consistent with previous studies suggesting that sensory stimulation or salient behavioral experiences occurring during wakefulness affect subsequent sleep by modulating the neural structures regulating sleep-wake cycles (Cantero et al., 2002; Drucker-Colin, 1995; García-García et al., 1998; Velluti, 1997). Indeed, all of the following stimuli also increase SWS: auditory cues (Cantero et al., 2002; Fruhstorfer et al., 1984, 1988); visual cues (Horne and Walmsley 1976); exercise (e.g., Bunnell et al., 1983; Horne and Moore, 1985; Horne and Staff, 1983; Youngstedt et al., 1997), and body warming (Bunnell et al., 1988; Dorsey et al., 1999; Horne and Reid, 1985; Sung and Tochihara, 2000). Thus, olfactory cues may share a common mechanism with other behavioral and sensory stimuli for modulating the release of specific sleep-inducing substances that promote deep sleep (García-García et al., 1998).

Lavender modulates intracellular cyclic adenosine monophosphate (cAMP) activity (Lis-Balchin and Hart, 1999), and its principal component, linalool, inhibits glutamate binding; both factors may produce sedative effects (Elisabetsky et al., 1995). The neuroanatomical pathways mediating lavender's sedative sleep effects, however, remain unknown. All odors, including lavender, activate the primary olfactory cortex and its neural connections, including the amygdala, anterior cingulate, claustrum, and the piriform, entorhinal, insular, and orbitofrontal cortices (see Bengtsson et al., 2001; Levy et al., 1997, 1999; Royet et al., 2000; Savic and Gulyas, 2000; Zatorre et al., 1992). These olfactory targets may subsequently transduce information to the various brain centers implicated in the control of the sleep-wake cycle, including its circadian component. Alternatively, lavender may exert its effects systemically through the blood after entry into the nasal passages.

This is the first study to examine the effects of an olfactory stimulus presented before bedtime on subsequent objective sleep. In all subjects, lavender odor produced increases in SWS compared with the control, and increased vigor the next morning. Lavender also showed differential gender effects for WASO latency, stage 2, and REM sleep: it increased stage 2 and decreased REM sleep and WASO latency in women, but produced the opposite effects in men. Our results have practical applications and merit future studies. Commercially available lavender oil may be used as a mild soporific and a nonphotic alternative or safe adjunctive (Atanassova-Shopova and Roussinov, 1970) to other substances, such as

valerian or melatonin, for relieving mild sleep disturbance. Other essential oils that also are natural sedatives, such as chamomile, may produce similar sleep effects; by contrast, stimulating odors such as jasmine, may disrupt sleep (Gyllenhaal et al., 2000). Aromatherapy shows promise for modifying sleep and perhaps its circadian timing in various populations, including insomniacs, depressed patients, and the elderly.

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#### REFERENCES

- Atanassova-Shopova, S., Roussinov, K.S. (1970). On certain central neurotropic effects of lavender essential oil. Bull. Instit. Physiology 8:69–76.
- Badia, P., Wesensten, N., Lammers, W., Culpepper, J., Harsh, J. (1990). Responsiveness to olfactory stimuli presented in sleep. *Physiol. Behav.* 48:87–90.
- Becker, E., Hummel, T., Piel, E., Pauli, E., Kobal, G., Hautzinger, M. (1993). Olfactory event-related potentials in psychosis-prone subjects. Int. J. Psychophysiol. 15:51–58.
- Benca, R.M., Obermeyer, W.H., Thisted, R.A., Gillin, J.C. (1992). Sleep and psychiatric disorders. A meta-analysis. *Arch. Gen. Psychiatry* 49:651–668.
- Bengtsson, S., Berglund, H., Gulyas, B., Cohen, E., Savic, I. (2001). Brain activation during odor perception in males and females. *Neuroreport* 12:2027–2033.
- Borbély, A.A. (1982). Circadian and sleep-dependent processes in sleep regulation. In: Aschoff, J., Daan, S., Groos, G., eds. *Vertebrate Circadian Systems*. Berlin: Springer-Verlag, pp. 237–242.
- Brand, G., Millot, J.L. (2001). Sex differences in human olfaction: Between evidence and enigma. Q. J. Exp. Psychol. B. 54:259–270.
- Buckle, J. (2001). The role of aromatherapy in nursing care. Nurs. Clin. North Am. 36:57-72.
- Bunnell, D.E., Bevier, W., Horvath, S.M. (1983). Effects of exhaustive exercise on the sleep of men and women. Psychophysiology 20:50–58.
- Bunnell, D.E., Agnew, J.A., Horvath, S.M., Jopson, L., Wills, M. (1988). Passive body heating and sleep: influence of proximity to sleep. *Sleep* 11:210–219.
- Campenni, C.E., Crawley, E.J., Meier, M.E. (2004). Role of suggestion in odor-induced mood change. Psychol. Rep. 94:1127–1136.
- Cantero, J.L., Atienza, M., Salas, R.M. (2002). Effects of waking-auditory stimulation on human sleep architecture. Behav. Brain Res. 128:53–59.
- Carskadon, M.A., Herz, R.S. (2004). Minimal olfactory perception during sleep: why odor alarms will not work for humans. Sleep 27:402–405.
- Cohen, J. (1988). Statistical Power Analysis for the Behavioral Sciences, 2nd ed.. Hillsdale, NJ: Lawrence Erlbaum Associates.
- Connell, F.E.A., Tan, G., Gupta, I., Gompertz, P., Bennett, G.C.J., Herzberg, J.L. (2001). Can aromatherapy promote sleep in elderly hospitalized patients? *Geriatr. Today: J. Can. Geriatr. Soc.* 4: 191–195.
- Davidson, A.J., Menaker, M. (2003). Birds of a feather clock together—sometimes: social synchronization of circadian rhythms. Curr. Opin. Neurobiol. 13:765–769.

- Diego, M.A., Jones, N.A., Field, T., Hernandez-Reif, M., Schanberg, S., Kuhn, C., McAdam, V., Galamaga, R., Galamaga, M. (1998). Aromatherapy positively affects mood, EEG patterns of alertness and math computations. *Int. J. Neurosci.* 96:217–224.
- Dollins, A.B., Zhdanova, I.V., Wurtman, R.J., Lynch, H.J., Deng, M.H. (1994). Effect of inducing nocturnal serum melatonin concentrations in daytime on sleep, mood, body temperature, and performance. *Proc. Natl. Acad. Sci.* 91:1824–1828.
- Dorsey, C.M., Teicher, M.H., Cohen-Zion, M., Stefanovic, L., Satlin, A., Tartarini, W., Harper, D., Lukas, S.E. (1999). Core body temperature and sleep of older female insomniacs before and after passive body heating. *Sleep* 22:891–898.
- Drucker-Colin, R. (1995). The function of sleep is to regulate brain excitability in order to satisfy the requirements imposed by waking. *Behav. Brain Res.* 69:117–124.
- Dunn, C., Sleep, J., Collett, D. (1995). Sensing an improvement: an experimental study to evaluate the use of aromatherapy, massage and periods of rest in an intensive care unit. *J. Adv. Nurs.* 21:34–40.
- Elisabetsky, E., Marschner, J., Souza, D.O. (1995). Effects of linalool on glutamatergic system in the rat cerebral cortex. Neurochem. Res. 20:461–465.
- Evans, W.J., Cui, L., Starr, A. (1995). Olfactory event-related potentials in normal human subjects: effects of age and gender. *Electroencephalogr. Clin. Neurophysiol.* 95:293–301.
- Fruhstorfer, B., Fruhstorfer, H., Grass, P. (1984). Daytime noise and subsequent night sleep in man. Eur. J. Appl. Physiol. Occup. Physiol. 53:159–163.
- Fruhstorfer, B., Pritsch, M.G., Fruhstorfer, H. (1988). Effects of daytime noise load on the sleep-wake cycle and endocrine patterns in man: I. 24 hours neurophysiological data. *Int. J. Neurosci.* 39: 197–209.
- García-García, F., Beltran-Parrazal, L., Jimenez-Anguiano, A., Vega-Gonzalez, A., Drucker-Colin, R. (1998). Manipulations during forced wakefulness have differential impact on sleep architecture, EEG power spectrum, and Fos induction. *Brain Res. Bull.* 47:317–324.
- Goel, N., Grasso, D.J. (2004). Olfactory discrimination and transient mood change in young men and women: variation by season, clinical state and time of day. *Chronobiol. Int.* 21:691–719.
- Goel, N., Kim, H., Lao, R.P. (2005). Gender differences in polysomnographic sleep in young healthy sleepers. Chronobiol. Int. 22(5):905–915.
- Gyllenhaal, C., Merritt, S.L., Peterson, S.D., Block, K.I., Gochenour, T. (2000). Efficacy and safety of herbal stimulants and sedatives in sleep disorders. Sleep Med. Rev. 4:229–251.
- Hardy, M. (1991). Sweet scented dreams. Int. J. Aromatherapy 3:12-13.
- Henkin, R.I., Levy, L.M. (2001). Lateralization of brain activation to imagination and smell of odors using functional magnetic resonance imaging (fMRI): left hemispheric localization of pleasant and right hemispheric localization of unpleasant odors. J. Comput. Assist. Tomogr. 25:493–514.
- Henry, J., Rusius, C.W., Davies, M., Veazey-French, T. (1994). Lavender for night sedation of people with dementia. *Int. J. Aromatherapy* 6:28–30.
- Hoddes, E., Zarcone, V., Smythe, H., Phillips, R., Dement, W.C. (1973). Quantification of Sleepiness: a new approach. *Psychophysiology* 10:431–436.
- Horne, J.A., Moore, V.J. (1985). Sleep EEG effects of exercise with and without additional body cooling. Electroencephalogr. Clin. Neurophysiol. 60:33–38.
- Horne, J.A., Östberg, O. (1976). A self-assessment questionnaire to determine morningnesseveningness in human circadian rhythms. Int. J. Chronobiol. 4:97–110.
- Horne, J.A., Reid, A.J. (1985). Night-time sleep EEG changes following body heating in a warm bath. *Electroencephalogr. Clin. Neurophysiol.* 60:154–157.
- Horne, J.A., Staff, L.H. (1983). Exercise and sleep: body-heating effects. Sleep 6:36-46.
- Horne, J.A., Walmsley, B. (1976). Daytime visual load and the effects upon human sleep. Psychophysiology 13:115–120.
- Hudson, R. (1996). The value of lavender for rest and activity in the elderly patient. Complement. Ther. Med. 4:52–57.
- Ilmberger, J., Heuberger, E., Mahrhofer, C., Dessovic, H., Kowarik, D., Buchbauer, G. (2001). The influence of essential oils on human attention. I: alertness. *Chem. Senses* 26:239–245.
- Itai, T., Amayasu, H., Kuribayashi, M., Kawamura, N., Okada, M., Momose, A., Tateyama, T., Narumi, K., Uematsu, W., Kaneko, S. (2000). Psychological effects of aromatherapy on chronic hemodialysis patients. *Psychiatry Clin. Neurosci.* 54:393–397.
- Jacob, S., McClintock, M.K. (2000). Psychological state and mood effects of steroidal chemosignals in women and men. Horm. Behav. 37:57–78.

- Jacob, S., Hayreh, D.J., McClintock, M.K. (2001). Context-dependent effects of steroid chemosignals on human physiology and mood. *Physiol. Behav.* 74:15–27.
- Jockovich, M., Cosentino, D., Cosentino, L., Wears, R.L., Seaberg, D.C. (2000). Effect of exogenous melatonin on mood and sleep efficiency in emergency medicine residents working night shifts. *Acad. Emerg. Med.* 7:955–958.
- Karamat, E., Ilmberger, J., Roblhuber, K., Rupp, C. (1992). Excitatory and sedative effects of essential oils on human reaction time performance. Chem. Senses 16:847.
- Kawai, T., Noro, K. (1996). Psychological effect of stereoscopic 3-D images with fragrances. Ergonomics 39:1364–1369.
- Klemm, W.R., Lutes, S.D., Hendrix, D.V., Warrenburg, S. (1992). Topographical EEG maps of human responses to odors. Chem. Senses 17:347–361.
- Kline, J.P., Blackhart, G.C., Woodward, K.M., Williams, S.R., Schwartz, G.E. (2000). Anterior electroencephalographic asymmetry changes in elderly women in response to a pleasant and an unpleasant odor. *Biol. Psychol.* 52:241–250.
- Knasko, S.C. (1992). Ambient odor's effect on creativity, mood, and perceived health. Chem. Senses 17: 27–35.
- Lao, R.P., Goel, N., Lee, A.K. (2004). Peppermint odor modifies subsequent sleep and sleepiness in young men and women. Sleep Res. 27:A402.
- Leathwood, P.D., Chauffard, F. (1982). Quantifying the effects of mild sedatives. *J. Psychiatr. Res.* 17: 115–122.
- Levick, S.E., Lorig, T., Wexler, B.E., Gur, R.E., Gur, R.C., Schwartz, G.E. (1993). Asymmetrical visual deprivation: a technique to differentially influence lateral hemispheric function. *Percept. Mot. Skills* 76:1363–1382.
- Levy, L.M., Henkin, R.I., Hutter, A., Lin, C.S., Martins, D., Schellinger, D. (1997). Functional MRI of human olfaction. J. Comput. Assist. Tomogr. 21:849–856.
- Levy, L.M., Henkin, R.I., Lin, C.S., Hutter, A., Schellinger, D. (1999). Odor memory induces brain activation as measured by functional MRI. J. Comput. Assist. Tomogr. 23:487–498.
- Lis-Balchin, M., Hart, S. (1999). Studies on the mode of action of the essential oil of lavender (Lavandula angustifolia P. Miller). Phytother. Res. 13:540–542.
- Lorig, T.S., Schwartz, G.E. (1988). Brain and odor: I. Alteration of human EEG by odor administration. *Psychobiology* 16:281–284.
- Lorig, T.S., Herman, K.B., Schwartz, G.E., Cain, W.S. (1990). EEG activity during administration of low-concentration odors. Bull. Psychonomic Soc. 28:405–408.
- Louis, M., Kowalski, S.D. (2002). Use of aromatherapy with hospice patients to decrease pain, anxiety, and depression and to promote an increased sense of well-being. *Am. J. Hosp. Palliat. Care* 19: 381–386.
- Ludvigson, H.W., Rottman, T.R. (1989). Effects of ambient odors of lavender and cloves on cognition, memory, affect and mood. Chem. Senses 14:525–536.
- Masago, R., Matsuda, T., Kikuchi, Y., Miyazaki, Y., Iwanaga, K., Harada, H., Katsuura, T. (2000). Effects of inhalation of essential oils on EEG activity and sensory evaluation. J. Physiol. Anthropol. 19:35–42.
- McNair, D.M., Lorr, M., Droppleman, L.F. (1992). *Profile of Mood States (Manual)*. San Diego, CA: Educational and Industrial Testing Service.
- Millot, J.L., Brand, G. (2001). Effects of pleasant and unpleasant ambient odors on human voice pitch. Neurosci. Lett. 297:61–63.
- Millot, J.L., Brand, G., Morand, N. (2002). Effects of ambient odors on reaction time in humans. Neurosci. Lett. 322:79–82.
- Mistlberger, R.E., Skene, D.J. (2004). Social influences on mammalian circadian rhythms: animal and human studies. *Biol. Rev. Camb. Philos. Soc.* 79:533–556.
- Motomura, N., Sakurai, A., Yotsuya, Y. (2001). Reduction of mental stress with lavender odorant. Percept. Mot. Skills 93:713–718.
- Nagai, M., Wada, M., Usui, N., Tanaka, A., Hasebe, Y. (2000). Pleasant odors attenuate the blood pressure increase during rhythmic handgrip in humans. *Neurosci. Lett.* 289:227–229.
- Pires, M.L., Benedito-Silva, A.A., Pinto, L., Souza, L., Vismari, L., Calil, H.M. (2001). Acute effects of low doses of melatonin on the sleep of young healthy subjects. J. Pineal Res. 31:326–332.
- Price, S., Price, L. (1999). Aromatherapy for Health Professionals. London: Churchill Livingstone.

- Raudenbush, B., Koon, J., Smith, J., Zoladz, P. (2003). Effects of odorant administration on objective and subjective measures of sleep quality, post-sleep mood and alertness, and cognitive performance. *North Amer. J Psych.* 5:181–192.
- Rechtschaffen, A., Kales, A. (1968). A Manual of Standardized Terminology, Techniques and Scoring System for Sleep Stages of Human Subjects. Washington, DC: National Institute of Health.
- Richards, K., Nagel, C., Markie, M., Elwell, J., Barone, C. (2003). Use of complementary and alternative therapies to promote sleep in critically ill patients. *Crit. Care Nurs. Clin. North Am.* 15:329–340.
- Romine, I.J., Bush, A.M., Geist, C.R. (1999). Lavender aromatherapy in recovery from exercise. Percept. Mot. Skills 88:756–758.
- Royet, J.P., Zald, D., Versace, R., Costes, N., Lavenne, F., Koenig, O., Gervais, R. (2000). Emotional responses to pleasant and unpleasant olfactory, visual, and auditory stimuli: a positron emission tomography study. J. Neurosci. 20:7752–7759.
- Sano, A., Sei, H., Seno, H., Morita, Y., Moritoki, H. (1998). Influence of cedar essence on spontaneous activity and sleep of rats and human daytime nap. *Psychiatry Clin. Neurosci.* 52:133–135.
- Savic, I., Berglund, H. (2000). Right-nostril dominance in discrimination of unfamiliar, but not familiar, odours. Chem. Senses 25:517–523.
- Savic, I., Gulyas, B. (2000). PET shows that odors are processed both ipsilaterally and contralaterally to the stimulated nostril. *Neuroreport*. 11:2861–2866.
- Savic, I., Berglund, H., Gulyas, B., Roland, P. (2001). Smelling of odorous sex hormone-like compounds causes sex-differentiated hypothalamic activations in humans. *Neuron.* 31:661–668.
- Schiffman, S.S., Sattely Miller, E.A., Suggs, M.S., Graham, B.G. (1995). The effect of pleasant odors and hormone status on mood of women at midlife. *Brain Res. Bull.* 36:19–29.
- Sung, E.J., Tochihara, Y. (2000). Effects of bathing and hot footbath on sleep in winter. J. Physiol. Anthropol. 19:21–27.
- Svoboda, K.P., Karavia, A.N., McFarlane, V. (2002). Case study: the effects of selected essential oils on mood, concentration and sleep in a group of 10 students monitored for 5 weeks. *Int. J. Aromatherapy* 12:157–161.
- Tisserand, R. (1988). Essential oils as psychotherapeutic agents. In: Van Toller, S., Dodd, G.H., eds. Perfumery: The Psychology and Biology of Fragrance. New York, NY: Chapman Hall, pp. 167–181.
- Torii, S., Fukuda, H., Kanemoto, H., Miyanchi, R., Hamauzu, Y., Kawasaki, M. (1988). Contingent negative variation and the psychological effects of odour. In: Van Toller, S., Dodd, G.H., eds. *Perfumery: The Psychology and Biology of Fragrance*. New York, NY: Chapman Hall, pp. 107–120.
- Touitou, Y., Portaluppi, F., Smolensky, M.H., Rensing, L. (2004). Ethical principles and standards for the conduct of human and animal biological rhythm research. *Chronobiol. Int.* 21:161–170.
- Velle, W. (1987). Sex differences in sensory functions. Perspect. Biol. Med. 30:490-522.
- Velluti, R.A. (1997). Interactions between sleep and sensory physiology. J. Sleep Res. 6:61-77.
- Waldman, C.S., Tseng, P., Meulman, P., Whittet, H.B. (1993). Aromatherapy in the intensive care unit. Care Critically Ill 9:170–174.
- Wolfe, N., Herzberg, J. (1996). Can aromatherapy oils promote sleep in severely demented patients? Int. J. Geriatr. Psychiatry 11:926–927.
- Wright, S.W., Lawrence, L.M., Wrenn, K.D., Haynes, M.L., Welch, L.W., Schlack, H.M. (1998). Randomized clinical trial of melatonin after night-shift work: efficacy and neuropsychologic effects. Ann. Emerg. Med. 32:334–340.
- Yagyu, T. (1994). Neurophysiological findings on the effects of fragrance: lavender and jasmine. *Integr. Psychiatry* 10:62–67.
- Youngstedt, S.D., O'Connor, P.J., Dishman, R.K. (1997). The effects of acute exercise on sleep: a quantitative synthesis. Sleep 20:203–214.
- Yousem, D.M., Maldjian, J.A., Siddiqi, F., Hummel, T., Alsop, D.C., Geckle, R.J., Bilker, W.B., Doty, R.L. (1999). Gender effects on odor-stimulated functional magnetic resonance imaging. *Brain Res.* 818:480–487.
- Zatorre, R.J., Jones-Gotman, M., Evans, A.C., Meyer, E. (1992). Functional localization and lateralization of human olfactory cortex. *Nature* 360:339–340.
- Zhdanova, I.V., Wurtman, R.J., Lynch, H.J., Ives, J.R., Dollins, A.B., Morabito, C., Matheson, J.K., Schomer, D.L. (1995). Sleep-inducing effects of low doses of melatonin ingested in the evening. *Clin. Pharmacol. Ther.* 57:552–558.