Lavender Discrimination in Parkinson's Disease

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Article

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Abstract

The scent of lavender has been purported to promote sleep in patients with neurodegenerative disease, but an obvious paradox is how, given the widely recognized deficits in olfaction observed in such patients, such an effect could occur. In this study we examined the ability of Parkinson's Disease patients to discriminate lavender from rose in a forced-choice discrimination task. Results indicated that most Parkinson's patients could not discriminate lavender above chance, although about a third were able to do so. This preserved ability was unrelated to disease severity or years with diagnosis. It was unrelated to age- and sex-adjusted performance on a standardized test of olfaction (University of Pennsylvania Smell Identification Test). These results were compatible with lavender's potential impact via trigeminal afferents and leave open the possibility that lavender could indeed impact sleep in some patients with neurodegenerative disease.

Introduction

Aromatherapy has been purported to have beneficial effects for agitation and sleep in dementia patients [1,2] although a recent review noted questionable quality and high risk of bias in most of this work [3]. Lavender, specifically, has been shown in many [4-10], but not all [11-13], studies to reduce agitation, promote relaxation and improve sleep in such patients. An obvious question when interpreting such potential beneficial effects is how, given the longstanding and widely recognized olfactory impairment across many forms of neurodegenerative diseases, including Alzheimer's Disease (AD) [14-16], Parkinson's Disease (PD) [16-19] and even prodromal forms of these conditions, including mild cognitive impairment [20-22] and REM Behavior Disorder [23], such stimuli might confer such benefits on agitation and/or sleep [12]. In this study, we examined the ability of PD patients to discriminate the scent of lavender at levels greater than chance. Availability of more conventional olfactory assessment (University of Pennsylvania Smell Identification Test: UPSIT) also afforded us the opportunity to determine the extent to which overall impairment or preservation of sense of smell might be related to such discrimination ability.

Results

Figure 1 shows the results from the forced-choice lavender discrimination task, expressed as number of correct choices (maximum correct = 6). Assuming that the likelihood of correctly identified pairs would resemble a binomial distribution, about a third (31.9%) of the PD patients were able to identify lavender at levels above chance (i.e., 5 or 6 pairs correctly identified). When compared to controls (93.3%), however, this percentage was considerably lower (Yates corrected chi-square= 14.85, $p = .000116$), indicating that PD patients performed more poorly on forced-choice lavender discrimination when compared to a non-neurologically impaired population.

The mean (SD) absolute number of correct responses on the UPSIT was 21.8 (7.5). When adjusted by sex and age, the mean (SD) percentile was 16.0 (19.9), suggesting that even with such demographic factors taken into account, the PD patients demonstrated clear olfactory impairment, predictably lower than expected norms. UPSIT-derived, age-adjusted percentile performance did not differ between women and men (18.9 [26.2] versus 14.6 [16.4], $t = 0.69$, $p = 0.49$).

We determined whether lavender discrimination was related to overall olfactory discriminative performance among the PD patients by examining UPSIT age- and sex-corrected percentile performances for those patients correctly identifying 5 or 6 pairs versus those correctly identifying 1 to 4 pairs. Differences were not statistically significant (17.8 [SD= 25.1] vs 15.1 [SD = 17.3]; $t = 0.43$, $p = 0.67$). Similarly, neither years with PD diagnosis (6.1 [SD = 5.1] versus 4.9 [SD = 3.2] years, $t = 0.97$, $p = 0.34$) nor UPDRS motor scores (14.9 [SD = 9.3] versus 17.6 [SD = 6.8], $t = 1.07$, $p = 0.29$) significantly differentiated the PD patients correctly identifying lavender versus those who did not.

Finally, we examined whether olfactory acuity specifically involving the 4 items involving rose scent on the UPSIT (1 item with rose as correct target; 3 items with rose as an incorrect distractor) were related to performance on the forced-choice lavender discrimination task. Women correctly identifying 5 or 6 of the lavender forced-choice items tended to be better in differentiation of the presence/absence of rose scent on the UPSIT, relative to women identifying 4 or fewer lavender forced-choice items on the UPSIT (3.17 [SD = 0.75] versus 2.22 [SD = 0.97], $t = 2.02$, $p = 0.06$), but differences for men did not approach statistical significance (2.22 [SD = 1.20] versus 2.00 [SD = 1.24], $t = 0.46$ $p = 0.65$).

Discussion

These results indicate that, despite having grossly impaired olfaction, as is typical of many neurodegenerative conditions [14–19], some PD patients were able to discriminate the scent of lavender from another floral scent at levels that exceeded chance. Furthermore, at least in women with PD, that ability was related somewhat to discrimination of a floral scent on a standardized test of olfaction (UPSIT). These results do not directly address whether a scent such as lavender, when presented at night to promote sleep in patients with advanced neurologic disease [4–10], might induce or sustain sleep in some patients, but they are certainly compatible with such an effect, to the extent that this selected aspect of olfaction evidently remains intact in a subset of these patients. Given the potential danger of many medications used to induce sleep in dementia patients (including older and newer generation anti-psychotic medications), many of which carry so-called “black box” warnings from the United States Food and Drug Administration [26], alternative medicine treatments for nocturnal agitation and disturbed sleep in dementia (often subsumed under the rubric of “sundowning,” [27]), such as aromatherapy, become a potentially attractive intervention for caregivers, despite the adequacy of the empirical data base confirming their efficacy [3].

Our findings do not address directly the mechanisms as to how lavender might promote sleep in patients with neurodegenerative disease. It has been long-established that some of the earliest stages of neurodegeneration may be manifested by protein aggregates in the olfactory bulb and/or olfactory nucleus [28–31]. However, even patients with complete anosmia can detect a wide range of scents [32], indicating that maxillary trigeminal afferents can play a role in identification of certain odors. In PD patients, such function may compensate to some extent in otherwise compromised odor identification via the first cranial nerve [33]. Lavender is a complex molecule containing various components such as linalool, camphor, eucalyptol, terpinene-4-ol, and linalyl acetate [34, 35], and various formulations of lavender oils may contain 2- to 3-fold the concentrations of these various components relative to other formulations [36]. We did not ascertain the varying amounts of these substances present in our samples, though specific odor discrimination studies involving linalool, often considered a key constituent for lavender's anti-microbial properties, have been shown to be detectable in non-PD anosmia patients and be rated as having modest levels of intensity [32]. More relevant for the current discussion are basic science receptor binding and infusion studies that have shown that linalool has anti-glutamatergic properties throughout the rat cerebral cortex and may dampen seizure susceptibility [37, 38], physiological effects which are compatible with the presumed sedative/hypnotic effects of lavender. Additionally, murine models using oral administration have demonstrated immediate effects on the sleep electroencephalogram (EEG) [39]. Further evidence for intactness of an alternative olfaction pathway for lavender and its composite volatile oils in PD patients derives from studies of EEG-derived event related potentials, in which olfactory stimuli (non-lavender) with presumed trigeminal influence showed similar responses in PD and controls [40, 41], and a study of single nostril odor identification in PD, which was interpreted to suggest greater likelihood of trigeminal mediation of scent identification [42].

Arguing against the interpretation that lavender identification relied solely on trigeminal involvement, however, was the suggestion that, at least in women, identification of the scent of rose on the UPSIT, a floral scent usually considered less likely to engage the trigeminal system [32], may have been more likely among those able to identify lavender in the forced-choice task. Like lavender, rose is a monoterpene, but more recent molecular characterization has shown that this scent consists of hundreds of volatile oils that demonstrate considerable molecular variability across different rose types [43]. When one such floral scent, geraniol, was placed head-to-head with linalool, younger anosmia patients without neurodegenerative disease showed far greater accuracy identifying the latter and also rated linalool as more intense, suggesting primacy of the trigeminal system in its detection [32].

It should be noted that not all studies have reported that lavender aromatherapy has beneficial effects on agitation in dementia. Using a within-subjects repeated ABCBA design, Snow et al [12] reported no such effects but left open the possibility that, consistent with post-mortem receptor binding studies suggesting that linalool may have direct anti-convulsant properties and indirect sedative properties [44], dermal contact with lavender oil might still have medicinal effects. For example, linalool and linalyl acetate have rapid skin absorption [34], which would be compatible with such effects. However, a cross-over trial using dermal application of lavender oil also failed to demonstrate immediate beneficial effects on agitation in a nursing home population [13].

There are some weaknesses associated with the approach that we have taken here. Our forced-choice discrimination approach, essentially constructed with available household materials (i.e., commercially available candle-shavings), demonstrates proof-of-concept for lavender discrimination but does not allow precise standardization of stimuli presentation, nor does it control for sniffing effort, which has been suggested to play a role in at least some of the olfactory performance deficits demonstrated by PD patients but which may otherwise be unelated to overall motor impairment [45]. We also did not find an association between PD patients' ability to discriminate lavender and the severity of their motor impairment on the UPDRS. The ability of at least some of the PD patients to discriminate lavender is somewhat surprising, since lack of standardization might have even increased the probability of a negative result. Though our results could be interpreted as compatible with the potential beneficial effects of lavender on sleep in some studies of patients with advanced neurodegenerative diseases [4–10], the presentation of odors during sleep has complex effects, since it is not always apparent that such stimuli, whether pleasant or noxious, impact objective sleep measures. For example, when presented intermittently during EEG monitored sleep in tightly controlled temporally sequences, even stimuli thought to activate olfaction primarily through trigeminal afferents may not always result in altered sleep architecture [46, 47], though acute changes in inspiration and expiration during stimuli presentation have been noted [48]. On the other hand, when presented prior to sleep, certain scents, like lavender, have been reported to enhance sleep quality and increase polysomnographically defined measures such as slow wave sleep, at least in young adults with presumably intact olfactory function [49, 50]. Interestingly, stimuli with both higher (e.g., lavender) and lower (e.g., vanilla) likelihood of trigeminal mediation were shown to enhance delta activity when presented during sleep in healthy younger persons as well [51]. The latter results cannot necessarily be extrapolated to those with neurodegenerative diseases, but they do allow for the possibility that aromatherapy might indeed impact sleep in such populations.

In summary, our results are compatible, at least in principle, with certain types of aromatherapy (e.g., lavender) being candidates for improving sleep in neurodegenerative disease. Clinical trials of lavender have varied widely in quality, and most have been poorly controlled to date [3]. Clearly additional work would be required to determine both the efficacy and mechanisms underlying such an intervention.

Methods

Participants

PD patients (n = 47; 15 women; 32 men; mean [SD] age = 62.7 [10.7]) participated under a protocol that met all Guidelines as indicated by the Declaration of Helsinki and was in accordance with Human Subjects research regulations as stipulated by the United States National Institutes of Health. The protocol was approved in advance by the Emory University Institutional Review Board. All patients provided written Informed Consent. PD was defined by the presence of at least two of the four cardinal signs of the disorder, including resting tremor, cogwheel rigidity, bradykinesia and postural reflex instability, with either resting tremor or bradykinesia required to be present. PD was diagnosed by a board-certified neurologist (LMT), who also administered part III of the Unified Parkinson's Disease Rating Scale (UPDRS) as part of the neurologic examination. Mean (SD) UPDRS score was 16.7 (SD = 7.7). Hoehn-Yahr stage was as follows: stage I (n = 5), stage 1.5 (n = 5); stage 2 (n = 18); stage 2.5 (n = 12); and stage 3 (n = 7). Patients had been diagnosed for a mean of 5.3 years (SD = 3.9) before participation in the protocol. All patients received medication per their customary schedule and were evaluated neurologically (both UPDRS and olfaction) in the “On” condition. Control subjects (n = 15) (forced-choice discrimination task only) were derived from office and technical staff and had no known neurodegenerative disease or olfactory impairment. Data were collected prior to the COVID-19 pandemic.

Forced-choice Lavender Discrimination Task

We assessed for ability to detect lavender by a six-trial forced choice discrimination task. Before beginning the task, participants were provided two large candles obtained from a commercial candle store (Illuminations, Inc., Los Angeles, CA), one in a lavender scent and one in a rose scent, to serve as targeted scents. Paired identical, small (approximately 3 cm x 5 cm x 6 cm) opaque vials, filled with shaved pieces of lavender-scented or rose-scented candles (of same origin as the targeted candles), were then presented to the person in pairwise fashion. The explicit task was to discriminate blindly which one of each vial contained lavender versus which contained rose. Vials were identical in size and appearance and numbered 1 to 12. For each pair (e.g., vials 1 and 2), the participant made a choice after smelling each vial of the pair. If the participant was uncertain, a guess was encouraged, and in no case did we administer the next pair (e.g., vials 3 and 4) until a choice was made for the preceding pair. Participants were not given feedback on the accuracy of their choice. Responses were recorded by the examiner by vial number. Participants were allowed to re-smell the targeted scented candles during the procedure. We recorded the number of correctly identified pairs (range 0 to 6). Based on a binomial distribution, we considered lavender identification to be accurate when 6 of 6 or 5 of 6 pairs were correctly identified. No attempt was made to standardize the magnitude of sniffing across trials or participants.

Standardized Olfactory Testing

We administered the 40-item version of the UPSIT to provide a normative referent for olfactory impairment [24, 25]. The UPSIT was administered on a separate testing session within 48 hours of the forced-choice lavender discrimination task. A total USPIT score was derived following the scoring procedures described in the UPSIT Manual [25]. Because we were particularly interested in the ability of participants to discriminate between lavender and another floral scent, we examined 4 specific items on the UPSIT that included rose as an alternative florally scented item. One UPSIT item (number 39) uses rose as a targeted correct response. Three other items (numbers 16, 31, and 36) include rose as a distractor response. We tallied each participant’s score as the sum for these four rose items correctly identified (1 target response; 3 distractor responses; range of possible scores 0 to 4).

Statistical Analyses

Distributions of correctly identified stimuli pairs on the forced-choice discrimination task in patients and controls were compared with the chi-square statistic. Comparisons of UPSIT percentile scores between the subset of patients who correctly identified 5 or 6 lavender vials on the forced choice task and those who correctly identified only 1 to 4 lavender vials employed two-group t-tests, adjusting for unequal variances when necessary. We relied upon two-tailed tests with a probability level set at .05.

Declarations

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Author Contributions

Both authors (DLB, LMT) contributed to the design of the study, data collection, data analyses and preparation of the manuscript

Data Availability

Data will be made available upon request of the authors

Competing Interests

The authors declare no competing interests. DLB has been a paid Consultant to Eisai, Ferring, Huxley, Idorsia and Merck over the last three years, all outside the scope of the current work. LMT is a member of the Board of Directors of the American Academy of Sleep Medicine, the AASM Foundation, and the American Board of Sleep Medicine. Any opinions expressed are those of the authors and do not necessarily reflect those of these organizations.

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Figures

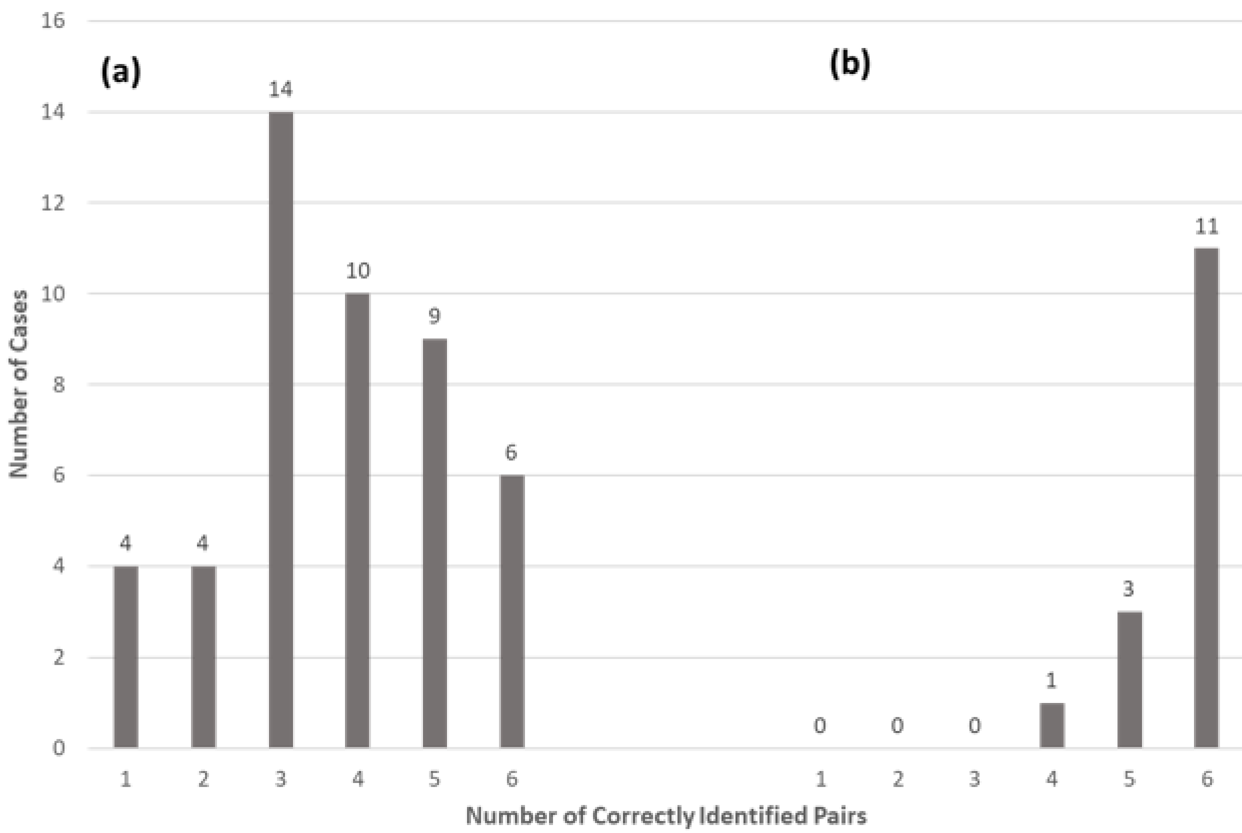

Figure 1

Frequency Distributions for Number of Correctly Identified Lavender/Rose Vials (range 0 to 6) in Parkinson’s Disease patients (a) and controls (b)