ORIGINAL ARTICLE

Patients With Seasonal Affective Disorder Have Lower Odor Detection Thresholds Than Control Subjects

Teodor T. Postolache, MD; Thomas A. Wehr, MD; Richard L. Doty, PhD; Leo Sher, MD; Erick H. Turner, MD; John J. Bartko, PhD; Norman E. Rosenthal, MD

Background: Behavioral changes in patients with seasonal affective disorder resemble seasonal changes in photoperiodic animals. Because the olfactory system has a modulatory role in seasonal photoperiodic responses in certain species, we hypothesized that olfactory function may differ between patients with seasonal affective disorder and healthy control subjects.

Methods: Fourteen patients who had winter seasonal affective disorder and 16 healthy volunteers were studied once in winter and once in the subsequent summer. We administered a phenyl ethyl alcohol detection threshold test to each side of the nose in a counterbalanced order, with the nostril contralateral to the tested site occluded. Patient and control data were compared using a 4-way repeated measure analysis of covariance (with group and gender as between-subjects factors, season and side-of-the-nose as within-subjects factors, and age as a covariate).

Results: The patients exhibited lower thresholds than did the controls ($F_{1,25}=9.2$; $P=.006$). There was no main effect of season.

Conclusion: In humans, marked seasonal behavioral rhythms with recurrent winter depression may be associated with a more acute sense of smell.

Arch Gen Psychiatry. 2002;59:1119-1122

MANY SPECIES exhibit seasonal changes in behavior and physiology, such as those associated with breeding, hibernation, and migration. Humans also exhibit seasonal changes, but in humans the changes are now of a more modest degree,[1,2] as humans have increasingly isolated themselves from the natural environment.[3] However, certain individuals experience marked seasonal changes in mood and behavior. Some, for example, have significant recurrent episodes of fall-winter depression with spontaneous remission in spring and summer (seasonal affective disorder winter type [SAD]).[4] Certain season-specific physiologic[5] and behavioral[4] changes that occur in patients with SAD, such as sleepiness, weight gain, loss of interest in sex, and decreased activity and social interactions, resemble some season-specific behavioral changes that occur in other mammals.[3]

Many organisms use changes in natural light to detect change of season and to regulate seasonal behavior. Light also is likely to be one of the most important factors in the regulation of seasonal changes that occur in SAD, inasmuch as winter symptoms improve after patients are exposed to bright artificial light.[4,6,7]

Olfactory bulbectomy disrupts seasonal responses to light in a variety of mammalian species.[8-10] Conversely, in laboratory rats[11] and house mice,[12] olfactory deafferentation releases seasonal responsiveness to light. With these examples in mind, we hypothesized that the olfactory acuity of patients with SAD would differ from healthy control subjects. We compared olfactory detection thresholds in patients and healthy controls once in the winter and again in the subsequent summer.

METHODS

SUBJECTS

Sixteen patients with SAD were enrolled in the study; 14 (7 men and 7 women) completed the protocol. The patients' ages ranged from 27 to 66 years, with a mean (SD) age of 42.3 (11.5) years. Patients were diagnosed

From the Section on Biological Rhythms, National Institute of Mental Health, National Institutes of Health, Bethesda, Md (Drs Postolache, Wehr, Sher, Turner, and Rosenthal); Psychopharmacology Consultation Service, St Elizabeths Hospital (Dr Postolache) and Department of Psychiatry, Georgetown University Medical Center, Washington, DC (Drs Postolache and Rosenthal); and Smell and Taste Center, University of Pennsylvania Medical Center, Philadelphia (Dr Doty). Dr Bartko is a private biostatistical consultant in Bethesda, Md.

Phenyl Ethyl Alcohol Odor Detection Thresholds in Patients With Seasonal Affective Disorder (SAD) and Control Subjects, in Winter and Summer*

Group/Season	Patients With SAD (n = 14)	Healthy Control Subjects (n = 16)
Winter	−7.39 (1.01)	−6.39 (1.08)
Summer	−8.28 (1.01)	−6.08 (1.08)
Adjusted average†	−7.84	−6.23

*Data are given as mean (SD). The detection threshold was set at $\log_{10}$ volume per volume of phenyl ethyl alcohol concentration, analysis of covariance (ANCOVA) adjusted.

†The difference between patients and control subjects is statistically significant ($F_{1,25}$ = 9.2; $P<.01$). Averages are ANCOVA adjusted for age, gender, and side-of-the-nose tested.

according to the criteria of Rosenthal et al.[4] In addition, patients had to meet the *DSM-IV* criteria for past major depressive episode and be free of any comorbid lifelong Axis I psychiatric disorders.

Twenty-one healthy controls were initially selected to participate; 16 (7 men and 9 women) completed the study. The controls' ages ranged from 23 to 61 years, with a mean (SD) of 39.0 (10.8) years. Healthy controls were required to have had no personal or family history of Axis I psychiatric disorders.

Patients and controls had to be medically healthy, as determined by medical history, physical examination, and routine laboratory test results. We excluded subjects who reported smoking tobacco within 1 year prior to or during the study, or who used psychotropic medications in the 3 months prior to or during the study. Subjects gave written informed consent after receiving a full explanation of the study, which was approved by the institutional review board of the intramural National Institute of Mental Health, Bethesda, Md.

PROCEDURES

Subjects were studied during the winter (December, January, or February), when patients were depressed, and during the following summer (June, July, or August), when patients were in remission. The criteria for depressed and remitted conditions were based on scores on the Structured Clinical Interview Guide for the Hamilton Depression Rating Scale, SAD version (SIGH- SAD)[13] as described in detail elsewhere.[14] After the olfactory test in the winter, patients received light treatment, which was gradually tapered in spring. At least 3 months elapsed between discontinuation of light treatment and summer olfactory testing.

The detection thresholds were measured using a single staircase paradigm.[15-17] Phenyl ethyl alcohol dissolved in *US Pharmacopeia*–grade light mineral oil, served as the olfactory stimulus. The odor presentation procedure is described in detail elsewhere.[17-19] Threshold testing was performed twice, once for each side of the nose, in random order. The naris opposite to the side being tested was occluded with an extensible closed cell foam tape coated with an acrylic adhesive (Microfoam tape; 3M Corp, St Paul, Minn).[17] No feedback was provided.

Patients were asked not to eat or drink for at least 2 hours before testing, and not to use cosmetics on the day of testing. All tests were scheduled between 2 and 5 PM. If an upper respiratory tract infection was present at the time of testing, the test was postponed until the subject had recovered for at least 2 weeks. The tester was blind to whether the subject was a patient or a control. These data were subjected to a 4-way repeated measures analysis of covariance, with group and gender as between-subjects factors, season and side-of-the-nose as within-subjects factors, and age as a covariate.

RESULTS

Patients with SAD had lower detection thresholds (mean = −7.84 $\log_{10}$ vol/vol concentration) than those of controls (mean = −6.23 $\log_{10}$ vol/vol concentration) ($F_{1,25}=9.2$; $P=.006$). Detection thresholds were not significantly related to age, gender, side-of-the-nose, season, or their interactions.

As listed in the **Table**, there was a nonsignificant trend (group × season interaction; $F_{1,26}=3.25$; $P=.08$) for a larger difference between patients and controls in the summer (2.2 $\log_{10}$ vol/vol concentration) than in the winter (1.0 $\log_{10}$ vol/vol concentration). A post hoc sample size analysis indicated that at least 35 subjects would be needed in each of the groups for the current group-season interaction to be statistically significant at an α level of .05 with statistical power at 80%.

The adjusted phenyl ethyl alcohol detection threshold mean of the controls (−6.23) falls within the 95% confidence interval of scores from healthy subjects used in recently published birhinal normative data for this test (−6.72 to −6.00).[17] However, the adjusted mean threshold value for patients with SAD (−7.84) falls outside of this range implying that patients with SAD are more sensitive to this odor than age-matched historic controls.[17]

COMMENT

Increased olfactory acuity in patients with SAD is consistent with a recent finding that patients with SAD report more discomfort than healthy controls when smelling certain odors.[20] As has been previously described in rodents, neuroanatomical connections exist between olfactory pathways and the suprachiasmatic nucleus of the hypothalamus,[21] a central structure that mediates behavioral responses to change of season that are induced by change in the length of daylight.[22] Furthermore, olfactory stimulation coadministered with light augments light-induced phase shifts in circadian rhythms generated by the suprachiasmatic nucleus and *fos* expression in its neurons.[23] Thus, it is possible that a lower detection threshold results in increased olfactory stimulation and, subsequently, via olfactory projections to the suprachiasmatic nucleus neurons, altering their response to changes in natural daylight.This could either contribute to, or compensate for, previously described vestigial photoperiodic responses in patients with SAD.[5]

In light of the evidence that depression and seasonality may be 2 distinct factors that coexist in patients with SAD,[24,25] our results might also reflect a relationship between olfaction and depression, rather than seasonality. Given a partial colocalization between olfactory and emotional processing, researchers had hypothesized an impaired olfactory performance in patients with recurrent depression. However, testing olfactory abilities (such as odor identification[14,26-30] and odor detection thresholds[14,26,31,32]) in patients with depressive disorders, produced inconsistent results. This lack of consistency could be a result of diagnostic heterogeneity, variable depression severity, variable testing methods, and small samples. Consistent with our current results, Gross-Isseroff et al[32] found a greater rather than weaker odor detection ability in patients with major depression than in healthy controls. Specifically, the authors reported that patients with major depression in remission after 6 weeks of antidepressant treatment exhibit higher olfactory acuity than healthy controls. Our results are similar to those Gross-Isseroff et al[32] in that the difference in odor detection thresholds between patients and controls was most apparent when patients were in remission.

What is the mechanism of increased olfactory acuity in patients with depression? Functional neuroimaging data suggest that the orbitofrontal cortex and the amygdala, neuroanatomical areas of partial overlap between olfactory and emotional processing, are overly activated in patients with major depression.[33,34] It is thus possible that increased activity in the orbitofrontal cortex or amygdala, persisting even when depression is in remission,[33] may be associated with increased olfactory acuity. During an episode of major depression, cognitive impairment related to the severity of depression may weaken patients' odor detection performance.

Although light treatment in winter is effective,[4,6,7] it does not make patients with SAD feel as well as they do in summer.[35] Since olfactory stimulation augments phase shifting effects of light and increases light-induced *fos* expression in the suprachiasmatic nucleus in rodents,[23] it seems worth investigating whether olfactory stimulation can augment the efficacy of light treatment.

Limitations of the study include a small sample size and an order effect (summer following winter) that might have contributed to the lack of statistical significance of the group-season interaction, but seem unlikely to have contributed to our main finding. Another limitation is not measuring nasal airflow. One cannot rule out that an ultradian rhythm in airflow (alternation in higher and lower airflow on each side of the nose),[36-38] might be related to an ultradian rhythm in monorhinal detection thresholds. Nevertheless, data based on actual measurement of odor detection thresholds, argue against a relationship between airflow and olfactory acuity.[39,40]

CONCLUSIONS

Patients with SAD had lower odor detection thresholds than healthy controls. One or more coexisting physiologic and clinical features of SAD (eg, vestigial responses to seasonal changes in natural light, marked seasonal behavioral rhythms, or recurrent depression) may be associated with a more acute sense of smell.

Submitted for publication September 5, 2001; final revision received February 8, 2002; accepted February 20, 2002.

This study was supported by the National Institute of Mental Health (Intramural Research Program) and by grant PO1 00161 from the the National Institute on Deafness and Other Communication Disorders, National Institutes of Health, Bethesda, Md.

The preliminary results of this study were presented at the International Congress on Chronobiology, Washington, DC, August 28, 1999.

We thank John Stiller, MD, and Daniel Aeschbach, PhD, for comments on the manuscript; Poupak Afshar for logistical support; Mulon Luo and Charles No for olfactory testing; Agatha O. Ndika for data management; Ronald Barnett, PhD, Frances Myers, Holly Lowe, and Todd Hardin for screening and rating patients; and Holly Giesen for editorial assistance.

Corresponding author and reprints: Teodor T. Postolache, MD, Section on Biological Rhythms, National Institute of Mental Health, National Institutes of Health, 10 Center Dr, Room 3S-231, Bethesda, MD 20892 (e-mail: postolache@nih.gov).

REFERENCES

1. Kasper S, Wehr TA, Bartko JJ, Gaist PA, Rosenthal NE. Epidemiological findings of seasonal changes in mood and behavior: a telephone survey of Montgomery Country, Maryland. *Arch Gen Psychiatry.* 1989;46:823-833.
2. Rosen LN, Targum SD, Terman M, Bryant MJ, Hoffman H, Kasper SF, Hamovit JR, Docherty JP, Welch B, Rosenthal NE. Prevalence of seasonal affective disorder at four latitudes. *Psychiatry Res.* 1990;31:131-144.
3. Wehr T. Photoperiodism in humans and other primates: evidence and implications. *J Biol Rhythms.* 2001;16:348-364.
4. Rosenthal NE, Sack DA, Gillin JC, Lewy AJ, Goodwin FK, Davenport Y, Mueller PS, Newsome DA, Wehr TA. Seasonal affective disorder: a description of the syndrome and preliminary findings with light therapy. *Arch Gen Psychiatry.* 1984; 41:72-80.
5. Wehr TA, Duncan WC Jr, Sher L, Aeschbach D, Schwartz PJ, Turner EH, Postolache TT, Rosenthal NE. A circadian signal of change of season in patients with seasonal affective disorder. *Arch Gen Psychiatry.* 2001;58:1108-14.
6. Eastman CI, Young MA, Fogg LF, Liu L, Meaden PM. Bright light treatment of winter depression. *Arch Gen Psychiatry.* 1998;55:883-889.
7. Terman M, Terman JS, Ross DC. A controlled study of timed bright light and negative air ionization for treatment of winter depression. *Arch Gen Psychiatry.* 1998;55:875-882.
8. Miro JL, Canguilhem B, Schmitt P. Effects of bulbectomy on hibernation, food intake and body weight in the European hamster, *Cricetus cricetus. Physiol Behav.* 1980;24:859-862.
9. Ruby NF, Zucker I, Licht P, Dark J. Olfactory bulb removal lengthens the period of circannual rhythms and disrupts hibernation in golden-mantled ground squirrels. *Brain Res.* 1993;608:1-6.
10. Schilling A, Perret M. Removal of the olfactory bulbs modifies the gonadal responses of photoperiod in the lesser mouse lemur (*Microcebus murinus*). *Biol Reprod.* 1993;49:58-65.
11. Nelson RJ, Zucker I. Photoperiodic control of reproduction in olfactory-bulbectomized rats. *Neuroendocrinology.* 1981;32:266-271.
12. Nelson RJ. Photoperiodic responsiveness in house mice. *Physiol Behav.* 1990; 48:403-408.
13. Williams JB, Link MJ, Rosenthal NE, Terman ME. *Structured Interview Guide for the Hamilton Depression Rating Scale, Seasonal Affective Disorder Version (SIGH-SAD).* New York: New York Psychiatric Institute; 1988.
14. Postolache TT, Doty RL, Wehr TA, Jimma LA, Han L, Turner EH, Matthews JR, Neumeister A, No C, Kroger H, Bruder GE, Rosenthal NE. Monorhinal odor identification and depression scores in patients with seasonal affective disorder. *J Affect Disord.* 1999;56:27-35.
15. Doty RL, McKeown DA, Lee WW, Shaman P. A study of the test-retest reliability of ten olfactory tests. *Chem Senses.* 1995;20:645-656.
16. Doty RL, Smith R, McKeown DA, Raj J. Tests of human olfactory function: principal components analysis suggests that most measure a common source of variance. *Percept Psychophys.* 1994;56:701-707.

17. Doty RL. *The Smell Threshold Administration Manual*. Haddon Heights, NJ: Sensonics Inc; 2000.
18. Doty RL, Brugger WE, Jurs PC, Orndorff MA, Snyder PJ, Lowry LD. Intranasal trigeminal stimulation from odorous volatiles: psychometric responses from anosmic and normal humans. *Physiol Behav*. 1978;20:175-185.
19. Doty RL, Gregor TP, Settel RG. Influence of intertrial interval and sniff-bottle volume on phenyl ethyl alcohol odor detection thresholds. *Chem Senses*. 1986;11:259-264.
20. Nawab SS, Miller CS, Dale JK, Greenberg BD, Friedman TC, Chrousos GP, Straus SE, Rosenthal NE. Self-reported sensitivity to chemical exposures in five clinical populations and healthy controls. *Psychiatry Res*. 2000;95:67-74.
21. Krout KE, Kawano J, Mettenleiter TC, Loewy AD. CNS inputs to the suprachiasmatic nucleus of the rat. *Neuroscience*. 2002;110:73-92.
22. Schwartz WJ, de la Iglesia HO, Zlomanczuk P, Illnerova H. Encoding le quattro stagioni within the mammalian brain: photoperiodic orchestration through the suprachiasmatic nucleus. *J Biol Rhythms*. 2001;16:302-311.
23. Amir S, Cain S, Sullivan J, Robinson B, Stewart J. Olfactory stimulation enhances light-induced phase shifts in free-running activity rhythms and *fos* expression in the suprachiasmatic nucleus. *Neuroscience*. 1999;92:1165-1170.
24. Young MA, Watel LG, Lahmeyer HW, Eastman CI. The temporal onset of individual symptoms in winter depression: differentiating underlying mechanisms. *J Affect Disord*. 1991;22:191-7.
25. Lam RW, Tam EM, Yatham LN, Shiah IS, Zis AP. Seasonal depression: the dual vulnerability hypothesis revisited. *J Affect Disord*. 2001;63:123-32.
26. Serby M, Larson P, Kalkstein D. Olfactory sense in psychoses. *Biol Psychiatry*. 1990;28:829-830.
27. Rupp C, Ilmberger J, Oberbauer H, Scholz A, Wanko C, Hinterhuber H. Olfactory deficits in schizophrenia and major depression[abstract]. In: International Symposium on Olfaction and Taste XII and AChems XIX; July 7-12, 1997; San Diego, Calif. Abstract 180.
28. Amsterdam JD, Settle RG, Doty RL, Abelman E, Winokur A. Taste and smell perception in depression. *Biol Psychiatry*. 1987;22:1481-1485.
29. Warner MD, Peabody CA, Csernansky JG. Olfactory functioning in schizophrenia and depression. *Biol Psychiatry*. 1990;27:457-467.
30. Oren DA, Schwartz PJ, Turner EH, Rosenthal NE. Olfactory function in winter seasonal affective disorder. *Am J Psychiatry*. 1995;152:1531-1532.
31. Pause BM, Miranda A, Göder R, Aldenhoff JB, Ferstl R. Reduced olfactory performance in patients with major depression. *J Psychiatr Res*. 2001;35:271-277.
32. Gross-Isseroff R, Luca-Haimovici K, Sasson Y, Kindler S, Kotler M, Zohar J. Olfactory sensitivity in major depressive disorder and obsessive compulsive disorder. *Biol Psychiatry*. 1994;35:798-802.
33. Drevets WC. Neuroimaging studies of mood disorders. *Biol Psychiatry*. 2000;48:813-829.
34. Drevets WC, Videen TO, Price JL, Preskorn SH, Carmichael ST, Raichle ME. A functional anatomical study of unipolar depression. *J Neurosci*. 1992;12:3628-3641.
35. Postolache TT, Hardin TA, Myers FS, Turner EH, Yi LY, Barnett RL, Matthews JR, Rosenthal NE. Greater improvement in summer than with light treatment in winter in patients with seasonal affective disorder. *Am J Psychiatry*. 1998;155:1614-1616.
36. Principato JJ, Ozenberger JM. Cyclical changes in nasal resistance. *Arch Otolaryngol*. 1970;91:71-77.
37. Mirza N, Kroger H, Doty RL. Influence of age on the nasal cycle. *Laryngoscope*. 1997;107:62-66.
38. Sobel N, Khan RM, Saltman A, Sullivan EV, Gabrieli JD. The world smells different to each nostril. *Nature*. 1999;402:35.
39. Eccles R, Jawad MS, Morris S. Olfactory and trigeminal thresholds and nasal resistance to airflow. *Acta Otolaryngol*. 1989;108:268-273.
40. Frye RE, Doty RL. The influence of ultradian autonomic rhythms, as indexed by the nasal cycle, on unilateral olfactory thresholds. In: Doty RL, Muller-Schwartze DE, eds. *Chemical Signals in Vertebrates VI*. New York, NY: Plenum Press; 1992:595-598.