Olfactory Impairments in Child Attention-Deficit/Hyperactivity Disorder

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Objective: This study compared unilateral olfactory identification abilities in children with and without attention-deficit/hyperactivity disorder (ADHD) and evaluated the utility of the University of Pennsylvania Smell Identification Test (UPSIT) as a potential screening tool for the diagnosis of ADHD.

Method: Subjects comprised 44 children with DSM-IV ADHD (aged 7–16 years) from 2 Melbourne, Australia, hospital outpatient clinics and 44 healthy children matched for age and sex. The children were assessed from March 2004 to October 2004 for olfactory identification ability using the UPSIT, and behavioral data were gathered using the Rowe Behavioral Rating Inventory. Background and demographic data were also obtained through hospital records and parental interview.

Results: Children with ADHD demonstrated significantly poorer olfactory identification ability compared to healthy controls ($p < .01$). A significant right nostril advantage for smell identification was evident in the control group ($p < .01$), whereas significant right nostril impairment was evident among the children with ADHD ($p < .01$).

Conclusion: The results provide the first evidence of olfactory identification deficits in children with ADHD. As such deficits implicate orbitofrontal regions, this finding is consistent with previous reports of prefrontal compromise in children with ADHD.

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Attention-deficit/hyperactivity disorder (ADHD) is a behavioral disorder that is characterized by a persistent and developmentally inappropriate pattern of hyperactivity, impulsivity, inattention, and distractibility.[1] While current diagnostic schemes recognize a predominantly inattentive subtype, a predominantly hyperactive-impulsive subtype, and a combined subtype,[2] these have been criticized for their heterogeneity and lack of symptom specificity.[3] Some researchers have asserted that ADHD with aggression represents an alternative distinct subtype within ADHD with a unique developmental course, symptoms, and prognosis.[4–6] Others have suggested that ADHD with comorbid aggression has a strong biological basis, possibly mediated by distinctive deficiencies in neurologic substrate, including the orbitofrontal cortex (OFC).[7,8]

Striking similarities are evident between symptoms of ADHD and OFC dysfunction. Patients with lesions to OFC typically display symptoms of disorganized hyperactivity, impulsivity, and distractibility[9,10] with disinhibited,

inappropriate behavior and aggressive outbursts.[10] Problems of behavioral response inhibition are also evident in ADHD.[11–13] Evidence of prefrontal compromise in ADHD has been reported in neuroimaging studies showing reductions in prefrontal gray and white matter volumes in children with ADHD compared to healthy controls,[14–16] particularly evident in the right hemisphere.[16–18] Hesslinger et al.[19] reported significant volume reductions in the left OFC of adults with ADHD.

Increasingly, neurobiological research has emphasized the importance of OFC function for controlling impulsive aggression.[20] Abnormalities of the left prefrontal cortex including reduced gray matter and reduced metabolic activity have been frequently observed in impulsive aggressive patients.[21,22] According to Davidson's inhibition control model of aggression,[20] underactivation of the OFC leads to poor regulation of emotional control and a greater vulnerability for impulsive aggression. Consequently, lesions or dysfunction of the OFC, rather than any other brain area, have been identified as producing the greatest risk for displays of impulsive aggression.[20]

As the OFC becomes functionally mature much earlier than other regions of the prefrontal cortex,[23] dysfunction of OFC, with its concomitant deficits of inattention, impulsivity, hyperactivity, and impulsive aggression, may be noticeable from early childhood. Consistent with this, a subset of hyperactive ADHD children present with an early pattern of impulsive aggression and emotional deregulation and cognitive problems of response inhibition.[6,24] These children may be at risk of progressing to violent and antisocial behavior in adulthood.[6] Since there is evidence for good treatment response in these children,[5,25] early identification may be very useful.

Tests of smell identification are a well-recognized means of indirectly assessing the integrity of the OFC. Intact OFC is essential for olfactory identification processing, which involves the recognition and naming of a perceived odor.[26] A reliable body of research confirms that *identification* of odors represents a secondary stage in olfactory processing mediated by the OFC[26–28] once intact *threshold detection levels* (acuity) have been established.

The primary olfactory cortex appears to be fully functional in childhood. Children from 8 years of age have demonstrated a threshold sensitivity for detecting odors that is equal to that of young adults.[29] In tasks of odor identification, which depend on secondary OFC processing, children show less accuracy than adults. Marked improvement in smell identification, however, occurs between the ages of 7 to 11, coinciding with prefrontal growth spurts during these ages.[30] Further incremental improvements in smell identification ability occur during adolescence leading to peak competency in early adulthood.[31,32] Interestingly, smell identification in healthy controls appears to depend on increased activation of the right hemisphere OFC,[33] and a strong right nostril advantage for smell identification is reported by many studies.[34,35]

The University of Pennsylvania Smell Identification Test (UPSIT)[32] has been widely used as a probe of OFC function in psychiatric disorders such as schizophrenia,[36] obsessive-compulsive disorder,[37] and Asperger's syndrome.[28] Despite the success of the UPSIT in detecting OFC functional impairments in schizophrenia,[36,38,39] the UPSIT has only been used in 2 studies of adults with ADHD.[40,41] Both Murphy et al.[41] and Gansler et al.[40] reported impaired olfactory identification abilities in adults with ADHD. To date, no study has used olfactory testing in children with ADHD to investigate OFC functioning.

Therefore, the present study aimed to investigate putative OFC dysfunction in ADHD with particular relevance to the subgroup of ADHD children with impulsive aggression relative to matched control participants.

Consistent with research showing early and ongoing OFC dysfunction in ADHD, it is expected that the ADHD group will demonstrate impaired olfactory identification as measured by lower total UPSIT scores compared to normal children. Further, as primary olfactory nerve projections are largely ipsilateral, olfactory tests presented monorhinally can assess left and right OFC function separately.[42] Since OFC dysfunction in ADHD may be predominant in the right hemisphere,[16–18] it is expected that the ADHD group will demonstrate a right nostril impairment in smell identification (in contrast to the right nostril advantage found in controls).[35] Finally, as evidence suggests that left OFC dysfunction underpins impulsive aggression,[43] it is predicted that children with ADHD and comorbid aggression will demonstrate greater deficits in left nostril odor identification, reflected in lower left nostril UPSIT scores, than nonaggressive ADHD children or healthy children.

METHOD

Participants

The ADHD group was recruited from outpatient mental health clinics at 2 major metropolitan hospitals in Melbourne, Australia. Forty-four children aged 7–16 years met the DSM-IV[2] criteria for ADHD diagnosis (40 combined-type, 4 inattentive) through semi-structured interview[44] and parent and child reports.[45,46] Forty-four healthy children matched for age, sex, years of education, and handedness formed a control group. The control group was similar in terms of age, sex, socioeconomic status, and years of education (Table 1), with no documented history of clinical behavioral or psychological problems, and was recruited as a sample of convenience from families known to the research group. Children with a documented history of organic brain disease, epilepsy, thyroid disease, head injury with loss of consciousness, nasal trauma, current viral illness, documented smell

Table 1. Demographic Characteristics of the ADHD and Control Groups[a]

Characteristic	ADHD Group			Control Group (N = 44)
	Total (N = 44)	Aggressive (N = 19)	Nonaggressive (N = 20)	
Age, mean (SD), y	12.16 (2.19)	11.63 (2.14)	12.40 (2.33)	12.23 (2.21)
Male, N (%)	35 (79.5)	15 (78.9)	17 (85.0)	35 (79.5)
Socioeconomic status, mean (SD)	4.0 (0.9)	4.2 (0.9)	3.7 (0.9)	4.3 (0.6)
Education, mean (SD), y	7.16 (2.2)	6.63 (2.1)	7.40 (2.3)	7.23 (2.2)
Right-handed, N (%)	40 (90.9)	18 (94.7)	17 (85.0)	43 (97.7)
IQ, mean (SD)	99.60 (14.19)	101.05 (12.15)	97.88 (16.54)	…
CBCL aggression score, mean (SD)	75.97 (12.3)	86.47 (5.96)	65.10 (8.07)	…

[a]Socioeconomic status was calculated using Daniel's (1983) Scale of Occupational Prestige.[48] Aggression was measured using the CBCL aggression subscale.[45] Full-scale IQ was measured using the WISC-III.[47]
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, CBCL = Child Behavior Checklist, WISC-III = Wechsler Intelligence Scale for Children-3rd Edition.
Symbol: … = not applicable.

impairments, poor hearing, a non–English-speaking background, or a full-scale IQ score below 70 on the Wechsler Intelligence Scale for Children-3rd Edition (WISC-III)[47] were excluded from participation. Children with a family history of diagnosed psychiatric illness were also excluded. In the ADHD group, 11 children were taking stimulant medication, and 33 had no medication on the day of UPSIT testing.

Materials and Method

Demographic and background information. Background information concerning the children with ADHD including demographic details, medical and behavioral data, and parental socioeconomic status was obtained through hospital records. Daniel's Scale of Occupational Prestige[48] was used to measure socioeconomic status of all families by rating parental occupation between 1 and 7, with lower scores reflecting high socioeconomic status. Both parents' occupational scores were averaged to calculate socioeconomic status.

Assessment of attentional function. Parents of all but 3 participants (2 control and 1 ADHD) completed the Rowe Behavioral Rating Inventory (RBRI),[49] consisting of 20 bipolar behavioral statements (e.g., "Can concentrate" vs. "Cannot concentrate"), which measure typical behavior problems exhibited in the home. Each item is rated on a 5-point, ordinal dot scale with higher scores indicating greater problems. The irritable/antisocial subscale has 10 items measuring problems with emotional and social lack of control, irritability, and aggression toward family and friends, with scores ranging from 10 to 50. The inattentive subscale is composed of 5 items that measure distractibility and aimless impulsive activity and is scored from 5 to 25. These RBRI subscales demonstrate reliability with high internal consistency (Cronbach's α = .89 and .81, respectively).

Measures of intelligence. Full-scale IQ scores (mean = 100, SD = 15) from the WISC-III[47] provided a measure of general intellectual functioning for the ADHD group only. IQ data were not collected from the control group because of time constraints. However, all controls were attending mainstream schooling with no evidence of learning disorders or intellectual impairment.

Measure of aggression. The Child Behavior Checklist (CBCL)[45] was utilized to identify behavioral problems including aggression in all but 5 of the children with ADHD. It is composed of 20 social competence items and 120 items reflecting behavioral or emotional problems experienced over the last 6 months. Each item consists of a statement (e.g., "Argues a lot") that is rated on a 3-step scale, in which 0 = "not true," 1 = "somewhat true," and 2 = "very true." Responses are summed to form a total behavior problem score (mean = 50, SD = 10). Twenty-three items refer to aggressive behaviors and are summed to form an aggression subscale. T scores of 70 and above represent behaviors in the clinical range.[50]

Smell identification. The UPSIT[32] was utilized as a measure of smell identification ability. It consists of 40 individual suprathreshold "scratch-and-sniff" microencapsulated patches on individual cards. The odors are grouped into 4 booklets of 10 cards. Each card also contains a single odor and a choice of 4 typed words to describe the smell (e.g., chocolate, peach, leather, pizza). Scores on the UPSIT smell test range between 0 and 40, with each correct identification scoring 1 point. The UPSIT contains normative data and scores for children's smell identification abilities. UPSIT test-retest reliability coefficients are high (r = 0.92), and satisfactory correlations (r = 0.73 to 0.78) exist between scores on each test booklet.[32]

Each odor patch was scratched and then presented to the participant, who was asked to select the word that best described the odor. The 4 odor choice words were read aloud, and participants were asked to indicate that they could detect a stimulus before attempting to identify it. Twenty of the odor patches were presented to the left nostril of the participant and twenty of the odor patches were presented to the right nostril of the participant in order to assess left and right OFC function separately. The participant was asked to block their untested nostril with a

simple external finger press[34] as per the normal Unilateral Test procedure.[32] The order of nostril presentation was counterbalanced across all participants.

Procedure

This study was approved by the Ethics Committees of the Royal Children's Hospital, Melbourne, the Maroondah Hospital, Melbourne, and the University of Melbourne, Australia. All participants and their parents received detailed information concerning this study and gave written informed consent before participation. Children were assessed during a home visit from March 2004 to October 2004.

The present research accessed previously collected data on the ADHD group from clinic records, including demographic details, WISC-III[47] scores, and CBCL[45] scores. Parents of all participants completed the RBRI[49] behavioral survey at the time of assessment for the current study.

The ADHD group (excluding the 5 who did not complete the CBCL) was divided into aggressive and nonaggressive subgroups for subanalysis (see Table 1) using the median aggression subscale T score (T = 77).

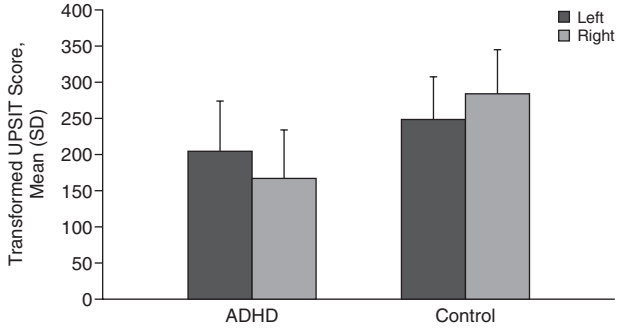
Statistical Analyses

Statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS) Version 11.5 (SPSS Inc., Chicago, Ill.). Independent group t tests and χ^2 significance tests were used to explore differences between groups on demographic variables, and equality of variance was checked using Levene's test. A squared transformation was performed on the UPSIT scores to reduce the effect of negative skewness before further analyses were conducted. Analysis of covariance, using RBRI inattentive scores as the covariate, was also conducted after checking for homogeneity of regression. A 2 (group) × 2 (nostril) mixed factorial analysis of variance (ANOVA), with nostril as the within-subjects variable, investigated the predicted right versus left nostril smell identification within the ADHD and control groups. A 3 (group) × 2 (nostril) mixed factorial ANOVA was conducted to examine the effect of nostril usage on smell identification for each aggressive status group.

RESULTS

Statistical analyses revealed no significant difference in age ($t = 0.15$, $df = 86$, $p = .89$), socioeconomic status ($t = 1.3$, $df = 86$, $p = .20$), handedness ($\chi^2 = 2.46$, $df = 1$, $p > .10$), or gender distribution ($\chi^2 < 0.001$, $df = 1$, $p = 1.00$) between the ADHD and the control group participants (see Table 1). No difference was found in total UPSIT scores for those receiving no medication and those receiving stimulants or other medications ($F = 2.02$, $df = 2,41$; $p = .15$). Within the ADHD group, the total UPSIT test results were not associated with IQ scores ($r = 0.29$, $p = .64$). The ADHD group's RBRI irritable/antisocial subscale (mean = 34.23, SD = 8.46) and inattentive subscale scores (mean = 17.42, SD = 4.99) were significantly higher than the control group (mean = 16.19, SD = 4.98, $t = 12.01$, $df = 68.3$, $p < .01$; mean = 8.0, SD = 2.75, $t = 10.8$, $df = 65.6$, $p < .01$, respectively).

Figure 1. Left and Right Nostril UPSIT Scores for the ADHD and Control Groups[a]



[a]Maximum score for each nostril is 400 (transformed), equivalent to a raw score of 20. The equivalent mean raw scores for the ADHD group are left = 14.3 and right = 13.0; and for the control group, left = 15.8 and right = 16.8.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, UPSIT = University of Pennsylvania Smell Identification Test.

A repeated measures ANOVA revealed, as predicted, a significant main effect of diagnostic group ($F = 44.65$, $df = 1,86$; $p < .01$), indicating the ADHD subjects were significantly poorer at smell identification than the control subjects. Furthermore, there was a highly significant group × nostril interaction ($F = 30.51$, $df = 1,86$; $p < .01$; Figure 1). Post hoc comparisons, using repeated-measures ANOVA separately for the 2 groups, revealed a significant right nostril advantage in the control group ($F = 15.10$, $df = 1,43$; $p < .01$) but a significant right nostril impairment in the ADHD group ($F = 15.41$, $df = 1,43$; $p < .01$). There was no effect of nostril ($F = 0.00$, $df = 1,86$; $p = .97$). This pattern did not differ in a subanalysis that included gender as a main effect—both male and female children with ADHD showed an impairment in smell identification and a specific disadvantage for the right nostril (male ADHD/control: left = 14.4/15.7, right = 12.7/16.6; female ADHD/control: left = 12.8/15.6, right = 12.6/17.4). Furthermore, the difference in UPSIT total performance between the ADHD and control groups remained significant after covarying for RBRI inattentive score ($F = 6.79$, $df = 1,82$; $p = .01$), as did the group × nostril interaction ($F = 23.01$, $df = 1,82$; $p < .01$).

Finally, a significant main effect of group in smell identification ($F = 19.32$, $df = 2,80$; $p < .01$) and a group × nostril interaction ($F = 13.62$, $df = 2,80$; $p < .01$) was found between the aggressive ADHD, nonaggressive ADHD, and control groups. Post hoc testing (Student-

Newman-Keuls) showed that these effects were because the ADHD groups (regardless of levels of aggression) performed more poorly than the controls (both comparisons, $p < .001$) but not different to each other ($p = .633$). Indeed, the mean difference between the 2 ADHD subgroups was only 7.8 (equivalent to a difference in raw score of 0.3). This finding was confirmed by examining the correlation coefficient between the continuous CBCL aggression score and the transformed UPSIT score (in the ADHD group only), which was nonsignificant ($r = 0.2$, $p = .221$).

DISCUSSION

The results provide evidence of a specific pattern of olfactory deficits in children with ADHD. As predicted, children with ADHD showed poorer olfactory identification abilities overall compared to normal children. Although this deficit was evident for both left and right nostril identification, the children with ADHD displayed significantly greater right nostril impairment. In contrast, the control group children displayed the expected significant right nostril advantage for odor identification. The prediction of greater olfactory identification deficits in children with ADHD and comorbid aggression was not supported by the results. These olfactory deficits in ADHD are consistent with reported differences in the underlying neural substrate of children with ADHD.[14–16]

This study is the first to report significant olfactory deficits in children with ADHD and is consistent with limited previous research reporting impaired olfactory processing in adults with ADHD.[39,40] It is possible that reduced ability to identify odors is due to reduced intellectual ability in the ADHD group; however, our data do not support this argument. First, the mean IQ for the ADHD group was average and included many intellectually highly able children. Secondly, within the ADHD group, measured intelligence was not associated with the smell identification results. This is consistent with Murphy and colleagues'[41] finding that olfactory identification represents a relatively independent component of cognition.

Our findings are also unlikely to be attributable to poor attention or restlessness while completing the smell test. Individual testing by the researcher provided an opportunity to monitor attention. The task was short and engaging for the children. Even when statistically controlling for background differences in attention between the children, significant group differences in olfactory abilities remained. Alternatively, Murphy et al.[41] interpreted the finding of olfactory deficits in adults with ADHD as resulting from diminished function in prefrontal cortex. As odor identification relies on orbitofrontal cortex functioning[34] once the integrity of threshold detection has been established, the results of the present study also support the notion of OFC dysfunction in children with ADHD.

A second major finding in the results was the predicted lateralization of olfactory processing in both the control and ADHD groups. In the control group, olfactory identification was more accurate for odors presented to the right nostril than the left nostril (as previously shown in adults[34]), suggesting early development of this hemispheric advantage.[51] In contrast, the ADHD group demonstrated a reversal of this asymmetry.

As all the children in the present study agreed they could smell the odors with either nostril, and as the odors presented to each nostril were suprathreshold in strength, the poor performance by the ADHD group is unlikely to result from a primary processing problem of odor detection that would implicate lower-order pathways between the olfactory bulb and limbic regions (see Brewer et al.[52] for review). Rather, the impaired right nostril performance by the ADHD group may reflect a specific deficit in the secondary processes of odor identification, which are dependent on OFC activation ipsilateral to the nostril stimulated.[26] While standard unilateral procedure involves maintaining the integrity of the axis of the septum, it is possible for the odorant to cross to the contralateral side within the nasopharynx upon exhalation or the relaxation of inhalation.[32] However, given our finding of a right nostril advantage in the control group is consistent with previous studies,[32,33] we do not think this methodological issue has contributed to the results. Nonetheless, future unilateral assessment of children should amend the standard procedural instructions to include a reminder at the presentation of each odor element to exhale through the mouth.

Right nostril impairment for recognizing odors in the ADHD group could potentially be due to predominantly right OFC dysfunction or developmental delay. This interpretation is consistent with reports highlighting underactivation of the right OFC in children with ADHD[12,13] and right hemisphere volume reductions in the prefrontal and OFC regions in children with ADHD.[14–16,19]

The third main finding of this study was that children with high levels of aggressive behavior and ADHD did not differ from their less aggressive peers, despite parental reports on the RBRI[49] and the CBCL[45] indicating that the aggressive children with ADHD had greater problems of irritability and antisocial activity. Thus, while the results of the present study suggest that both ADHD groups may share a common impairment in right OFC function, the basis for aggressive behavior in these patients remains to be explored.

This failure to find clear significant olfactory differences between the aggressive and nonaggressive ADHD groups may reflect a methodological weakness in the definition of these 2 groups. The majority of the ADHD children in the present study, although randomly selected, had CBCL aggressive scores in the clinical range. Consequently, the nonaggressive group may not have been sufficiently differentiated from the aggressive group to allow

detection of any significant group differences in left nostril olfactory tests. Future research incorporating children with ADHD from the general community as well as hospital outpatients' clinics may provide a more representative sample and may enable a clearer distinction of the olfactory deficits related to ADHD alone, as opposed to those apparent in ADHD with aggression.

Two other methodological considerations should be taken into account in interpreting these data. First, we did not assess IQ in the control group, so it is unknown how well matched the 2 groups were on this variable or the effect of such differences on smell identification. While it is possible that the control group may have had a higher average IQ than the ADHD group, their UPSIT performance was similar to previous research reporting control group performance in young people. Second, the small number of girls in the ADHD group means it is unclear to what extent these findings are generalizable to females. Replication of this study with more equal gender distribution would help clarify the relationship of gender to OFC dysfunction.

In summary, the results of the present study provide further evidence supporting a biologically based prefrontal impairment in ADHD and may have implications for its early detection and treatment.

REFERENCES

1. Tannock R. Attention-deficit/hyperactivity disorder: advances in cognitive, neurobiological, and genetic research. J Child Psychol Psychiatry 1998 Jan;39(1):65–99
2. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision. Washington, DC: American Psychiatric Association; 2000
3. Barkley RA. Behavioral inhibition, sustained attention, and executive functions: constructing a unified theory of ADHD. Psychol Bull 1997; 121:65–94
4. Milich R, Balentine AC, Lynam DR. ADHD combined type and ADHD predominantly inattentive type are distinct and unrelated disorders. Clin Psychol Sci Pract 2001;8:463–488
5. Jensen PS, Hinshaw SP, Kraemer HC, et al. ADHD comorbidity findings from the MTA study: comparing comorbid subgroups. J Am Acad Child Adolesc Psychiatry 2001;40:147–158
6. McKay KE, Halperin JM. ADHD, aggression, and antisocial behavior across the lifespan: interactions with neurochemical and cognitive function. Ann N Y Acad Sci 2001;931:84–96
7. Biederman J, Faraone SV, Keenen K, et al. Further evidence for family-genetic risk factors in attention-deficit/hyperactivity disorder: patterns of comorbidity in probands and relatives of psychiatrically and pediatrically referred samples. Arch Gen Psychiatry 1992;49:728–738
8. Hinshaw SP. Impulsivity, emotion regulation and developmental psychopathology: specificity versus generality of linkages. Ann N Y Acad Sci 2003;1008:149–159
9. Murad A. Orbitofrontal syndrome in psychiatry. Encephale 1999;25: 634–637
10. Berlin HA, Rolls ET, Kischka U. Impulsivity, time perception, emotion and reinforcement sensitivity in patients with orbitofrontal cortex lesions. Brain 2004;127:1108–1126
11. Barkley RA, Grodzinsky G, DuPaul GJ. Frontal lobe functions in attention-deficit/hyperactivity disorder: a review and research report. J Abnorm Child Psychol 1992;20:163–188
12. Durston S, Tottenham NT, Thomas KM, et al. Differential patterns of striatal activation in young children with and without ADHD. Biol Psychiatry 2003;53:871–878
13. Rubia K, Overmeyer S, Taylor E, et al. Hypofrontality in attention-deficit/hyperactivity disorder during higher-order motor control: a study with functional MRI. Am J Psychiatry 1999;156:891–896
14. Castellanos FX, Giedd JN, Marsh WL, et al. Quantitative brain magnetic resonance imaging in attention-deficit/hyperactivity disorder. Arch Gen Psychiatry 1996;53:607–616
15. Filipek PA, Semrud-Clikeman M, Steingard RJ, et al. Volumetric MRI analysis comparing subjects having attention-deficit/hyperactivity disorder with normal controls. Neurology 1997;48:589–601
16. Mutofsky SH, Cooper KL, Kates WR, et al. Smaller prefrontal and premotor volumes in boys with attention-deficit/hyperactivity disorder. Biol Psychiatry 2002;52:785–794
17. Giedd JN, Blumenthal J, Molloy E, et al. Brain imaging of attention-deficit/hyperactivity disorder. Ann N Y Acad Sci 2001;931:33–49
18. Stefanatos GA, Wasserstein J. Attention-deficit/hyperactivity disorder as a right hemisphere syndrome: selective literature review and detailed neuropsychological studies. Ann N Y Acad Sci 2001;931:172–195
19. Hesslinger B, Tebartz van Elst L, Thiel T, et al. Frontoorbital volume reductions in adult patients with attention-deficit/hyperactivity disorder. Neurosci Lett 2002;328:319–321
20. Davidson RJ, Putman KM, Larson CL. Dysfunction in the neural circuitry of emotion regulation: a possible prelude to violence. Science 2000;289:591–594
21. Woermann FG, Elst LT, Koepp MJ, et al. Reduction of frontal neocortical grey matter associated with affective aggression in patients with temporal lobe epilepsy: an objective voxel by voxel analysis of automatically segmented MRI. J Neurol Neurosurg Psychiatry 2000;68:162–169
22. New AS, Hazlett EA, Buchsbaum MS, et al. Blunted prefrontal cortical 18fluorodeoxyglucose positron emission tomography response to meta-chlorophenylpiperazine in impulsive aggression. Arch Gen Psychiatry 2002;59:621–629
23. Fuster JM. The Prefrontal Cortex. New York, NY: Raven's Press; 1980
24. Connor DF, Edwards G, Fletcher KE, et al. Correlates of comorbid psychopathology in children with ADHD. J Am Acad Child Adolesc Psychiatry 2003;42:193–200
25. Sonuga-Barke EJ, Daley D, Thompson M, et al. Parent-based therapies for preschool attention-deficit/hyperactivity disorder: a randomized, controlled trial with a community sample. J Am Acad Child Adolesc Psychiatry 2001;40:402–408
26. Martzke JS, Kopala LC, Good KP. Olfactory dysfunction in neuropsychological disorders: review and methodological considerations. Biol Psychiatry 1997;42:721–732
27. Qureshy A, Kawashima R, Imram MB, et al. Functional mapping of human brain in olfactory processing: a PET study. J Neurophysiol 2000; 84:1656–1666
28. Suzuki Y, Critchley H, Rowe A, et al. Impaired olfactory identification in Asperger's Syndrome. J Neuropsychiatry Clin Neurosci 2003;15: 105–107
29. Cain WS, Stevens JC, Nickou CM, et al. Life-span development of odor identification, learning, and olfactory sensitivity. Perception 1995; 24:1457–1472
30. Anderson V. Cerebral Development. Anderson V, Northam E, Wrennall J, et al, eds. Philadelphia, Pa: Psychology Press; 2001
31. Jehl C, Murphy C. Developmental effects on odor learning and memory in children. Ann N Y Acad Sci 1998;855:632–634
32. Doty RL, Shaman P, Dann M. Development of the University of Pennsylvania Smell Identification Test: a standardized microencapsulated test of olfactory function. Physiol Behav 1984;32:489–502
33. Good KP, Martzke JS, Honer WG, et al. Left nostril olfactory identification impairment in a subgroup of male patients with schizophrenia. Schizophr Res 1998;33:35–43
34. Zatorre RJ, Jones-Gotman M. Human olfactory discrimination after unilateral frontal or temporal lobectomy. Brain 1991;114:71–84
35. Savage R, Combs DR, Pinkston JB, et al. The role of temporal lobe and orbitofrontal cortices in olfactory memory function. Arch Clin Neuropsychol 2002;17:305–318
36. Brewer W, Edwards J, Anderson V, et al. Neuropsychological, olfactory, and hygiene deficits in men with negative symptom schizophrenia. Biol Psychiatry 1996;40:1021–1031
37. Barnett R, Maruff P, Purcell K, et al. Impairment of olfactory identification in obsessive-compulsive disorder. Psychol Med 1999;29:1227–1233
38. Brewer WJ, Pantelis C, Anderson V, et al. Stability of olfactory

identification deficits in neuroleptic-naive patients with first-episode psychosis. Am J Psychiatry 2001;158:107–115
39. Brewer W, Wood SJ, McGorry PD, et al. Impairment of olfactory identification ability in individuals at ultra-high risk for psychosis who later develop schizophrenia. Am J Psychiatry 2003;160:1790–1794
40. Gansler DA, Fucetola R, Krengel M, et al. Are there cognitive subtypes in adult attention-deficit/hyperactivity disorder? J Nerv Ment Dis 1998;186:776–781
41. Murphy KR, Barkley RA, Bush T. Executive functioning and olfactory identification in young adults with attention-deficit/hyperactivity disorder. Neuropsychology 2001;15:211–220
42. Moberg PJ, Turetsky BI. Scent of a disorder: olfactory functioning in schizophrenia. Curr Psychiatry Rep 2003;5:311–319
43. Tebartz van Elst L, Woermann FG, Lemieux L, et al. Affective aggression in patients with temporal lobe epilepsy: a quantitative MRI study of the amygdala. Brain 2000;123:234–243
44. Silverman WK, Albano AM. Anxiety Disorders Interview Schedule: Child and Parent Versions. New York, NY: Graywind Publications; 1996
45. Achenbach T. Manual for the Child Behavior Checklist. Burlington, Vermont: University of Vermont, Department of Psychiatry; 1991
46. Conners C. Conners Rating Scales Manual: Conners Parent Ratings Scales, Conners Teacher Ratings Scales, Instruments for use with Children and Adolescents. New York, NY: Multihouse Systems Inc; 1989
47. Wechsler D. Wechsler Intelligence Scale for Children. 3rd ed. San Antonio, Tex: The Psychological Corporation; 1991
48. Daniel A. Power, Privilege and Prestige: Occupations in Australia. Melbourne, Australia: Longman-Cheshire; 1983
49. Rowe KJ, Rowe KS. Rowe Behavioural Rating Inventory Profile User's Guide: Interactive Software for the Assessment and Monitoring of Child/Student Externalizing Behaviours at Home or at School. Melbourne, Australia: Centre of Applied Educational Research and Department of Paediatrics, University of Melbourne; 1995
50. Achenbach TM, Edelbrook CS. Behavioral problems and competencies reported by parents of normal and disturbed children aged 4 through 16. Monogr Soc Res Child Dev 1981;46(1):1–82
51. Dade LA, Jones-Gotman M, Zatorre RJ, et al. Human brain function during odor encoding and recognition: a PET activation study. Ann N Y Acad Sci 1998;855:572–574
52. Brewer WJ, Wood SJ, DeLuca C, et al. Olfactory processing and brain maturation. In: Brewer WJ, Castle D, and Pantelis C, eds. Olfaction and the Brain. Cambridge, United Kingdom: Cambridge University Press; 2006

Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Childhood and Adolescent Mental Health section. Please contact Karen D. Wagner, M.D., Ph.D., at kwagner@psychiatrist.com.

