Impaired Olfactory Identification in Asperger's Syndrome

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The authors measured odor detection threshold and odor identification in 12 males with Asperger's syndrome and 12 matched control subjects. Relative to control subjects, Asperger's syndrome subjects were not impaired at odor detection but were significantly impaired at olfactory identification.

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Asperger's syndrome (AS), like autism, is a pervasive developmental disorder characterized by social deficits and obsessional stereotypic behaviors, but with normal general cognitive and language development. The term *autistic spectrum disorder* has been suggested to encompass autism-like conditions, and many adults with AS are phenotypically similar to high-functioning adults with autism.[1] Neuropathological studies have reported generalized abnormalities in brain anatomy,[2] yet animal models[3] and neuropsychological[4] and neuroimaging[5,6] studies suggest localized functional abnormalities of medial temporal lobe structures and prefrontal cortex in autistic spectrum disorders.

In nonhuman and human primates, damage to orbitofrontal cortex and medial temporal lobe, including amygdala, results in deficits in social behavior.[3,7,8] Medial temporal lobe lesions in infant monkeys produce social indifference and stereotypic behaviors analogous to those of autism.[3] Moreover, in adult humans, damage to orbitofrontal cortex may result in decreased empathy, inappropriate social interaction, and increased obsessionality.[7] Thus, selective dysfunction of medial temporal and orbitofrontal areas may be associated with features of autistic spectrum disorders.

In human and nonhuman primates, medial temporal and orbitofrontal areas are also involved in processing of olfactory information.[9,10] Lesions of medial temporal lobe structures impair odor detection, whereas orbitofrontal lesions impair olfactory identification.[9,10] We therefore examined odor detection and identification to assess the functional integrity of brain areas implicated in the control of social behavior and to determine whether specific neurobiological abnormalities are associated with AS.

METHODS

All subjects were participants in a clinical research program approved by the local Research Ethical Committee. Written informed consent was obtained from the subjects after complete description of the study. Subjects were healthy, medication-free nonsmokers who were screened to exclude conditions affecting olfactory function. Detailed neuropsychometry was available for all AS subjects but not for all controls. Thus, AS subjects and control subjects were matched for estimated full-scale IQ (est.FSIQ) by using the National Adult Reading Test (NART). We studied 12 males who met ICD-10R criteria for Asperger's syndrome and Autism Diagnostic Interview (ADI-algorithm) criteria for autistic disorder. The AS subjects' mean age was 33 years (SD = 8), and mean est.FSIQ was 107 (SD = 15). Two AS subjects were left-handed. We also studied 12 male control subjects, matched for handedness, age, and overall intelligence. The control subjects' mean age was 31 years (SD = 5), and mean est.FSIQ was 112 (SD = 8).

Odor detection thresholds were assessed by using a modified version of the two-bottle test of Cain et al.[11]

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Ten dilutions of the odorant 1-butanol were prepared in de-ionized water, beginning with a 4% concentration by volume (Step 0) and decreasing stepwise in concentration. Each step was one-third of the preceding dilution. Subjects were presented with a forced choice of two alternatives (odorant and blank) and sampled the saturated vapor phase of odorant solutions birhinically, beginning with the lowest concentration (Step 9). The presentation of odorant/blank pairs was randomized. Incorrect choice led to a one-step increase in concentration, thereby defining detection threshold.

Olfactory identification ability was assessed with the University of Pennsylvania Smell Identification Test (UPSIT).[12] UPSIT is a highly standardized and widely used procedure involving a scratch-and-sniff test of 40 microencapsulated odorants with a forced choice of 4 alternatives per item.

Group differences in performance of both olfactory tests were examined by using two-tailed Student's *t*-tests. Within AS and control groups, we tested for correlations (Pearson) between olfactory identification and age or est.FSIQ.

RESULTS

There was no significant difference between AS and control subjects in their ability to detect 1-butanol ($t = 0.97$, df = 22, $P = 0.39$). However AS subjects, compared with control subjects, were significantly impaired on olfactory identification (UPSIT score), making a mean of 10.9 errors (SD = 4.6), compared with 3.8 (SD = 1.6) in control subjects ($t = 4.18$, df = 22, $P = 0.0007$; Table 1).

Within the AS group and within the control group, there was no correlation between UPSIT score and age or est.FSIQ.

DISCUSSION

We report normal odor detection, but impaired olfactory identification, in people with AS. Medial temporal lobe structures are implicated in odor detection, whereas orbitofrontal cortex is implicated in olfactory identification;[9,10] therefore, our results suggest that AS is associated with orbitofrontal, but not medial temporal lobe, dysfunction.

It is controversial whether generalized or regionally specific brain abnormalities underlie the behavioral deficits that are characteristic of autistic spectrum disorders. Neuropathological studies of autistic spectrum disorders report diffuse abnormalities in brain development,[2] and studies of brain morphometry report distributed abnormalities in cerebellum and parietal lobe[13] as well as in medial temporal lobe and prefrontal regions.[14] In contrast, neuropsychological and functional neuroimaging studies suggest a localization of brain dysfunction to prefrontal and medial temporal lobe.[4–6]

Our results, obtained by using olfactory processing as an "independent" probe for regional functional integrity, imply orbitofrontal dysfunction and argue against an obligatory abnormality of medial temporal lobe function in the pathogenesis of AS. Interestingly, impaired olfactory identification is also reported in obsessive-compulsive disorder (OCD), which has also been linked to orbitofrontal dysfunction.[15] Orbitofrontal cortex is anatomically and functionally connected to medial temporal lobe structures, including amygdala. Functional imaging studies reporting amygdala dysfunction during emotional processing in people with autistic spectrum disorders[6] may thus reflect activity differences consequent to orbitofrontal dysfunction or frontotemporal connectivity. Other prefrontal regions are implicated in AS.[5,14] However, our findings are consistent with the importance of the orbitofrontal cortex in social control and behavioral flexibility.[7]

Localized orbitofrontal dysfunction, nevertheless, does not disprove a generalized effect of brain development. Widespread neurodevelopmental abnormalities may result in selective dysfunction of regions such as orbitofrontal cortex that integrate sensory information across modalities. Moreover, a general impairment

TABLE 1. Comparison of odor identification and odor detection threshold in subjects with Asperger's syndrome and matched control subjects

	Asperger's Syndrome ($n = 12$)		Control ($n = 12$)		Analysis[a]
Variable	Mean	SD	Mean	SD	*P*
Age, years	32.9	8.1	30.8	5.3	0.47
Estimated full-scale IQ	107	15	112	3	
Odor detection threshold (dilution step)	6.0	0.9	6.4	1.1	0.39
Odor identification (number of errors on UPSIT)	10.9	4.6	3.8	1.6	0.0007[b]

Note: UPSIT = University of Pennsylvania Smell Identification Test.
[a]Two-tailed unpaired *t*-tests.
[b]Significant difference between AS and control subjects ($t = 4.18$, df = 22).

of associative cognitive mechanisms may explain deficits in olfactory identification. However, the circumscribed nature of the social and behavioral features of AS argues against a generalized cognitive deficit in association. We observed no correlation between UPSIT score and variables including age, IQ, schooling, and socioenvironmental backgrounds of subjects, and therefore the lower UPSIT scores of AS subjects in our study are unlikely to be attributable to lack of exposure to odorants as a consequence of diminished socialization and circumscribed behavioral patterns.

We selected individuals with AS to test the functional integrity of brain regions implicated in social and emotional behavior in the absence of confounding general intellectual deficits or language delay. However, our sample size was relatively small and consisted only of male adults. Further studies are therefore needed to determine if our findings generalize to women, and to other autistic spectrum disorders, including autism. Moreover, because autistic spectrum disorders are developmental in origin, examination of olfactory processing in children and adolescents may provide insights into the functional maturation of regions implicated in both olfaction and social behavior.

In summary, we report deficits in olfactory identification, but not detection, in Asperger's syndrome, suggesting that functional abnormalities of orbitofrontal cortex are associated with the social deficits of this autistic spectrum disorder.

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