OLFACTORY FUNCTION IN HUNTINGTON’S DISEASE PATIENTS AND AT-RISK OFFSPRING

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Odor identification ability and detection threshold sensitivity were measured in 25 probands with Huntington’s disease, 12 at-risk offspring, and 37 unrelated controls. Relative to controls and at-risk offspring, HD patients exhibited significant impairment on both measures of olfactory function. By contrast, at-risk offspring did not evidence any olfactory impairment relative to controls. Thus, impaired olfactory function does not aggregate in the family members of HD patients, and does not serve as an indicator of genetic vulnerability to the disorder.

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Olfactory dysfunction accompanies several neurological disorders, including Alzheimer’s disease (Doty, Reyes & Gregor, 1987; Peabody & Tinklenberg, 1985), idiopathic Parkinson’s disease (Ansari & Johnson, 1975; Doty, Stern, Pfeiffer, Gollomp & Hurtig, 1992), amyotrophic lateral sclerosis (Sajjadian, Doty, Gutnick, Shirugi, Sivak & Perl, 1994), and Korsakoff’s syndrome (Mair, Doty, Kelly, Wilson, Langlais, McEntee & Vollmecke, 1986). A possible genetic contribution to the olfactory dysfunction of AD is suggested by findings of decreased olfactory dysfunction in patients with questionable AD (Nordin &
Murphy, 1996), as well as in family members of AD patients (Serby, Mohan, Aryan, Williams, Mohs & Davis, 1996).

It is now well-established that patients with Huntington’s disease (HD) exhibit olfactory dysfunction (Moberg, Pearlson, Speedie, Lipsey, Strauss & Folstein, 1987; Nordin, Paulsen & Murphy, 1995). Similar to AD, olfactory impairment appears to occur early in the disease process, prior to the onset of significant motor or cognitive dysfunction (Moberg et al., 1987). Presumably, the olfactory loss has, at least in part, a genetic basis, since HD is an autosomal dominant genetic disorder with 100% penetrance; offspring have an approximate 50% risk of carrying the genetic mutation which produces the disease (Caine, Hunt, Weingartner & Ebert, 1978).

Given the early appearance of olfactory dysfunction in HD patients, the question as to whether persons genetically predisposed to this disorder experience olfactory dysfunction remains unanswered. We administered tests of odor identification and detection to HD patients, neurologically normal at-risk offspring, and unrelated, demographically balanced, healthy control subjects to address this issue.

**METHOD**

**Subjects**

Twenty-five patients with Huntington’s Disease (HD), 12 at-risk offspring (AR), and 37 unrelated, healthy control subjects (CT) were recruited from the Department of Neurology at St. Barnabas Medical Center. All patients had a clear family history of HD in at least one first degree relative. All examinations were conducted by a neurologist using a structured neurologic exam. At-risk relatives were examined periodically for the emergence of any symptoms of HD. Exclusion criteria for all subjects included: (1) neurologic disorder (other than HD for patients); (2) psychiatric disorder; (3) head trauma; (4) substance abuse; (5) medical conditions that may alter cerebral functioning; (6) upper respiratory infection; or (7) other conditions known to affect olfactory functioning. Controls were also screened for neurological and psychiatric history in first degree relatives. Written informed consent was obtained for all subjects prior to participation.

Demographic information is presented in Table I. No differences in education ($F[2,68] = 0.45, p = .63$), sex ($\chi^2 = 1.80, df = 2, p = .40$), ethnic background ($\chi^2 = 0.15, df = 2, p = .92$), or smoking ($\chi^2 = 0.85, df = 4, p = .93$) were observed. Significant effects for age ($F[2,68] = 3.93, p = .024$) and Mini-Mental State
Examination (MMSE) (Folstein, Folstein & McHugh, 1975) scores \( F[2,68] = 17.09, p < .001 \) were seen, with HD patients being older than the AR group and more cognitively impaired relative to both AR and CT groups. Age and MMSE scores were subsequently used as covariates in all analyses.

### Assessment of Olfactory Function

**Olfactory Identification.** Olfactory identification performance was assessed using the University of Pennsylvania Smell Identification Test (UPSIT) (Doty, Shaman & Dann, 1984). The UPSIT is a 40-item, forced-choice microencapsulated test of olfactory identification. The specific stimuli, basis for their selection, as well as the reliability and sensitivity of this test, have been described in detail elsewhere (Doty et al., 1984; Doty, Agrawal & Frye, 1989).

After the UPSIT, subjects were given the Picture Identification Test (PIT), a test analogous to the UPSIT except that line drawings related to the quality of the odorant are presented instead of odorant labels (Vollmecke & Doty, 1985). This test was designed to screen for cognitive deficits that may confound UPSIT score. Most subjects scored 40/40 on this test and none scored below 37/40.

**Odor Detection Threshold.** All subjects received a single staircase, forced-choice odor detection threshold test to estimate basal detection sensitivity to phenyl ethyl alcohol (PEA). This test, which is described in detail elsewhere (Doty, Gregor & Settle, 1986), uses the geometric mean of the last four staircase reversal points of a total of seven as the estimate of threshold sensitivity.
RESULTS

Olfactory Identification

Analysis of covariance (ANCOVA) with diagnosis and sex as grouping factors and age and MMSE score as covariates demonstrated a significant deficit in UPSIT performance for the HD group relative to controls and at-risk offspring ($F[2,66] = 30.11, p < .001$) (upper panel Fig. 1). No significant diagnosis x sex interaction was observed ($F[2,66] = 3.39, p = .07$), nor was a main effect seen for sex ($F[1,66] = 3.05, p = .08$). Planned contrasts indicated that AR subjects did not differ from the CT group ($F[1,43] = 0.15, p = .70$) on UPSIT performance.

Olfactory Threshold

Odor detection thresholds also differed between the three groups ($F[2,66] = 8.33, p = .001$), with HD patients performing below AR and CT groups (lower panel Fig. 1). There was no main effect for sex ($F[1,66] = 0.13, p = .71$), or diagnosis x sex interaction ($F[2,66] = 0.01, p = .98$). Analogous to UPSIT performance, AR and CT groups did not differ from one another on PEA detection thresholds ($F[1,43] = 0.18, p = .67$).

Within the HD group, there was no relationship between symptom duration and scores on the UPSIT ($r = .02, p = .91$) or PEA thresholds ($r = .06, p = .77$).

To assess proband versus offspring deficits directly, within family analysis was conducted on a subgroup of 12 HD patients, their individually matched offspring, and controls (Table II). Pairwise contrasts showed that HD patients scored more poorly on the UPSIT and PEA detection threshold relative to controls and their at-risk offspring. In contrast, AR family members did not differ on any olfactory measure relative to individually-matched controls.

DISCUSSION

Results indicate that HD patients evidence significant deficits in the ability to detect and identify odors relative to at-risk offspring and matched controls. These findings were further supported by within family contrasts, with 100% of HD patients performing below individually-matched controls and their at-risk family member. AR subjects did not differ from controls on either olfactory task. The absence of olfactory deficits in the at-risk group suggests that the dysfunction occurs near the time of the phenotypic expression of the clinical signs of HD. In contrast, a recent study of UPSIT performance in family members of AD patients
FIGURE 1  Bar charts of raw UPSIT and PEA odor detection threshold (log vol/vol) scores for CT, AR, and HD groups. Mean ± SEM.
(Serby et al., 1996) showed significant deficits in performance, indicating a genetic vulnerability to olfactory dysfunction. Overall, olfactory dysfunction does not aggregate in the family members of HD patients and does not appear to serve as an indicator of genetic vulnerability to the disorder.

The assessment of the genetic contribution to olfactory dysfunction seen in HD was achieved through use of at-risk offspring who have an approximate 50% probability of contracting the illness. It can be argued that deficits were not seen because we happened to sample offspring who fell in the noncontracting 50% of the at-risk population. However, follow-up of 9 AR subjects revealed that 4 (56%) had been subsequently diagnosed with HD. Comparisons of this subgroup to the other AR and CT subjects did not yield significant differences on any olfactory measure (all ps > .05). Future studies utilizing direct genetic assessment will further explicate these findings.

**References**


