Brief report

Odor identification deficits in frontotemporal dementia: A preliminary study

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Abstract

Multiple neurodegenerative disorders (e.g. Alzheimer's disease, Dementia with Lewy bodies, Parkinson's disease, and Huntington's disease) show olfactory deficits. Olfactory functioning has not been well studied in frontotemporal dementia (FTD). In the current study, individuals with FTD, Alzheimer's disease (AD), and healthy elderly controls were compared using an odor identification task. Results showed significant differences in odor identification between individuals with FTD and the healthy elderly control group. There were no differences between the FTD and AD groups. Using a cut score of 8/12, discriminant function analysis showed that the overall classification rate for the FTD and control groups was 71.4%, with a sensitivity rate of 87.5% and a specificity rate of 65%. This preliminary research demonstrates olfactory deficits in FTD, which appear to be similar in magnitude to the olfactory deficits seen in AD.

1. Introduction

It has been well established that declines in olfaction are common in neurodegenerative disorders and other dementing illnesses. Specifically, impairments on olfactory identification tasks have been found with Alzheimer's disease (AD), vascular dementia, dementia with Lewy bodies, Parkinson's disease, and Huntington's disease (Knupfer & Spiegel, 1986; Mesholam, Moberg, Mahr, & Doty, 1998; Moberg et al., 1987; Serby, Larson, & Kalkstein, 1991; Westervelt, Stern, & Tremont, 2003). To our knowledge, there has been only one study of olfactory functioning in frontotemporal dementia (FTD; Luzzi et al., 2007). This study examined olfactory functioning in patients with AD, the semantic dementia variant of FTD, the behavioral variant of FTD, and corticobasal degeneration. The investigators found that patients with semantic dementia had severely impaired odor identification, likely as a function of their loss of semantic knowledge (odor discrimination was intact); the patients with the behavioral variant of FTD had more mild deficits. Patients with the non-fluent aphasia variant of FTD were not studied.

The neuroanatomy of the olfactory system supports the likelihood of olfactory deficits in FTD. Olfactory axons synapse with second-order neurons in the olfactory bulb. These second-order neurons continue into the periamygdaloid cortex and surrounding temporal regions as well as areas of the orbitofrontal cortex (Savic, 2001). Functional

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Table 1
Sample characteristics

|	FTD	AD	NC	p
Gender (male/female)	6/8	6/8	6/8	
Age	64.9 (10.0)	68.8 (8.9)	65.9 (8.2)	0.500
Education	12.8 (3.1)	13.1 (2.9)	13.7 (2.4)	0.654
MMSE	20.7 (5.1)	24.1 (3.0)	29.1 (0.7)	0.000
3MS	67.1 (17.1)	75.8 (10.8)	96.8 (3.1)	0.000
CDR global score	1.2 (0.5)	1.0 (0)		0.174
CDR total box score	6.1 (2.7)	4.6 (1.4)		0.078
BSIT	7.0 (3.0)	7.8 (2.4)	10.4 (0.9)	0.001

Note: FTD, frontotemporal dementia; AD, Alzheimer's disease; NC, normal control; MMSE, Mini Mental State Examination; 3MS, Modified Mini Mental State Examination; CDR, Clinical Dementia Rating; BSIT, Brief Smell Identification Test.

imaging studies have shown activation of the anterior cingulate and right orbitofrontal cortex with processing of odorous stimuli in healthy females (Savic & Gulyas, 2000). Olfactory processing has also been shown to activate areas of the temporal and insular cortices in both hemispheres (Kettenmann, Hummel, Stefan, & Kobal, 1997). Therefore, given the neuroanatomic locations that are disrupted in FTD and areas of the temporal and frontal lobes that are processing centers for olfactory information, we hypothesized that olfaction would be disrupted in FTD.

2. Method

Seventeen participants with FTD were administered the Brief Smell Identification Test along with a mental status examination (3MS/MMSE; Folstein, Folstein, & McHugh, 1975; Teng & Chui, 1987) and Clinical Dementia Rating (CDR; Morris, 1993) as part of a full clinical examination. Diagnoses of FTD were made based upon criteria published by Neary et al. (1998). Neary et al. describe three subtypes of frontotemporal lobar degeneration. These include the frontotemporal dementia subtype characterized by personality change and disordered social conduct (referred to here as the behavioral subtype); a progressive non-fluent aphasia subtype characterized by loss of initiation of speech output over time; and a semantic aphasia subtype characterized by impaired understanding of the meaning of words and objects. Of the approximately 600 patients receiving diagnoses of dementia in this clinic since 2000, 17 met the Neary criteria for FTD. Three participants with the semantic dementia subtype of FTD were excluded from the present study to rule-out confounds due to loss of semantic knowledge. Individuals with non-fluent aphasia were not excluded as those participants displayed language skills that were adequate to complete a full examination, and they did not differ from the behavioral subtype in their ability to follow a three-part command. In addition, their language difficulties did not seem to interfere with their performance on the olfactory identification task (i.e., patients were not demonstrating/indicating difficulty understanding the instructional set or content). The 14 remaining participants (6 with the behavioral subtype, 8 with non-fluent aphasia) were matched based on age and education to 14 individuals with probable AD and 14 healthy older controls. Diagnoses of AD were based upon criteria published by the NINCDS-ADRDA Work Group (McKhann et al., 1984). An AD comparison group was used given that AD is one of the most common differential diagnoses from FTD, and measures discriminating the diseases would be useful clinical tools. In addition, olfactory impairments have been extensively examined in AD, and thus, this group was used as an anchor for comparison to the individuals with FTD. The healthy older control group consisted of community dwelling individuals without any history of diseases or brain injuries known to affect olfactory functioning, concerns about their memory, or declines in daily functioning. All healthy control participants had current MMSE total scores of 28/30 or better. Characteristics of the sample are presented in Table 1.

These three groups (FTD, AD, and controls) were compared using the Brief Smell Identification Test (BSIT) (Doty, Marcus, & Lee, 1996), a 12-item, multiple choice, odor identification task. Although designed to be self-administered, the BSIT was administered to each patient by the examiner to minimize the cognitive demands of the task. The Brief Smell Identification Test was presented bi-rhinally. The BSIT is a practical test in a clinical setting as it is simple, rapid to administer, and contains normative data.
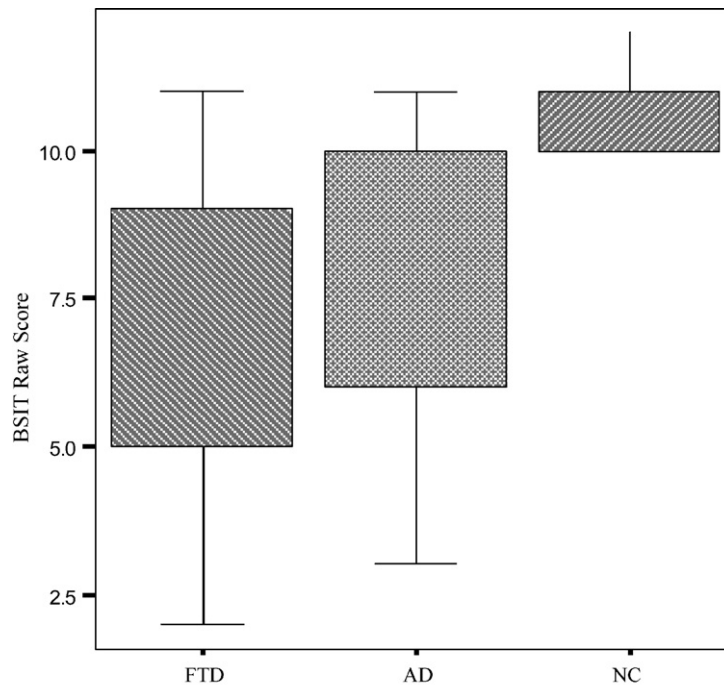
Note. FTD = frontotemporal dementia; AD = Alzheimer's disease; NC = normal control

Fig. 1. Brief Smell Identification Score (BSIT) by group.

3. Results

Analysis of variance (ANOVA) revealed that the three groups did not differ in terms of age ($p = 0.500$) or educational level ($p = 0.654$). There were no significant differences between male and female gender within- and across-groups. A t-test showed that the two dementia groups did differ in terms of global cognitive functioning on the MMSE ($p = 0.045$), with the AD group having higher MMSE scores. These two groups did not significantly differ in terms of CDR sum of boxes, or in terms of 3MS score. Analyses were also completed covarying MMSE scores, but there was no difference in results.

In comparing the three groups on the BSIT, the main effect of an ANOVA was significant ($F(2,39) = 8.73$, $p = 0.001$; see Fig. 1). In conducting post hoc analyses, the FTD group was significantly more impaired than the control group ($p = 0.001$). There were no significant differences between the FTD and AD groups ($p = 0.635$). Although results were non-significant, there was a trend in which, as frontotemporal dementia increases in severity (as measured by decreased mental status scores), olfactory identification abilities worsen ($r = 0.49$, $p = 0.07$); however, this will need to be replicated in future research with larger samples. There were no significant differences between individuals with the non-fluent aphasia subtype ($M = 7.13$, S.D. $= 3.27$) and individuals with the behavioral subtype ($M = 6.83$, S.D. $= 2.86$; $p = 0.86$).

Using a cutoff score of 8/12, discriminant function analysis showed a strong association between groups and predictors (using the FTD and control groups), χ^2 (1) $= 12.70$, $p = 0.000$ on the BSIT. The overall classification rate was 71.4%, with a sensitivity rate of 87.5% and a specificity rate of 65%. The proportional area under the receiver operating characteristic curve was 88.8%.

4. Discussion

The findings from this preliminary clinical study show that individuals with FTD have significant impairments on an odor identification task, of the same magnitude of those seen in AD. Olfactory deficits in FTD may be expected due to the neuroanatomical location of the expected degeneration, as the temporal and frontal lobes contain primary

Table 2
BSIT score frequencies for experimental and control groups

BSIT raw score	FTD	AD	NC
0/12	0	0	0
1/12	0	0	0
2/12	1	0	0
3/12	2	1	0
4/12	0	0	0
5/12	2	1	0
6/12	1	3	0
7/12	1	1	0
8/12	0	2	1
9/12	4	2	0
10/12	2	2	6
11/12	1	2	6
12/12	0	0	1

Note: FTD, frontotemporal dementia; AD, Alzheimer's disease; NC, normal control.

and secondary areas for olfactory processing. Of note, as we have observed in AD (Westervelt, Carvalho, & Duff, 2007), although the FTD group as a whole was impaired on the BSIT, there was notable range in patient performance (range: 2/12 to 11/12; 57 percent of the patients with FTD were below the 16th percentile according to normative data; see Table 2 for score frequency data). The clinical implications of these findings (e.g., ability of odor identification tests to identify patients with early disease, predict disease course or treatment response), however, have not yet been established.

There were several limitations to the current study, the most significant of which was the small sample size given the relative rarity of the disease. Despite the small sample, the findings were robust enough to detect statistically significant differences. In addition, the presence of aphasia in the FTD group is a potential confound. However, although there were small sample sizes in the groups, there were no significant differences between the behavioral group and the group with non-fluent aphasia, suggesting that the deficits on the odor identification task in the individuals with non-fluent aphasia are reflective of olfactory impairments rather than attributable to language difficulties. Assessment of other aspects of olfaction and cognition (e.g., threshold testing to assess olfactory sensitivity, unilateral olfactory deficits, and a visual analog of the BSIT to assess for the non-olfaction related cognitive demands of the task) would have been beneficial in determining the underlying cause of impairment on the BSIT, though these data were not available for this retrospective clinical study. Lastly, pathologic confirmation of diagnosis was not available for most patients (one patient with behavioral FTD was pathologically confirmed). However, studies have shown 85% sensitivity and 99% specificity for post-mortem confirmation of antemortem diagnosis of FTD based upon the consensus criteria (Knopman, Boeve, & Parisi, 2005), suggesting misdiagnosis was unlikely.

In sum, our results suggest odor identification deficits are present in FTD, and that these deficits may be similar in magnitude to those seen in AD. Future studies may wish to replicate the findings with a larger sample and examine other factors which may impact odor identification performance. Furthermore, the onset and course of these deficits has not been established; exploration into whether early deficits may help identify patients in the beginning stage of FTD or whether the presence/extent of deficits may be predictive of clinical aspects of the disease (e.g., course) may be beneficial.

Acknowledgement

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