A Digital Olfactometer for Smell Threshold Measurements in Neurodegenerative Disease Diagnostics

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Abstract—Ink-jet microdispensing technology was used to develop an instrument for the quantitative determination of the olfactory threshold. An electrical pulse applied to the piezoelectric microdispenser causes a drop of fluid to be ejected through a precise orifice. An electronic console actuates the piezoelectric dispensing elements and controls the number of drops that are dispensed and evaporated to create a fragrance cloud. The number of drops that are generated, evaporated and presented to the patient’s nose for detection is adjusted according to a preset algorithm until the patient’s smell threshold is discovered. Neurodegenerative disease patients tested with the developed olfactometer showed a significant elevation of their olfactory threshold as compared to normal controls. This result agrees with literature studies that indicate the sense of smell is one of the first affected by neurodegenerative disease. Through its precise control and detection capability, the digital olfactometer described in this paper can be used as an early screening tool for neurodegenerative diseases through olfactory threshold determination.

I. INTRODUCTION

A study of the US population based on the 2000 Census reports that 4.5 million people had Alzheimer’s disease, and the prevalence (the number of people with the disease at any one time) is expected to at least double by 2050 for every 5-year age group beyond age 65. Nearly half of all people aged 85 or older currently have Alzheimer’s disease. Researchers estimate that by 2050, 13.2 million Americans will have Alzheimer’s disease if no preventive treatments become available [1]. With advancements in physical and mental health care more Americans will be reaching older ages. As the number of individuals 85 years of age or older increases so will the number of Alzheimer’s cases.

The annual cost of caring for an Alzheimer’s disease patient depends upon the severity of the disease with a total estimated direct and indirect annual cost of care for Alzheimer’s disease patients of $100 billion. The cost and the implications of the disease on the caregivers and families make early detection and diagnosis of neurodegenerative disease and especially Alzheimer’s disease a high priority. Early diagnosis coupled with interventions that could delay the onset of the disease or slow down its progress would significantly aid the caregivers and reduce the cost of care.

Studies indicated that, in its initial stages, Alzheimer’s disease attacks medial temporal lobe structures that are critical in smell identification [2], [3]. As the disease progresses, further deficits appear in the patient’s ability to identify and detect odors, and the patient becomes unaware of the deficit [4]–[6]. A method capable of quantifying the patients’ olfactory capability will not only facilitate early diagnosis of neurodegenerative diseases like Alzheimer’s or Parkinson’s, but will also provide the means to track the progression of the disease [7], [8].

A recently published odor recognition study [9] carried out at Rush Alzheimer’s Disease Center in Chicago evaluated 589 patients once a year over a five year period. A strong correlation was found between participants which developed the kind of mild cognitive impairment that can be a warning sigh of future Alzheimer’s disease and those that scored below average in the odor identification test. The ability to measure smell threshold was not available for this evaluation.

The olfactometer technology described in this paper is based on digitally controlled, high precision ink-jet dispensing technology and is capable of determining the olfactory threshold. The threshold for specific odorants is determined to a very high-resolution because ink-jet microdispensers are capable of delivering nanomolar quantities of odorant per ejected drop. The system can dispense many odorants through the use of interchangeable cartridges. A wider dynamic range of odorant delivery can be achieved by using cartridges with different dilutions of the same odorant.

Olfactometer Design

The digital olfactometer (Fig. 1) consists of piezoelectric ink-jet microdispenser modules – each module is used for a different odorant or odorant dilution – placed two on each side of a heating element in a “V” configuration (Fig. 2) [10], [11]. Each microdispenser module (Fig. 3) is composed

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of a piezoelectric dispenser with a reservoir and electrical connections for the actuating signal. The olfactometer is connected electrically to a control unit that selects the dispenser and number of drops of the specified odorant to be dispensed. The drops are dispensed onto the heated surface and the odorant vapor cloud is presented to the patient’s nose by a miniature fan. Details of the digital olfactometer will be covered in the presentation.

II. Procedure for Testing

All olfactory threshold testing was conducted in the Human Performance Laboratory at Presbyterian Hospital of Dallas in a well-ventilated room.

A. Set-up

The odorants (phenethyl alcohol and lemon extract) were loaded using sterile syringes into the reusable, sterilized cartridges. Several bursts of drops were ejected from each of the microdispensers to ensure priming. A new disposable paper nose cone used to direct the flow of the odorants was installed for each test subject. The test administrator gave the test subject the instructions regarding the procedure.

B. Testing

The testing followed a methodology that is illustrated in Fig. 4. For each trial within a test, discrete levels of odorants were presented to the subject’s nose who was then asked to sniff on verbal cue and then provide a suitable response: “yes” (odorant detected) or “no” (odorant not detected). The test administrator interpreted the subject’s responses and then adjusted the control stimulus intensity (number of drops) up or down depending on the subject’s current and previous responses.

The starting level for the stimulation was set at 134 drops which was established in a previous study. This corresponds to 105 nanomoles for phenethyl alcohol. Because the composition of the lemon extract was not known, it was not possible to calculate the corresponding number of moles. The first trial in a test establishes the stimulus level direction: "down" for a "yes" response, "up" for a "no" response. The test progresses similarly until a change in response pattern occurs (YYYN or NNNY). When such a change occurs, the next trial is conducted at the same level as the previous trial. For subsequent trials the direction of stimulus level is changed only when one of the following takes place:

1) The subject does not detect the stimulus on two consecutive trials while moving to a lower concentration (YYYNC response pattern). In this case the following trial has the level set to the next higher level.

2) The subject reports detection of the stimulus on two consecutive trials while moving up to a higher concentration (NYYNY response pattern). The following trial is performed at the next lower level.

A test is concluded when a third direction change occurs.

Fig. 1. Olfactometer using ink-jet microdispensers and its control electronics console.

Fig. 2. Diagram of the ink-jet based vapor generator component. The dispensing modules are placed in a V configuration such that the odorant droplets land on the centrally placed heater. Another pair of microdispenser modules is placed behind the one shown in the sketch for a total of four modules.

Fig. 3. Microdispenser module. The reservoir is made of small capillary Teflon™ tubing and is loaded with odorant through the top. Electrical contacts plug in a matching connector in the olfactometer that provides the electrical signal from the control console and the mechanical support.
between the same two levels. The final estimate of the olfactory threshold is determined as the average of stimulus levels corresponding to the last two direction changes. The procedure described above is a modified staircase that was used in previous olfaction studies.

Fig. 4 presents the individual trial results and the convergence toward the olfactory threshold for representative “control” and “smell deficient” patients. The control patient can detect smaller and smaller amounts of odorants until the detection / non-detection oscillates between two levels. The “smell deficient” patient has a similar oscillatory behavior between two levels that have a significantly higher amount than the starting level.

C. Test Results

Healthy control candidates were recruited to cover a wide age range (approximately 10 subjects per age decade from 20's through 80's) and to have a good representation of both males and females. All control candidates were administered the Folstein Mini-Mental Status Examination (MMSE) [13] to test for cognitive impairment as well as the clock drawing and clock copying tests to examine the integrity of frontal and parietal lobe function. To be included within the control group the test subjects had to have a MMSE score higher than 29, copy drawing and clock copying scores of 4/4 and to have: (a) no family history of AD and/or PD, (b) no occurrence of any head trauma, (c) no decrease in memory, (d) no decrease in the ability to smell, (e) no presence of allergies, and (f) had not smoked during the last 10 years. Alzheimer’s and Parkinson’s patients were recruited from the Neurology Outpatient Clinic at Presbyterian Hospital of Dallas (PHD).

Fig. 5 summarizes the olfactory thresholds for control male test subjects and patients diagnosed with Alzheimer’s or Parkinson’s. The clinical studies evaluating the digital olfactometer were preformed in their laboratory.

III. CONCLUSION

The olfactometer was able to detect differences between the control patients and the patients diagnosed with a neurodegenerative disease. More experiments are necessary to better establish the correlation between the increase in the olfactory threshold and neurodegenerative disease. With the capability of precisely quantifying the threshold, the change in the olfaction threshold can be followed as the disease progresses.

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