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(54) Title: METHODS AND TESTS FOR DEGENERATIVE DISORDERS OF THE CENTRAL NERVOUS SYSTEM

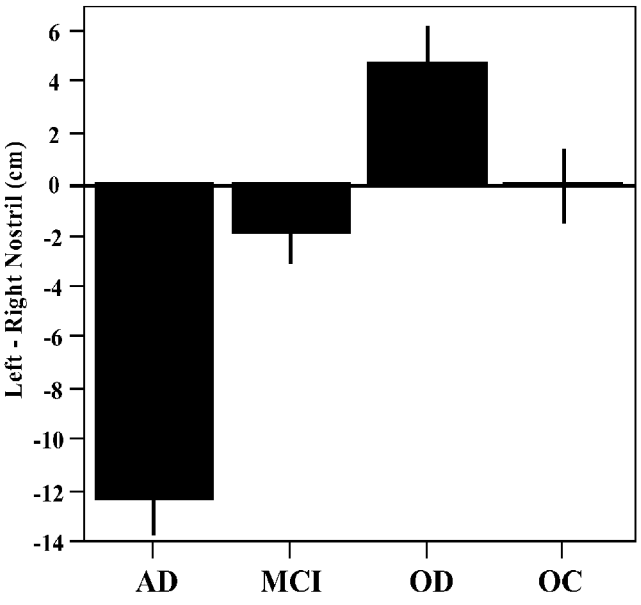

FIG. 1

(57) Abstract: The present disclosure provides methods and tests for diagnosis and screening of degenerative disorders of the central nervous system, such as Alzheimer's disease and Parkinson's disease. The method includes the following steps: placing a container containing a pure odorant under a nostril of a patient; moving the container closer to the nostril of the patient; measuring the odor detection distance between the patient's nostril and the location of the container where the patient first detected the odor; repeating the above steps with the other nostril; and determining the difference between the odor detection distance for each nostril, wherein an odor detection difference of at least about 5 cm in favor of the right nostril indicates a likelihood of Alzheimer's disease.

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METHODS AND TESTS FOR DEGENERATIVE DISORDERS OF THE CENTRAL NERVOUS SYSTEM

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority to U.S. provisional applications entitled, "Methods and Tests for Degenerative Disorders of the Central Nervous System," having serial number 61/754,150, filed on January 18, 2013, which is entirely incorporated herein by reference.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

This invention was made with Government support under Contract No.: 00074691 awarded by the National Institutes of Health. The Government has certain rights in this invention.

BACKGROUND

Approximately one in eight people over the age of 65 and half of those over 85 have Alzheimer's disease (AD)[1]. The NINCDS-ADRDA criteria for diagnosing AD require an extensive evaluation by a clinician[2,3]. To help confirm the diagnosis of AD several institutions use biomarkers such as f^{11}C- PiB, a radioisotope that marks cerebral amyloid during PET imaging[4] or examination of the cerebral spinal fluid for the ratio of tau to amyloid-β 1-42 levels[5]. All of these tests are expensive and require highly trained personnel or equipment that is available in only a limited number of locations.

Moreover, except for the lumbar puncture, which is invasive with potential complications, these procedures are neither highly sensitive nor specific for AD[2-7]. For instance, the NINCDS and ADRDA criteria for diagnosis were found to have a sensitivity of 81% and a specificity of 70%. Also, a trained clinician must spend extensive time evaluating patients to meet these criteria and the clinician must determine that the impairment is related to a

decrement in cognition and not by a psychiatric disorder. Also, with respect to many of the laboratory tests, many healthy elderly individuals can be positive for $f^{11}C$-PiB, and the percentage of elderly people with positive scans increases with age. For example, 30% of those in their 70s who do not have AD will have positive scans. Additionally, this test may also be positive in other dementing diseases such as Lewy body dementia, and is thus not specific for AD. Thus, many of the clinical and diagnostic tests currently used to help diagnose AD are expensive and require highly trained personnel or equipment available only in limited locations. Except for the lumbar puncture tests, which are invasive with potential complications, most of the procedures discussed above are not readily available, highly sensitive, or specific for AD.

SUMMARY

Briefly described, embodiments of the present disclosure provide methods, kits, and systems for diagnosing and characterizing degenerative disorders of the central nervous system (CNS), such as, Alzheimer's disease, Parkinson's disease, and other CNS disorders.

The present disclosure provides embodiments of methods of diagnosing Alzheimer's disease in a patient, the method including the following steps: placing a container containing a pure odorant under a nostril of a patient suspected of having Alzheimer's disease, where the container is placed at a sufficient distance that the patient cannot detect the odorant, the patient's other nostril is closed and the patient cannot see the odorant, and the odorant is not capable of detection by trigeminal nerve stimulation; moving the container closer to the nostril of the patient at a consistent rate until the patient detects the odor; measuring the odor detection distance between the patient's nostril and the location of the container where the patient first detected the odor; repeating the above steps with the other nostril; and determining the difference between the odor detection distance for each nostril, where an odor detection difference of at least about 5 cm in favor of the right nostril (e.g., the odor detection difference for the left nostril is at least about 5cm less than the odor detection distance of the right nostril) indicates a likelihood of Alzheimer's disease.

In embodiments, the present disclosure also provides methods of diagnosing a degenerative disease of the central nervous system (CNS) in a patient, the methods

including the following steps: placing a container containing a pure odorant under a nostril of a patient suspected of having a degenerative disease of the CNS, where the container is placed at a sufficient distance that the patient cannot detect the odorant, the patient's other nostril is closed and the patient cannot see the odorant, and the odorant is not capable of detection by trigeminal nerve stimulation; moving the container closer to the nostril of the patient at a consistent rate until the patient detects the odor; measuring the odor detection distance between the patient's nostril and the location of the container where the patient first detected the odor; repeating the above steps with the other nostril; and comparing the odor detection distance for each nostril, where a difference of at least about 5 cm between the detection distance for each nostril or a difference of at least about 10 between the odor detection distance for the patient and the average odor detection distance for a control patient indicates the presence of a neurodegenerative disease. In embodiments of the foregoing method, where the odor detection distance of the left nostril is at least about 5 cm worse than the odor detection distance for the right nostril, the patient has a likelihood of Alzheimer's disease. In embodiments of the foregoing method where the odor detection difference between the right and left nostrils is less than or equal to about 3 cm, and wherein the average odor detection distance for both nostrils of the patient is at least about 10 cm worse than the average odor detection distance of a control patient, the patient has a likelihood of Parkinson's disease.

The present disclosure also provides embodiments of methods of determining the hemisphere of a patient's brain affected with CNS disorder, the method including the following steps: placing a container containing a pure odorant under a nostril of a patient having a CNS disorder selected from the group consisting of: epilepsy, cerebellar tumor and ataxia, where the container is placed at a sufficient distance that the patient cannot detect the odorant, the patient's other nostril is closed, the patient cannot see the odorant, and the odorant is not capable detection by trigeminal nerve stimulation; moving the container closer to the nostril of the patient at a continuous rate until the patent detects the odor; measuring the odor detection distance between the patient's nostril and the location of the container

where the patient first detected the odor; repeating the above steps with the other nostril; and comparing the odor detection distance for each nostril, where the identity of the more impaired nostril indicates the hemisphere affected by the CNS disorder.

In all of the above-described methods, in embodiments the odorant is peanut butter or the odorant compound in peanut butter. In other embodiments, the odorant material is selected from the group including: coffee grounds and chocolate. In embodiments, the odorant does not contain alcohol.

In embodiments, the present disclosure also provides kits for testing or diagnosing a degenerative disease of the central nervous system (CNS) in a patient, the kit including a sealed container including a pure odorant that is not capable of detection by trigeminal nerve stimulation, and instructions for use including the following steps: instructing a patient having a CNS disorder to seal one nostril or sealing the patient's nostril with a device, while leaving the other nostril open; placing the container containing the pure odorant under the open nostril of the patient, where the container is placed at a sufficient distance that the patient cannot detect the odorant, and where the patient cannot see the odorant; moving the container closer to the open nostril of the patient at a continuous rate until the patent detects the odor; measuring the odor detection distance between the patient's nostril and the location of the container where the patient first detected the odor; repeating the above steps with the other nostril; and comparing the odor detection distance for each nostril and calculating an odor detection difference for the patient, where the odor detection distance and odor detection difference can be used to diagnose a degenerative disease of the CNS.

In embodiments, the present disclosure also provides systems for testing or diagnosing a degenerative disease of the central nervous system (CNS) in a patient, the system including a device capable of being mounted on a subject's head, where the device includes the follwoign: a portion that removably secures the device to the subject's head; a nose plug for closing one nostril of a subject at a time; a distance-measuring device; and a receptacle coupled to the distance-measuring device, where the receptacle is adapted to hold a disposable container of odorant material, and where the receptacle can be moved

along the distance-measuring device to measure the distance of the odorant container to an open nostril of the subject.

Other methods, compositions, plants, features, and advantages of the present disclosure will be or become apparent to one with skill in the art upon examination of the following drawings and detailed description. It is intended that all such additional compositions ,plants, methods, features, and advantages be included within this description, and be within the scope of the present disclosure.

BRIEF DESCRIPTION OF THE DRAWINGS

Further aspects of the present disclosure will be more readily appreciated upon review of the detailed description of its various embodiments, described below, when taken in conjunction with the accompanying drawings.

FIG. 1 is a graph illustrating the mean L – R nostril odor detection difference (cm) for each group. AD is Alzheimer's disease, MCI is mild cognitive impairment, OD is other dementias, and OC is older controls. ANOVA confirmed a significant difference between groups ($F(3,90) = 28.33$, $p < 0.0001$) and the L – R nostril distance of the AD patients was significantly larger than all other groups ($p < 0.0001$).

FIG. 2 illustrates the frequency distribution of the difference score of the L – R nostril detection distance (cm) for each group. The frequency distribution of the AD group is significantly different from all other groups, Fisher exact of the $\chi 2$, $p < 0.0001$.

FIG. 3 is a bar graph illustrating the mean L – R nostril odor detection difference (cm) for each group, including PD, showing the odor detection is asymmetrically impaired in AD and symmetrically impaired in PD. AD is Alzheimer's disease, MCI is mild cognitive impairment, OD is other dementias, PD is Parkinson's disease, and OC is older controls.

FIG. 4 illustrates the mean L – R nostril detection difference for the groups, including PD, demonstrating that the left nostril relatively worse (shorter detection distance) than right nostril odor detection by an average of 10 cm in the patients with AD.

FIG. 5A illustrates the mean odor detection distance and FIG. 5B illustrates the mean L – R odor detection distance for groups including CBD separated out from the OD group.

FIGS. 6A and 6B are graphs illustrating the number of participants who correctly or incorrectly identified the odor as peanut butter in each group with their left vs. right nostril. FIG. 6B shows the data with the CBD patients separated out from the OD group.

FIGS. 7A and 7B are bar graphs illustrating average distance (cm) of odor recognition for the left and right nostril of each group, showing that odor recognition distance follows the same pattern as odor detection distance for all groups. FIG. 7B includes and FIG. 7A does not include the PD group.

DESCRIPTION

Before the present disclosure is described in greater detail, it is to be understood that this disclosure is not limited to particular embodiments described, and as such may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting.

Where a range of values is provided, it is understood that each intervening value, to the tenth of the unit of the lower limit unless the context clearly dictates otherwise, between the upper and lower limit of that range and any other stated or intervening value in that stated range, is encompassed within the disclosure. The upper and lower limits of these smaller ranges may independently be included in the smaller ranges and are also encompassed within the disclosure, subject to any specifically excluded limit in the stated range. Where the stated range includes one or both of the limits, ranges excluding either or both of those included limits are also included in the disclosure.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. Although any methods and materials similar or equivalent to those described herein can also be used in the practice or testing of the present disclosure, the preferred methods and materials are now described.

Any publications and patents cited in this specification that are incorporated by reference are incorporated herein by reference to disclose and describe the methods and/or materials in connection with which the publications are cited. The citation of any publication is for its disclosure prior to the filing date and should not be construed as an admission that the present disclosure is not entitled to antedate such publication by virtue of prior disclosure. Further, the dates of publication provided could be different from the actual publication dates that may need to be independently confirmed.

As will be apparent to those of skill in the art upon reading this disclosure, each of the individual embodiments described and illustrated herein has discrete components and features which may be readily separated from or combined with the features of any of the other several embodiments without departing from the scope or spirit of the present disclosure. Any recited method can be carried out in the order of events recited or in any other order that is logically possible.

Embodiments of the present disclosure will employ, unless otherwise indicated, techniques of medicine, biology, statistics, biochemistry, molecular biology, and the like, which are within the skill of the art. Such techniques are explained fully in the literature.

It must be noted that, as used in the specification and the appended embodiments, the singular forms “a,” “an,” and “the” include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to “a cell” includes a plurality of cells. In this specification and in the embodiments that follow, reference will be made to a number of terms that shall be defined to have the following meanings unless a contrary intention is apparent.

Prior to describing the various embodiments, the following definitions are provided and should be used unless otherwise indicated.

Definitions

In describing the disclosed subject matter, the following terminology will be used in accordance with the definitions set forth below.

As used herein the term "pure odorant" refers to an aromatic compound detectable by a patient via olfactory nerve stimulation that does not simultaneously stimulate the trigeminal nerve. Since alcohol can stimulate the trigeminal nerve, alcohol-based odorants are not considered "pure odorants" for purposes of the present disclosure.

In the present disclosure, the term "odor detection" refers to the point at which a patient realizes (e.g., becomes aware of) the presence of an odorant.

The "odor detection distance" refers to the distance between the source of the odorant (e.g., container containing the odorant compound) and the patient's nostril at the point of odor detection.

As used herein, the term "odor recognition" or "odor identification" refers to the point at which a patient can identify the source of an odor that has been detected. Thus, odor recognition differs from odor detection in that odor recognition includes the further step of recognizing/identifying the particular odor (e.g., peanut butter or coffee vs. just "an odor"). The "odor recognition distance" refers to the distance between the source of the odorant and the patient's nostril at the time that "odor recognition" occurs.

Discussion

The embodiments of the present disclosure encompass methods and tests for degenerative and/or cognitive disorders of the central nervous system. In embodiments, tests and methods of the present disclosure can diagnose or aid in diagnosing Alzheimer's disease (AD), can distinguish between AD and other forms of degenerative disorders of the CNS, can help to identify the location of injury and/or impairment in CNS disorders characterized by unilateral and/or asymmetrical localization, such as epilepsy, tumor, or other brain injury.

Early diagnosis of Alzheimer's disease (AD) may reduce disability, enhance quality of life, and aid clinical trials. Also, distinguishing AD from other forms of cognitive impairment can aid in treatment, and reduce unnecessary testing and treatment, among other advantages. Thus, a sensitive, specific, inexpensive and readily available clinical screening test for AD during the earliest possible phase could provide substantial benefits to the medical community.

Many of the eight structures lying on the surface of the basal forebrain and within the mesial temporal lobes that comprise olfactory cortex[8,9] are the sites of initial pathology in AD[10-12]. Because olfactory dysfunction occurs in preclinical AD[13,14], assessing olfactory sensitivity during the neurologic examination could prove especially helpful for early diagnosis. Portions of olfactory cortex are the initial sites of AD pathology and people with AD often have more degeneration of their left than right hemisphere. Since the olfactory epithelium projects mainly to the ipsilateral olfactory cortex, patients with AD may demonstrate an asymmetrical (left greater than right) decrement of odor detection sensitivity. The present disclosure provides a quick, accurate and sensitive test based on this asymmetrical degeneration of odor detection.

An odor detection test designed by Davidson and Murphy called the Alcohol Sniff Test has a low cognitive load and good test-retest reliability[15,16]. However, because the presence of alcohol can be detected by the trigeminal nerve this alcohol test can interfere with testing function of the olfactory nerve and its cerebral connections. To quickly test the olfactory nerve (CN I) in a clinical setting, embodiments of tests and methods of the present disclosure use pure odorants, rather than alcohol-based odorants. Pure odorants appropriate for use in the methods and tests of the present disclosure do not stimulate the trigeminal nerve, but are solely detectable by CN I. Exemplary odorants for use in the methods and tests of the present disclosure include pure odorants such as peanut butter, the primary odorant compound in peanut butter (e.g., non-alcohol based 2-ethyl-pyrazine (also sometimes called 2-ehtyl-1,4-diazine; 2-ethylpyrazine; and pyrazine, 2-ehtyl) chemical compound $C_6H_8N_2$, MW 108.14), coffee grounds, chocolate, pure peach, and other pure, non-alcohol based odorants. Example 1, below, describes in greater detail embodiments of the present disclosure using peanut butter as the odorant. To test for asymmetry, the test was conducted unirhinally, one nostril at time.

Considering that the olfactory network from olfactory epithelium to olfactory cortex is primarily ipsilateral[8,9,17,18] and that voxel-based morphometric (VBM) studies of grey matter volume loss consistently find significantly greater left than right mesial temporal lobe atrophy at the earliest phases of AD[19-21], the Example below determined that patients with AD experience an asymmetrical decrease in their ability to detect an odor and if the UPBODT could be used as

a marker to detect AD. These results can be expanded for the identification and/or classification of other cognitive disorders of the CNS that also involve asymmetrical impairment of odor detection by the olfactory nerve (e.g., ataxia, Epilepsy) and/or symmetrical but marked decreases in odor detection, such as Parkinson's disease.

Participants with probable AD, mild cognitive impairment (MCI), other causes of dementia (OD), Parkinson's disease (PD), and matched controls (OC) were tested, with closed eyes, for their ability to detect an odor, one nostril at a time, as described in greater detail in Example 1 and the corresponding figures. Briefly, a small container of peanut butter was opened, held medially at the bottom of a 30 cm ruler, and moved up 1cm at a time during the participants' exhale. Upon odor detection, the distance between the subject's nostril and container was measured. This non-invasive and inexpensive left-right nostril odor detection test appears to be a sensitive and specific test for probable AD as well as other CNS disorders.

Thus, embodiments of the present disclosure include methods of diagnosing and/or testing Alzheimer's disease in a patient. In embodiments, such methods include the following steps: placing a container containing a pure odorant under a nostril of a patient suspected of having Alzheimer's disease at a sufficient distance that the patient cannot detect the odorant, moving the container closer to the nostril of the patient at a consistent rate until the patient detects the odor, measuring the odor detection distance between the patient's nostril and the location of the container where the patient first detected the odor, repeating the above steps with the other nostril; and determining the difference between the odor detection distance for each nostril. During testing of each nostril, the patient's other nostril is closed and the patient is unable to see the odorant container (e.g., so that the patient will not see the container and confuse sight detection with odor detection). In embodiments, the patient may also be instructed to close the mouth to prevent any airflow through the closed nostril via the mouth or any other odor stimulus via the lower nasal passages at the back of the throat. Also, for the methods of the present disclosure the odorant is not capable detection by trigeminal nerve stimulation. Thus, odorants appropriate for use in the present disclosure that stimulate the olfactory nerve (CN1) without

simultaneous trigeminal nerve stimulation include pure odorants that do not contain alcohol. In embodiments pure odorants include, but are not limited to, peanut butter, the odorant compound from peanut butter, coffee (e.g., coffee, coffee grounds, etc.), chocolate (in various forms), peach, and the like.

In the embodiments of the present disclosure, an odor detection difference at least about 5 cm in favor of the right nostril (e.g., the left nostril exhibits greater impairment (e.g., the right nostril has a greater detection distance than the left)) indicates a likelihood of Alzheimer's disease. In embodiments of the tests and methods of the present disclosure, the container of pure odorant is moved closer to the test nostril at a rate of about 1 cm/exhale.

Similar to the methods and tests described above for testing and/or diagnosing AD, the present disclosure also includes methods of testing and/or diagnosing a degenerative disease of the central nervous system (CNS) in a patient. In embodiments, such methods include the following steps: placing a container containing a pure odorant under a nostril of a patient suspected of having a degenerative disease of the CNS disease at a sufficient distance that the patient cannot detect the odorant and where the odorant is not capable of detection by trigeminal nerve stimulation, moving the container closer to the nostril of the patient at a consistent rate until the patient detects the odor, measuring the odor detection distance between the patient's nostril and the location of the container where the patient first detected the odor, repeating the steps above with the other nostril, where each nostril not being tested is closed (e.g., not exposed to odor stimulation) during the testing of the other nostril. In embodiments of the methods of the present disclosure, the container of pure odorant is moved closer to the test nostril at a rate of about 1 cm/exhale.

The method then includes comparing the odor detection distance for each nostril, wherein a difference between the detection distances for each nostril or a difference between the odor detection distance for the patient and the average odor detection distance for a control patient indicates the presence of a neurodegenerative disease. For instance, a difference between the detection distance for each nostril in the patient being tested (e.g., asymmetric impairment in one nostril) may indicate the presence of a neurodegenerative

disease such as AD (where the left nostril is more impaired, Table 1), or epilepsy or tumor where the epilepsy, injury, or tumor is located on the hemisphere of the brain associated with the impaired nostril. On the other hand, symmetric impairment may indicate other cognitive degenerative disorders, such as Parkinson's disease (PD) where symmetric but significant impairment was observed (Table 3).

In embodiments of the present methods and tests, when the degenerative CNS disease being tested is Alzheimer's, when the odor detection distance of the left nostril is at least about 5 cm worse (e.g., at least about 5 cm less than/shorter than) than the odor detection distance for the right nostril, the patient has a likelihood of Alzheimer's disease. In embodiments, when the odor detection distance of the left nostril is at least bout 10 cm less than the odor detection distance for the right nostril, the patient has a likelihood of Alzheimer's disease. In embodiments, the methods of the present can be used to diagnose early or moderate Alzheimer's disease. In embodiments of methods of the present disclosure, if an odor detection difference of at least about 5 cm in favor of the right nostril (e.g., the detection difference of the left nostril is less than the detection difference of the right nostril by at least about 5 cm) is obtained using the test of the present disclosure, the patient may be preliminarily diagnosed with Alzheimer's disease and referred for further testing with conventional tests for AD. In embodiments, the patient is preliminary diagnosed with AD and referred for further testing when the odor detection difference is at least about 10 cm in favor of the right nostril.

Embodiments of the present disclosure also include method of diagnosing a degenerative disease of the central nervous system (CNS) in a patient using the methods described herein, where a difference of at least about 5 cm between the detection distance for each nostril or a difference of at least about 10 between the odor detection distance for the patient and the average odor detection distance for a control patient indicates the presence of a neurodegenerative disease. As set forth above, when the odor detection difference of the left nostril is at least about 5cm worse than the odor detection distance for the right nostril, then the patient has a likelihood of AD as the diagnosed degenerative

disease of the CNS. In embodiments of the present disclosure, when the degenerative CNS disease is Parkinson's disease, when the odor detection difference between the right and left nostrils is less than or equal to about 3 cm, and the average odor detection distance for both nostrils of the patient is at least about 10 cm less than (e.g., a shorter detection difference, which indicates increased impairment) the average odor detection distance of a control patient, the patient has a likelihood of Parkinson's disease.

Embodiments of the present disclosure also include methods of determining the hemisphere of a patient's brain affected with CNS disorder. In embodiments, such methods include similar steps as described above. A container containing a pure odorant is placed under a nostril of a patient having a CNS disorder, such as but not limited to epilepsy, cerebellar tumor, injury, and ataxia. The container is placed at a sufficient distance that the patient cannot detect the odorant, and the patient's other nostril is closed (or otherwise shielded from odor detection). In embodiments, the patient is unable to see the odorant or the container holding the odorant. As in the above described tests and methods, the odorant is not capable detection by trigeminal nerve stimulation. Thus, in embodiments, the odorant is a pure odorant such as, but not limited to peanut butter, coffee, chocolate, and the like. The odorant is moved closer to the nostril of the patient at a continuous rate (e.g., 1 cm/exhale) until the patent detects the odor. The odor detection distance (the distance between the patient's nostril and the location of the container where the patient first detected the odor) is measured, and then the steps are repeated with the other nostril. After performing the method on both nostrils, the odor detection distances for each nostril are compared, where the identity of the more impaired nostril indicates the hemisphere affected by the CNS disorder. In embodiments of these methods and tests, where the condition is epilepsy, the more impaired nostril indicates the ipsilateral hemisphere as the hemisphere of seizure origin in patients with temporal lobe epilepsy. In embodiments where the condition is ataxia injury or a cerebellar tumor, the more impaired nostril indicates the contralateral cerebellum as the more effected by ataxia or by a cerebellar tumor.

The present disclosure also includes kits for the conduction of the above described tests of the present disclosure. For instance, such a kit might include a sealed container including a pure odorant (e.g., peanut butter, a composition including a pure peanut butter odorant compound, coffee grounds, chocolate, or other pure odorant-containing composition). The kit may also include a measuring device (e.g., a ruler, tape measure, etc.) and instructions for use of the kit and conduction of the test. If convenient, the kit may also include a blindfold or other eye shielding device and a single-nostril nose-clip or other device for closing or obstructing one nostril of a patient while leaving the other nostril accessible for odor detection.

The present disclosure also includes devices and systems that could be used to carry out the tests and methods described above. In embodiments, such devices can help reduce the possibility of human error in administering the test. For instance, one embodiment of a system according to the present disclosure could include a system including a head mounted device having a head-mounting portion that removably secures the device to the subject's head, a nose plug for independently sealing one nostril at a time (optionally with a sterile disposable nostril portion that is replaced with a new sterile disposable nostril portion for each nostril for each patient), and a distance-measuring device (e.g., a ruler) with an attached receptacle for holding a disposable container containing an odorant material (e.g., peanut butter). The receptacle is coupled to the distance-measuring device in such a way that the receptacle can be moved along the distance-measuring device to measure the distance of the odorant container to an open nostril of the subject (e.g., the nostril that is not closed with the nose plug). In embodiments, the receptacle can be mounted on a slide that is coupled to the ruler so that it is capable of being advanced along the ruler. In embodiments, the slide-mounted receptacle can be automatically advanced each time sensors detect an exhale from the subject. One of skill in the art can imagine other embodiments and adaptations to such a device to increase testing consistency and automation.

Although the tests above are described with respect to determining a detection distance, it is contemplated that the methods and test of the present disclosure can also be adapted to provide an odor threshold related to concentration rather than distance from the nostril. Although such test may require more complicated equipment, the detection difference concept can be applied to odorant concentration. Thus, the present disclosure also provides methods and tests for diagnosing a degenerative disease of the central nervous system (CNS) in a patient via odor detection threshold. In embodiments, such methods include exposing one nostril of a patient suspected of having a degenerative disease of the CNS to a concentration of a pure odorant below the patient's detection threshold, where the odorant is not capable of detection by trigeminal nerve stimulation. The concentration of the odorant is gradually increased over separate trials and at a consistent rate until the patient detects the odor. In embodiments, odor detection threshold is tested using a forced choice task in which the patient is asked to compare and determine which of two samples of air has an odor and which does not. The odor concentration is increased at set increments until the patient is able to reliably identify over consecutive trials which air sample contains the odorant. The concentration of the odorant is recorded/measured at the point when the patient first detects the odor, and then the steps are repeated with the other nostril. Then the odor detection concentrations for each nostril are compared, where a difference between the detection concentrations for each nostril or a difference between the odor detection concentration for the patient and the average odor detection concentration for a control patient indicates the presence of a neurodegenerative disease. Such analysis is conducted in a similar manner as described above for detection distance.

One of skill in the art can also envision devices and systems that could be used to carry out the tests and methods described above. For instance, one embodiment of a system according to the present disclosure could include a device for providing a regulated concentration of a pure odorant, wherein the pure odorant compound can be inserted into a compartment or receptacle of the device. The system also includes tubes or other via for transporting the odorant to the nostril(s) of the patient. The system also includes a dial or

interface for controlling the concentration and timing of release of odorant and for recording and/or displaying the concentration level at given intervals during the test such that the concentration of the odorant can be determined at each trial of the test (e.g., by a user or a program).

Additional details regarding the tests and methods of the present disclosure are provided in the Examples below. The specific examples below are to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever. Without further elaboration, it is believed that one skilled in the art can, based on the description herein, utilize the present disclosure to its fullest extent. All publications recited herein are hereby incorporated by reference in their entirety.

It should be emphasized that the embodiments of the present disclosure, particularly, any "preferred" embodiments, are merely possible examples of the implementations, merely set forth for a clear understanding of the principles of the disclosure. Many variations and modifications may be made to the above-described embodiment(s) of the disclosure without departing substantially from the spirit and principles of the disclosure. All such modifications and variations are intended to be included herein within the scope of this disclosure, and protected by the following embodiments.

The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to perform the methods and use the compositions and compounds disclosed herein. Efforts have been made to ensure accuracy with respect to numbers (*e.g.*, amounts, temperature, *etc.*), but some errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, temperature is in °C, and pressure is at or near atmospheric. Standard temperature and pressure are defined as 20°C and 1 atmosphere.

It should be noted that ratios, concentrations, amounts, and other numerical data may be expressed herein in a range format. It is to be understood that such a range format is used for convenience and brevity, and thus, should be interpreted in a flexible manner to include not only the numerical values explicitly recited as the limits of the range, but also to

include all the individual numerical values or sub-ranges encompassed within that range as if each numerical value and sub-range is explicitly recited. To illustrate, a concentration range of "about 0.1% to about 5%" should be interpreted to include not only the explicitly recited concentration of about 0.1 wt% to about 5 wt%, but also include individual concentrations (*e.g.*, 1%, 2%, 3%, and 4%) and the sub-ranges (*e.g.*, 0.5%, 1.1%, 2.2%, 3.3%, and 4.4%) within the indicated range. In an embodiment, the term "about" can include traditional rounding according to significant figures of the numerical value.

EXAMPLES

Now having described the embodiments of the present disclosure, in general, the following Examples describe some additional embodiments of the present disclosure. While embodiments of the present disclosure are described in connection with the following examples and the corresponding text and figures, there is no intent to limit embodiments of the present disclosure to this description. On the contrary, the intent is to cover all alternatives, modifications, and equivalents included within the spirit and scope of embodiments of the present disclosure.

EXAMPLE 1

The present example, describes a quick clinical test of the CN1 odor detection in patients for the testing, diagnosis, localization and/or classification of cognitive disorders of the CNS, including Alzheimer's disease (AD).

METHODS

PARTICIPANTS

Medical records were reviewed for 133 consecutive new patients evaluated in a clinical setting from August 31, 2010 when the UPBODT was first included in the neurological exam to March 16, 2012, which was the date of the data review request. Medical history was gathered from both the patient and from a knowledgeable family member or caregiver. A board certified

neurologist performed a detailed general examination and neurological examination. All patients were cognitively assessed using the full Florida Mental State Exam[22], which includes the Mini-Mental Status Examination[23], the Hopkins Verbal Learning Test[24], the Boston Naming Test[25], the Controlled Oral Word Association test[26] , the Gerstmann's syndrome score[27], as well as other neuropsychological tests. Gerstmann's syndrome is commonly seen in Alzheimer's patients and so within the FMSE this syndrome is actually scored with a possible 5 points given for the ability to calculate, 3 possible points given for the ability to tell left from right, and 1 possible point given for the ability to properly name the index finger. A brain MRI scan and diagnostic laboratory studies were obtained to evaluate for reversible causes of dementia.

In accordance with the current criteria [2,3], the patients in this study diagnosed with probable Alzheimer's disease had 1) an insidious onset; 2) a clear-cut history of worsening of cognition by report or observation; 3) the initial and most prominent cognitive deficits on history and examination was amnesia (defective episodic memory) and cognitive dysfunction, such as disorders of language (e.g., anomia) and/or visuospatial disorders; and 4) did not have evidence of a stroke, Lewy body dementia, frontotemporal lobar degeneration, or other known neurological diseases that can cause a cognitive decline.

From the 133 new patients seen between the specified dates, 27 patients were excluded, who did not complete the evaluation and/or were not diagnosed with a specific disease that induced their cognitive disorder. From the remaining 106, 35 patients were excluded with histories that introduced confounding variables for olfactory dysfunction. This list included comorbid dementia or other neurological disorder, MRI evidence of a cerebral infarction or brain tumor, and any history of severe head injury with a loss of consciousness, hypoxia, seizures, or nasal polyps. Out of concern for their ability to understand the task, three patients with severe AD (MMSE <10) were also excluded. Based on these exclusionary criteria 68 patients were included.

For the purposes of this study the eligible patients were grouped into three groups; 18 diagnosed with probable AD (AD)[2, 3], 24 diagnosed with amnestic mild cognitive impairment (MCI)[27], and 26 patients diagnosed with various other causes of dementia (OD). The number of

patients in each group was determined by the number of patients seen during the specified time period and by their diagnoses. Because this was a retrospective study on an existing data set, a power analysis was not done. A large effect would indicate clinical relevance, and, according to Keppel, the effect would need to reach significance with a number of 17 in each group to achieve a power of 0.80[29]. The 26 cognitively normal control participants recruited from the community were age and gender matched to the AD patients, cognitively assessed with the FMSE, and screened using the same exclusionary criteria. All gave written, informed consent a HIPAA waiver of consent was obtained for all patients, and the University of Florida Institutional Review Board approved the study. We followed the reporting guidelines set forth by the STROBE Statement for case-control, observational studies[30].

APPARATUS

14 g of peanut butter, plain ground peanuts, within an air tight, one-ounce container was used as the olfactory stimulus. A 30 cm metric ruler was used to measure the distance from the nostril to the stimulus upon odor detection.

PROCEDURE

The participants were instructed to close their eyes and mouth and to breathe normally through their nose without sniffing or inhaling deeply. They were asked to use their finger to close one nostril. The metric ruler was held up next to their open nostril and carefully aligned within the participants' sagittal plane to avoid potential effects from possible hemispheric neglect. They were asked to inform the examiner when they first detected an odor and if possible, to identify it. After their eyes, mouth, and one nostril were closed, the container of peanut butter was opened at the bottom of the ruler and moved up 1 cm upon each exhale until the person indicated that they detected the odor. The distance between the edge of the nostril and the top of the container was measured and recorded. The procedure was repeated with the other nostril after a 90 sec delay. In addition to providing precision, moving the stimulus up 1 cm/exhale helps provide equality of space and time of the odor plume for each patient.

To avoid bias, the person testing odor detection was never the same person who performed the cognitive testing, the physical neurological exam, or gathered any patient history

and was blind to the diagnosis at the time of the testing. Additionally, the diagnosis of our patients was usually not confirmed until months after our initial clinical testing when these patients' lab and imaging results had been received.

Participants were allowed to choose the order their nostrils were tested, as many patients with AD have left/right confusion[27] and using these terms in the instructions would raise the cognitive load. The nostril chosen first was not related to handedness ($t = 0.124$, $df = 92$, $p = 0.904$) nor did it differ from a random order generated by Excel ($t = -1.377$, $df = 206$, $p = 0.17$). Also, results for odor detection and odor recognition were similar and only the detection results will be discussed here.

STATISTICAL METHODS

T-tests were used to test whether handedness was related to the first nostril chosen and whether the nostril chosen by the patients differed from that assigned by random order. We performed an analysis of variance (ANOVA) with Fisher's PLSD post-hoc tests on age, gender, and years of education between our participant groups. We also conducted an ANOVA on the difference score of the left minus right nostril odor detection distance of each group. We ran a 2-way interaction multivariate analysis of variance (MANOVA) with the between subject factor being diagnostic group and within subject factor of detection distance of the left and right nostril. A Fisher's PLSD test was used for post-hoc analyses. We used the chi-square test to detect any significance between groups of the frequency distribution of participants' left minus right nostril odor detection difference. We calculated the sensitivity and specificity with a binary classification test using the left minus right nostril odor detection difference as the dichotomizing variable. 2-tailed Pearson's r tests were employed to examine correlations between odor detection distances of each nostril and cognitive tests scores. To test for order effects we used a Fisher's exact test. These analyses were performed with SPSS 21.0 (IBM, Armonk, NY) and StatView 5.01 (SAS Institute, Cary, NC) statistical software.

RESULTS

DEMOGRAPHICS

The demographic descriptions and the cognitive testing scores for each group are described in Table 1. AD is more commonly diagnosed in women than men, possibly related to women having longer life expectancy[31]. The AD, OD, and matched control (OC) groups ($F(2,66) = 2.64$, $p = 0.035$) had more women than men, so that only the gender ratio of the AD group and the MCI group were significantly different from each other ($p = 0.007$). There were no significant age differences between groups. There were no significant differences among the patient groups in the average years of education; however, the control group had significantly more years of education than the patient groups. A multiple regression analysis was run to insure that the variable years of education was not significantly contributing to the variable of interest, an asymmetry of odor detection (left minus right nostril odor detection distance). Only diagnosis made a significant contribution to left minus right odor detection difference ($t = 4.861$, $p < 0.001$). Years of education did not ($t = 0.266$, $p = 0.791$).

ODOR DETECTION ASYMMETRY IN ALZHEIMER'S

For participants with AD, the mean odor detection distance from the left nostril to the edge of the peanut butter container (5.1 cm) was significantly less than that of the other groups ($F(3,90) = 22.28$, $p < 0.0001$). In contrast, the mean detection distance of the right nostril of the AD patients (17.4 cm) was not different from the other groups (Table1.1).

An ANOVA confirmed that the mean difference of left minus right nostril odor detection distance was significantly different between groups ($F(3,90) = 28.33$, $p < 0.0001$) and that the AD group demonstrated significantly more asymmetry of odor detection between nostrils than all other groups due to a left nostril impairment ($p < 0.0001$) (FIG.1). The mean, standard error of the mean, and 95% Confidence Intervals of L – R nostril odor detection distance (cm) for AD were as follows: -12.4 ±0.5, (-15.0,-9.8); for MCI: -1.9 ±1.2, (-4.2,0.4) for OD: 4.8 ±1.0, (2.6,6.9), and for OC: 0.0 ±1.4 (-2.2,2.1) (FIG. 1). The frequency distribution of the left minus right (L – R) nostril odor detection distance of the AD group was also significantly different from the OD group ($\chi^2(N=44) = 39.96$, $p < 0.0001$), the OC group ($\chi^2(N=44) = 29.91$, $p < 0.0001$), and even

the MCI group (χ^2(N=42) = 18.68, p < 0.0001) (FIG. 2). No overlap was detected between the AD group and the other groups.

Compared to patients with other causes of dementia this nostril asymmetry of odor detection unveiled by the UPBODT was 100% sensitive and 100% specific for AD. Compared to matched controls, it was 100% sensitive and 92% specific for probable AD (2 SE cut-off using L-R nostril detection difference to dichotomize). In fact, this level of sensitivity and specificity held true when the L – R nostril detection difference was ≥ -5 cm.

In this study, all of the AD patients, and none of the OD patients, had a left nostril detection distance at least 5 cm less than their right nostril detection distance (FIG. 2) (Table 2). However, in 14 out of the 18 probable AD patients the difference was ≥ -10 cm. The remaining four with a smaller L-R nostril detection distance difference were also moderate to moderate-severe in their disease course. With MMSE scores of 10 and 11, these patients just missed the MMSE exclusionary cut-off score. In addition, the smaller difference was not a consequence of their left nostril being less impaired, but of their right nostril being more impaired than the other AD patients. For a diagnosis of early to moderate AD, a more definitive critical difference of left minus right nostril detection distance may be ≥ -10 cm.

UNI-RHINAL ODOR DETECTION AND COGNITIVE PERFORMANCE

Since the olfactory cortex is anatomically proximal to the areas important in episode memory[8-12], it was posited that odor detection might be more highly correlated with episodic memory than with other cognitive measures. Significant positive correlations were found between the left nostril odor detection distance and tests that rely on left hemisphere functions like language and calculation (Table 1). The right nostril odor detection distance did not correlate with any of the cognitive measures analyzed.

DICHOTOMOUS ODOR DETECTION SENSITIVITY IN MCI GROUP

Ten MCI patients had the AD-like nostril asymmetry of odor detection and 14 did not (FIG. 2). Even so, the mean L – R nostril odor detection difference of the MCI group was significantly different from the AD group and the OD group (p < 0.0001) but not from the OCs (FIG.1). Significant difference was also detected between the frequency distribution of the MCI

patients' L - R nostril odor detection difference and that of the AD group and the OD group (χ^2 (N=50) = 6.14, p = 0.013), but not from that of the OC group (χ^2(N=50) = 1.75, p = 0.186) (FIG. 2).

UNI-RHINAL ODOR DETECTION IN THE OTHER DEMENTIA GROUP

The OD participants' performance on the UPBODT could also be divided into two major groups; 15 were symmetric across nostrils and 11 were asymmetric with the left nostril being better than the right, a pattern opposite of the participants with AD (Table 2). Overall, the left nostril was significantly better than the right nostril at odor detection in the OD group (p = 0.007) and was significantly better than the AD and the MCI groups' (p < 0.001) left nostril. However, it was not significantly different from the OC group's left nostril odor detection distance (Table 1). The mean L – R nostril odor detection distance of the OD group was significantly different from the AD and MCI groups (p < 0.0001), as well as the OC group (p = 0.003) (FIG. 1). Significant difference was detected in the frequency distribution of the L – R nostril odor detection differences of the OD group compared to the AD group, the MCI group, and even to the OC group (χ^2 (N=52) = 4.15, p = 0.042) (FIG. 2).

NO ORDER EFFECTS

To learn if nostril-testing sequence influenced performance, either because of foreknowledge and familiarity of the odor stimulus such that the second nostril is superior, or conversely that the second nostril tested is inferior because of adaptation effects, the performance of the first versus the second nostril tested were compared, and no significant difference was found (χ^2 (N = 94) = 0.04, p = 0.841).

DISCUSSION

A left nostril impairment of odor detection was present in all the patients with probable AD. This pattern of odor detection was not present in the older control group in which detection distances were symmetric across the nostrils and was absent in the patients with other dementias whose detection distances were either symmetric or slightly asymmetric with a right nostril impairment. Thus, the sensitivity and specificity of this peanut butter odor detection test appear promising for accurately diagnosing AD. Further analysis of these odor detection test

results and correlation with these participants' neuropathology or laboratory markers such as spinal fluid assays for amyloid-β_{1-42} /tau has not yet been conducted.

Ten of the 24 participants with MCI had the same nostril odor asymmetry as the participants with AD. Future longitudinal studies can be performed to determine the ability of this test to predict those patients with MCI, as well as older people who do not meet the MCI or AD criteria, but who will later convert to AD. All of the participants in the three patient groups of this study were already demented at the time of odor detection testing. Following cognitively normal older participants to see how far out this simple test may predict those who will later develop AD would also be informative. Both studies could prove extremely valuable for clinical trials investigating methods to prevent AD.

Besides helping to detect early Alzheimer's, this simple diagnostic tool may also help track the course of the disease. The asymmetry was greatest at the earlier phases of the disease course. As the disease progressed, the right nostril became more impaired at odor detection and the asymmetry decreased.

Systematic studies of olfactory function for diagnostic purposes found AD to be positively associated with olfactory dysfunction. Unfortunately, because of confounding variables of olfactory dysfunction and the fact that olfactory dysfunction occurs with many neurological disorders associated with dementia [32-39], the predictive value of olfactory testing for AD was deemed limited[38-40]. The odor detection test used in most studies has been a threshold task that requires more time than a clinic visit allows and informs of the lowest concentration the odor can be detected, not the farthest distance. No study has combined a unirhinal method with a stimulus that can solely be detected by the olfactory nerve, and none have measured the distance of odor detection. Previous findings that in AD odor identification correlated more with neuropsychological tests and was effected earlier than olfactory detection thresholds tested bi-rhinally[13,32,38,39,41] are consistent with the present findings that odor detection in the right nostril of early to moderate AD patients is not different from cognitively normal controls.

A study by Bahar-Fuchs and coworkers[42] compared unirhinal tests of odor identification and odor memory between AD patients, MCI patients, and healthy controls. They reported that

while healthy controls performed the best and AD patients performed the worst on odor identification, the disparity did not depend on nostril side. While not reported by these investigators, within their data was evidence that olfactory memory was significantly worse in the left nostril than the right nostril in both the AD and MCI groups, but was not different between nostrils in the healthy controls[42]. They, however, did not test odor detection.

One caveat to the UPBODT as a diagnostic tool is that it cannot be reliably used in patients with comorbid dementias or that have a history of any other common cause of olfactory loss besides aging. The olfactory test used in this study was designed to overcome the impracticalities that normally inhibit olfactory testing during a typical clinic visit. In the future, investigators using more formal, closed-circuit devices such as an olfactometer, may want to determine the relationship between odor detection in AD and MCI and the degree of atrophy in the olfactory and entorhinal cortices. Another caveat to this and the voxel based morphometric studies of atrophy may be that left hemisphere deficits are more easily detected by patients and their loved ones than right hemisphere deficits. This detection asymmetry may induce AD patients with left hemispheric dysfunction to seek medical attention sooner than those with right hemispheric dysfunction.

Primary olfactory cortex is one of the first sites of pathology in AD[10-12]. In contrast, the primary visual and auditory cortices are usually spared in people with AD. Except for the olfactory cortex, it is primarily the hippocampus, portions of the default network, and sensory association cortices that deteriorate in patients with AD. Thus the only sensory test that may be sensitive and specific for AD are tests of olfaction, and this quick, non-invasive, left-right nostril peanut butter odor detection test may be an ideal instrument for the early detection of AD.

Table 1 Characteristics of the participants & Correlations between odor detection distances and cognitive test scores.

	AD N = 18	**MCI** N = 24	**OD** N = 26	**OC** N = 26	Corr. With R nostril	Corr. With L nostril
L nostril (cm)	5.1 ± 4.9	15.0 ± 10.7	20.2 ± 8.5	18.0 ± 9.1		
R nostril (cm)	17.4 ± 6.6	17.0 ± 10.2	15.5 ± 9.7	17.9 ± 8.7		
Age	75.5 ± 9.7	74.5 ± 10.5	70.7 ± 7.8	69.1 ± 9.6		
Sex	15 F/3 M	10 F/14 M	16 F/10 M	17 F/11 M		
Education (yrs)	15.3 ± 6.3	15.4 ± 2.9	15.7 ± 3.1	17.9 ± 3.0		
MMSE	19.2 ± 4.8	26.2 ± 2.6	25.3 ± 5.1	29.2 ± 0.8	.140	.338**
Gerstmann's	4.4 ± 2.3	7.1 ± 1.7	6.8 ± 2.7	8.5 ± 1.1	.128	.303**
BNT	36.8 ± 14.7	52.4 ± 6.7	48.3 ± 13.4	59.3 ± 1.5	.095	.294**
HVLT learning	11.3 ± 5.5	18.1 ± 5.4	17.9 ± 7.3	28.7 ± 4.8	.106	.286**
HVLT delay	0.6 ± 1.4	3.7 ± 3.7	5.1 ± 3.8	10.3 ± 1.9	.018	.240*
HVLT recognize	4.7 ± 2.5	7.24 ± 3.4	8.46 ± 2.8	11.2 ± 1.1	.042	.281**
Category fluency	8.5 ± 4.2	12.9 ± 4.1	12.2 ± 4.5	23.0 ± 4.4	.123	.241*
Word fluency	24.6 ± 12.1	34.3 ± 10.9	23.7 ± 13.6	46.4 ± 13.5	.131	.095

Deomographic, odor detection distances (cm), and test score data are mean ± SD. Corr = 2-tailed Pearson's Correlations, r. * significance at $p < 0.03$, ** significance at $p < 0.01$

AD = Alzheimer's disease, MCI = mild cognitive impairment, OD = other dementias, OC = matched controls, MMSE = Mini Mental State exam (high score = 30), a Gerstmann's syndrome "score", a subscore within the FMSE (high score = 9, did not include agraphia), BNT = Boston Naming Test (high score = 60), HVLT = Hopkin's Verbal Learning Test (high score = 36 for learning, 12 for delay, 12 for recognition) category-semantic fluency, and the letter-word fluency

Table 2. Odor detection symmetry across nostrils of each group.

	Symmetric	Asymmetric Left worse (shorter detection distance on left)	Asymmetric Right worse (shorter detection distance on right)
AD	0	18	0
MCI	11	10	3
OD	15 (3 corticobasal degeneration, 3 Parkinson-dementia complex disease, 2 frontotemporal lobar degeneration, 2 vascular dementia, 1 depressive pseudo-dementia, 1 Hashimoto's encephalopathy, 1 hemachromatosis, 1 posterior cortical atrophy, 1 Fahr's disease)	0	11 (5 corticobasal degeneration, 2 iatrogenic on anti-cholinergic medications, 1 depressive pseudo-dementia, 1 Hashimoto's encephalopathy, 1 Lewy-body dementia, 1 semantic dementia)
OC	21	2	3

To be considered symmetric, the difference between the R and L nostril odor detection distance was ≤ 3 cm. To be considered asymmetric, the difference between a person's R and L nostril odor detection distance was ≥ 4 cm.

EXAMPLE 2

The present example describes the clinical test and uses the same methodology as set forth above in Example 1, but includes data for patients with Parkinson's disease (PD) as well as additional subjects in the other test groups.

METHODS

Testing procedures, statistical methods, and analytical methods were the same as set forth in Example 1, above.

RESULTS & DISCUSSION

The results of the testing and statistical analysis including the PD patients are presented in Tables 3 and 4, below, and FIGS. 3 and 4. As illustrated in FIG. 3, ANOVA confirmed a significant difference between groups. Left Nostril: ($F(4,130) = 17.7$, $p < 0.0001$); odor detection was worse in both AD and PD versus all other groups ($p < 0.0001$). The mean, standard error, and 95% confidence interval for OC = 18.5 ±1.5 (15.5,21.4); AD = 5.5 ±1.6 (2.3,8.7); MCI = 14.7 ±1.7 (11.3,18.1); OD = 20.2 ±1.7 (16.9,23.6); PD = 5.7 ±1.8 (2.2,9.2). Right Nostril: $F(4,130) = 4.6$, $p = 0.002$, odor detection worse in PD versus AD and OD, both $p = 0.002$ and PD versus MCI and OC, both $p < 0.0001$. The mean, standard error, and 95% CI for OC = 16.7 ±1.6 (13.5,20.0); AD = 15.3 ±1.8 (11.8,18.8); MCI = 17.0 ±1.9 (13.3,20.7); OD = 15.5 ±1.8 (11.8,19.1); PD = 7.1 ±2.0 (3.3,11.0). The L- R nostril distance of the AD patients was significantly larger than all other groups. FIG. 4 illustrates that there is no overlap between AD and the other groups or OD and the other groups. $F(4,130) = 20.3$, $p < 0.0001$. AD vs all other groups, $p < 0.0001$. OD vs AD, MCI, PD, $p < 0.0001$ and OD vs OC, $p = 0.04$. MCI vs AD, OD, $p < 0.0001$ and MCI vs OC, $p = 0.02$. Mean L – R nostril detection distance, standard error, and 95% C.I. for OC = 1.8 ±1.1 (-0.5,3.9); for AD = -9.8 ±1.2 (-12.2,-7.3); for MCI = -2.4 ±1.3 (-4.9,0.2); for OD = 5.4 ±1.3 (2.7,8.0); for PD = -1.3 ±1.3 (-3.7,1.2).

For further analysis, the 23 patients in the OD group were further subdivided into a subset of 8 patients that were diagnosed with corticobasal degeneration (CBD), and the remaining 15 with other, specified causes of dementia (OD). CBD patients were separated out to compare their results to the PD patients' results. CBD can start with memory impairment and be difficult to distinguish from AD but it can also start with motor symptoms such as rigidity, akinesia, poor coordination, and impaired balance, which can make it difficult to clinically differentiate from PD. To determine whether CBD patients' odor detection was significantly

different from the PD patients, the data were analyzed with the small sample of CBD patients separated out from the OD group. FIGS. 5A & 5B illustrate that patients with PD are more symmetric and more impaired at odor detection than those with CBD. CBD follow the same pattern as the remaining OD. For FIG. 5A, Right Nostril: The mean, standard error, and 95% C.I. for CBD: 13.1 ±3.2 (6.7,19.5); for OD without CBD: 16.7 ±1.6 (13.6,19.9). PD trends at being worse than CBD, $p = 0.08$. Left Nostril: The mean, standard error, and 95% C.I. for CBD: 18.6 ±2.8 (13.0,24.3); for OD without CBD: 24.6 ±2.1 (20.5,28.7). PD worse than CBD, $p < 0.0001$. For FIG. 5B, L – R Nostril Detection: The mean, standard error, and 95% C.I. for CBD: 5.5 ± 2.3, (1.0,10.0); for OD without CBD: 5.3 ±1.7 (2.0,8.6). PD more symmetric across nostrils than CBD, $p < 0.0001$.

The results show that within the AD group, the UPBODT appears to track disease progression. As patients progressed from early AD to moderate and severe AD, the asymmetry of odor detection decreased due to the right nostril becoming impaired as well. The three AD patients that were symmetrically impaired had (L,R) odor detection distances of (4,3), (0,0), and (0,0) and MMSE scores of 9, 9, and 11 (data not shown). The one AD patient that was more impaired in the right nostril had (L,R) odor detection distances of (9,3) and a MMSE score of 8 (data not shown). The AD patients were grouped by their L – R odor detection distance difference into ranges of -15 to -23, -10 to -14, -5 to -9 and 0 to 6 and then ANOVAs were run to compare their cognitive testing scores and confirm whether the UPBODT results follow AD progression (Table 5, below). Furthermore when including only the AD patients in the analysis, MMSE scores highly correlated with the L – R nostril detection difference (Pearson 2-tailed = -0.674, $p < 0.0001$) such that as the negative difference was greater, the MMSE score was significantly higher. It appears that at the early phase of AD, the left nostril is significantly impaired and the right nostril is normal compared to OCs. Then as the disease progresses, the right nostril begins to become impaired. As the patient becomes more moderate to severe, both nostrils become increasingly impaired until finally, in the later stages of AD, the patient becomes completely anosmic.

Sensitivity and specificity of the UPBODT for correctly diagnosing AD was calculated with a binary classification test using the left minus right nostril odor detection difference as the dichotomizing variable. Compared to older controls, the UPBODT was 85.7% sensitive and 93.9% specific for Alzheimer's disease. Compared to patients with other causes of dementia, the UPBODT was 85.7% sensitive and 100% specific. Compared to Parkinson's patients, the UPBODT was 85.7% sensitive and 88.5% specific for Alzheimer's disease. If the discussion above is taken into consideration and the more severe patients with MMSE scores ≤ 11 are removed from the analysis, the UPBODT was 100% sensitive for early to moderate Alzheimer's disease.

When calculating the sensitivity and specificity of the UPBODT for PD, the number of participants that had poor odor detection, < 8 cm in each nostril, and were also symmetric with a L – R nostril detection distance difference ≤ 4 cm, were counted for each group. The number of those who met both criteria versus those that did not was used as the dichotomizing variable. Four PD patients had normal and symmetrical odor detection of peanut butter and four PD patients had asymmetrical odor detection. Compared to older controls, the UPBODT was 69.2% sensitive and 84.8% specific for Parkinson's disease. Compared to patients with corticobasal degeneration, the UPBODT was 69.2% sensitive and 100% specific for Parkinson's disease.

Although not the primary focus of this study, with additional testing in this example, including patients with Parkinson's disease, it was found that such patients demonstrated symmetric and significant impairment in odor detection. This is in contrast with the AD patients, who showed significant asymmetric impairment with the left nostril significantly more impaired than the right. In the PD patients, both nostrils showed significant odor detection impairment as compared to the control patients. This indicates that symmetric impairment may also be a diagnostic indicator for PD, and that this test can be used as a diagnostic tool to both identify cognitive impairment as well as to distinguish between different diseases, such as AD and PD which can exhibit similar clinical symptoms.

Table 3 Characteristics of the participants & Correlations between odor detection distances and cognitive test scores.

Deomographic, odor detection distances (cm), and test score data are mean ± SD. Corr = 2-tailed Pearson's Correlations, r^2. * significance at $p < 0.03$, ** significance at $p < 0.01$

AD = Alzheimer's disease, MCI = mild cognitive impairment, OD = other dementias, PD = Parkinson's disease; OC = matched controls, MMSE = Mini Mental State exam (high score = 30), a Gerstmann's syndrome "score", a subscore within the FMSE (high score = 9, did not include agraphia), BNT = Boston Naming Test (high score = 60), HVLT = Hopkin's Verbal Learning Test (high score = 36 for learning, 12 for delay, 12 for recognition) category-semantic fluency, and the letter-word fluency test from the Controlled Oral Word Association (COWA). For all tests, a higher score indicates better cognitive function. UPDRS = Unified Parkinson's Disease Rating Scale, maximum value (worst score) of 108; MHYS = Modified Hoehn and Yahr Scale, maximum value (worst score) of 5.

	AD N = 28	**MCI** N = 25	**OD** N = 23	**PD** N = 26	**OC** N = 33	Corr. With R nostril	Corr. With L nostril
L nostril (cm)	5.5 ± 5.3	14.7 ± 10.6	22.5 ± 5.7	5.5 ± 8.5	18.5 ± 9.1		
R nostril (cm)	15.3 ± 8.3	17.0 ± 10.0	17.1 ± 9.0	6.9 ± 8.9	16.7 ± 9.6		
Age	76.8 ± 9.7	74.3 ± 10.4	71.4 ± 7.7	70.1 ± 7.1	71.8 ± 9.3		
Sex	23 F/5 M	10 F/15 M	16 F/10 M	11 F/15 M	17 F/11 M		
Education (yrs)	14.4 ± 5.5	15.5 ± 2.8	16.4 ± 2.7	16.8 ± 4.3	18.2 ± 4.3		
UPDRS				21.1 ± 9.6			
MHYS				2.1 ± 0.5			
MMSE	18.0 ± 5.7	26.3 ± 2.6	25.2 ± 5.2	28.2 ± 2.1	29.2 ± 0.8	.140	.338**
BNT	34.8 ± 16.4	52.5 ± 6.6	48.2 ± 13.5		59.2 ± 1.8	.095	.294**
HVLT learning	10.6 ± 5.0	18.3 ± 5.3	17.3 ± 7.1		28.5 ± 5.1	.106	.286**
HVLT delay	0.7 ± 1.4	3.8 ± 3.6	4.8 ± 3.7		10.2 ± 2.0	.018	.240*
HVLT recognize	3.8 ± 2.7	7.3 ± 3.4	8.4 ± 2.9		11.0 ± 1.1	.042	.281**
Category fluency	9.0 ± 4.4	13.2 ± 4.2	11.8 ± 4.4		22.6 ± 4.5	.123	.241*
Word fluency	25.1 ± 11.6	34.4 ± 10.7	23.5 ± 13.6		44.8 ± 14.8	.131	.095

Table 4. Odor detection symmetry across nostrils of each group.

	Symmetric	Asymmetric Left worse	Asymmetric Right worse
AD	**3**	**24**	**1**
MCI	**11**	**10**	**3**
OD	**14 (5 corticobasal degeneration, 2 frontotemporal lobar degeneration, 2 vascular dementia, 1 depressive pseudo-dementia, 1 Hashimoto's encephalopathy, 1 hemachromatosis, 1 posterior cortical atrophy, 1 Fahr's disease)**	**0**	**9 (3 corticobasal degeneration, 2 iatrogenic on anti-cholinergic medications, 1 depressive pseudo-dementia, 1 Hashimoto's encephalopathy, 1 Lewy-body dementia, 1 semantic dementia)**
PD	**22**	**3**	**1**
OC	**26**	**2**	**5**

To be considered symmetric, the difference between the R and L nostril odor detection distance was ≤ 3 cm. To be considered asymmetric, the difference between a person's R and L nostril odor detection distance was ≥ 4 cm.

Table 5. The UPBODT appears to track the progression of Alzheimer's disease.

	L - R Range (cm)	MMSE	BNT	HVLT recognize	HVLT learn	Gerstmann Score	Word Fluency	Category Fluency	HVLT delay
N=5	-15 to -23	22 ±2	45±6	7±1	14±2	6±2	23±5	9±2	1±1
N=12	-10 to -14	20 ±1	40±4	4±1	11±1	5±2	29±3	10±1	1±0
N=6	-5 to -9	17 ±2	30±5	4±1	10±2	3±1	23±5	9±2	0±1
N=4	0 to 6	9 ±2	13±7	1±1	6±2	3±2	18±6	6±2	1±1
Sig.	F(3,23)= p =	8.6 0.001	5.5 0.006	4.3 0.02	2.5 0.08	NS	NS	NS	NS

This table contains data analyzed from the AD group only. The AD group is broken down into four nominal categories based on the patient's L – R nostril odor detection difference distance.

The tests displayed here are described in Table 1. Sig = significance and the F values and p values for each ANOVA are given.

EXAMPLE 3

The present example uses the same methodology as set forth above in Example 1, except odor recognition/identification was also tested/recorded and analyzed and correlated with the odor detection results above.

METHODS

Testing procedures, statistical methods, and analytical methods were the same as set forth in Example 1, above, except that after odor detection, the clinician continues to move container of odorant (peanut butter) closer to the patient's nostril at a rate of 1cm/exhale after detection until the patient is able to correctly identify the odor (in this case, peanut butter. The odor recognition distance is the distance recorded at which the subject correctly identified the odor (if at all).

RESULTS & DISCUSSION

The results of the testing and statistical analysis are presented in FIGS. 6A, 6B, and 7A and 7B.

With a correct response coded as 1 and an incorrect response as 2, ANOVA confirmed significant differences between groups in the ability to correctly identify peanut butter odor for both the left ($F(4,130) = 15.81$, $p < 0.0001$) and the right nostril ($F(4,130) = 8.94$, $p = p < 0.0001$) due to the AD, PD, and MCI groups being significantly more impaired than the OD, CBD, and OC groups, which were not different from each other. (FIGS. 6A & 6B). For each group, including the AD group, Fisher's exact tests did not detect a significant difference between the number of participants that were able to correctly identify peanut butter odor with their left nostril and the number of those that were able to with their right nostril.

FIGS. 7A and 7B compare the average distance of odor recognition for the left and right nostril of each group, with FIG. 7B including additional subjects with PD into the analysis.

ANOVA confirmed a significant difference between the groups for the left nostril odor recognition distance (FIG. 7A; $F(3,90) = 5.38$, $p = 0.002$) due entirely to the left nostril impairment of the AD group. The odor recognition distance of the right nostril was not different between groups in FIG. 7A. For FIG. 7A, the mean, SE, and 95% Confidence Intervals for the Left nostril for AD were 4.39 ± 1.23, (1.80, 6.98); for MCI were 14.46 ± 2.21, (9.88, 19.04); for OD were 15.00 ± 2.06, (10.77, 19.23); and for OC were 13.96 ± 1.93, (9.99, 17.93). When including the additional AD patients and the PD patients in the analyses (FIG 7B), the overall effect of the Left nostril odor recognition distance was significant between groups ($F(4,130) = 11.33$, $p < 0.0001$) with both the AD and PD patients having significantly worse odor recognition distances than the other groups, $p < 0.0001$. The Right nostril odor recognition distance was overall different between groups ($F(4,130) = 4.44$, $p = 0.002$ with the PD patients having significantly worse odor detection distance than AD ($p = 0.02$), MCI ($p < 0.0001$), OD ($p = 0.002$), and OC ($p = 0.001$). The other groups were not different from each other.

Keeping in mind that these results are for only one odor, odor identification was equally poor in the left and right nostril for both the AD patients and the MCI patients. So, while odor detection was impaired in the left nostril and normal in the right nostril of AD patients, odor identification was impaired in both nostrils. This finding is congruent with previous bi-rhinal studies that have found odor detection to be less impaired than odor identification in AD. This finding also corroborates with the uni-rhinal study by Bahar-Fuchs et al. using 10 odors that found no significant difference in odor identification ability between the two nostrils in AD or MCI and that both groups were significantly impaired compared to controls[42]. The AD patients' left nostril and the PD patients' left and right nostril odor detection impairment had the expected effect on odor recognition distance and the results of this measure followed the same pattern as odor detection distance. The results show that Parkinson's patients were significantly and symmetrically impaired at odor detection in both nostrils. Parkinson's patients' odor identification errors were due entirely to anosmia. For the Alzheimer's patients, their odor identification errors were due either to anosmia, anomia, or agnosia.

REFERENCES

The following references are incorporated herein by reference.

1. Alzheimer's Disease Education & Referral (ADEAR) Center, A service of the National Institute on Aging, National Institute of Health, US Department of Health and Human Services. Alzheimer's Disease Fact Sheet. Avialable from: http://www.nia.nih.gov/alzheimers/publication/alzheimers-disease-fact-sheet. Accessed July 12, 2012

2. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* 1984;34:939-944.

3. McKhann GM, Knopman DS, Chertkow H, et al., . The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011; 7: 263–269.

4. Klunk WE, Engler H, Nordberg A, et al. Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. Ann Neurol 2004;55(3):306-319.

5. Blennow K. Cerebrospinal fluid biomarkers for Alzheimer's disease. NeuroRx 2004;1(2):213-225.

6. Rowe CC, Villemagne VL. Brain amyloid imaging. J Nucl Med 2011;52(11):1733-1740.

7. Irwin DJ, McMillan CT, Toledo JB, Arnold SE, Shaw LM, Wang LS, Van Deerlin V, Lee VM, Trojanowski JQ, Grossman M. Comparison of Cerebrospinal Fluid Levels of Tau and Aβ 1-42 in Alzheimer Disease and Frontotemporal Degeneration Using 2 Analytical Platforms. Arch Neurol Epub 2012 Apr 9

8. Allison AC. The secondary olfactory areas in the human brain. J Anat 1954;88:481-488.

9. Carmichael ST, Clugnet MC, Price JL. Central olfactory connections in the Macaque Monkey. J Comp Neurol 1994;346:403-434.

10. Ferreya-Moyona H, Barragan E. The olfactory system and Alzheimer's disease. Int J Neurosci 1989;49:157-197.

11. Price JL, Davis PB, Morris JC, White DL. The distribution of tangles, plaques and related immunohistochemical markers in healthy aging and Alzheimer's disease. Neurobio of Aging 1991;12:295-312.

12. Braak H, Braak E. Staging of Alzheimer's disease-related neurofibrillary changes. Neurobio of Aging 1995;16:271-8, discussion 278-284.

13. Graves AB, Bowen JD, Rajaram L, et al. Impaired olfaction as a marker for cognitive decline: interaction with apolipoprotein E epsilon4 status. Neurology 1999;53(7):1480-1487.

14. Tabert MH, Liu X, Doty RL, et al. A 10-item smell identification scale related to risk for Alzheimer's disease. Ann Neurol 2005;58(1):155-160.

15. Davidson TM, Murphy C. Rapid clinical evaluation of anosmia-The Alcohol Sniff Test. Arch Otolaryngol Head Neck Surg 1997;123:591-594.

16. Davidson TM, Freed C, Healy MP, Murphy C. Rapid clinical evaluation of anosmia in children: The Alcohol Sniff Test. Ann NY Acad Sci 1998;855:787-792.

17. Shipley M, Ennis M. Functional organization of the olfactory system. J Neurobiol 1999;30:123-176.

18. Mori K, Nagao H, Yoshihara Y. The olfactory bulb: coding and processing of odor molecule information. Science 1999;22:711-715

19. Whitwell JL, Przybelski SA, Weigand SD, Knopman DS, Boeve BF, Petersen RC, Jack Jr CR. 3D maps from multiple MRI illustrate changing atrophy patterns as subjects progress from mild cognitive impairment to Alzheimer's disease. Brain 2007;130:1777-1786.

20. Ferreira LK, Diniz BS, Forlenza OV, Busatto GF, Zanetti MV. Neurostructural predictors of Alzheimer's disease: A meta-analysis of VBM studies. Neurobio Aging 2011;32:1733-1741.

21. Rami L, Solé-Padullés C, Fortea J, et al. Applying new research diagnostic criteria: MRI findings and neuropsychological correlations of prodromal AD. Int J Geriatric Psychiatry 2012;27(2):127-134.

22. Doty L, Bowers D, Heilman KM. Florida Mental Status Exam for progressive dementia screening. The Gerontologist 1990;30(Special issue): 20A.

23. Folstein MF, Folstein SE, & McHugh PR. "Mini-Mental State" A Practical method for grading the cognitive state of patients for the clinic. J of Psychiatric Res 1975;12:189-198.

24. Brandt J. The Hopkins Verbal Learning Test: Development of a new memory test with six equivalent forms. The Clin Neuropsychol 1991;5(2):125-142.

25. Kaplan EF, Goodglass H, & Weintraub S. The Boston naming test, 2nd ed. Philadelphia: Lea and Febinger, 1983.

26. Benton AL. Development of a multilingual aphasia battery: Progress and problems. J Neurolog Sci 1969;9:39-48.

27. Benton AL. Gerstmann's syndrome. Arch Neurol 1992;49:445-447.

28. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. Arch Neurol 1999;56:303-308.

29. Keppel G, Wickens TD. Design and Analysis: a researcher's handbook. 4th ed. Upper Saddle River (NJ): Pearson Prentice Hall; 2004.

30. Vandenbroucke JP, von Elm E, Altman DG, Gøtzsche PC, Mulrow CD, Pocock SJ, Poole C, Schlesselman JJ, Egger M. STROBE Initiative. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. Ann Intern Med. 2007 Oct 16;147(8):W163-94.

31. Hebert LE, Scherr PA, McCann JJ, Beckett LA, Evans DA. Is the Risk of developing Alzheimer's disease greater for women than for men? Amer J Epidemiol 2001;153(2):132 136.

32. Knupfer L, Spiegel R. Differences in olfactory test performance between normal aged,Alzheimer and vascular type dementia individuals. Int J Geriatr Psychiatry 1986;1:3-14.

33. Moberg PJ, Pearlson GD, Speedie LJ, Lipsey JR, Strauss ME, Folstein. Olfactory recognition: differetial impairments in early and late Huntington's and Alzheimer's diseases. J Clin Exp Neuropsychol 1987;9(6):65-74.

34. Razani J, Murphy C, Davidson TM, Grant I, McCutchan A. Odor sensitivity is impaired in HIV-positive cognitively impaired patients. Physiol Behav 1996;59(4-5):877-881.

35. Bailie, JM, Gilbert PE, Murphy C. (2003). Odor identification deficits in Lewy body variant of Alzheimer's disease. J Int Neuropsychol Soc 2003;9:164-165.

36. Hulshoff Pol HE, Hijman R, Tulleken CA, Heeren TJ, Schneider N, van Ree JM. Odor discrimination in patients with frontal lobe damage and Korsakoff's syndrome. Neuropsychologia 2002;40(7):888-891.

37. Luzzi S, Snowden JS, Neary D, Coccia M, Provinciali L, Ralph MAL. Distinct patterns of olfactory impairment in Alzheimer's disease, semantic dementia, frontotemporal dementia, and corticobasal degeneration. Neuropsychologia. 2007;45;1823-1831.

38. Rahayel S, Frasnelli J, Joubert S. The effect of Alzheimer's disease and Parkinson's disease on olfaction: A meta-analysis. Behav Brain Res. 2012 Mar;231:60-74.

39. Mesholam RI, Moberg PJ, Mahr RN, Doty RL. Olfaction in neurodegenerative disease: a meta-analysis of olfactory functioning in Alzheimer's and Parkinson's diseases. Arch Neurol. 1998 Jan;55(1):84-90.

40. Sun GH, Raji CA, MacEachern MP, Burke JF. Olfactory identification testing as a predictor of the development of Alzheimer's dementia: a systematic review. Laryngoscope 2012 Jul;122(7):1455-62.

41. Koss E, Weiffenbach JM, Haxby JV, Friedland RP. Olfactory detection and identification performance are dissociated in early Alzheimer's disease. Neurology. 1988 Aug;38(8):1228-32.

42. Bahar-Fuchs A, Moss S, Rowe C, Savage G. Olfactory performance in AD, aMCI, and healthy ageing: A unirhinal approach. Chem Senses 2010; 35: 855-862.

Claims:

1. A method of diagnosing Alzheimer's disease in a patient, the method comprising:

a) placing a container containing a pure odorant under a nostril of a patient suspected of having Alzheimer's disease, wherein the container is placed at a sufficient distance that the patient cannot detect the odorant, wherein the patient's other nostril is closed and the patient cannot see the odorant, and wherein the odorant is not capable of detection by trigeminal nerve stimulation;

b) moving the container closer to the nostril of the patient at a consistent rate until the patient detects the odor;

c) measuring the odor detection distance between the patient's nostril and the location of the container where the patient first detected the odor;

d) repeating steps a-c with the other nostril; and

e) determining the difference between the odor detection distance for each nostril, wherein an odor detection difference of at least about 5 cm in favor of the right nostril indicates a likelihood of Alzheimer's disease.

2. The method of claim 1, wherein the odorant is peanut butter or the odorant compound in peanut butter.

3. The method of claim 1, wherein the odorant is selected from the group consisting of: coffee grounds and chocolate.

4. The method of claim 1, wherein the odorant does not contain alcohol.

5. The method of claim 1, wherein the container of pure odorant is moved closer to the test nostril at a rate of about 1 cm/exhale.

6. A method of diagnosing a degenerative disease of the central nervous system (CNS) in a patient, the method comprising:

a) placing a container containing a pure odorant under a nostril of a patient suspected of having a degenerative disease of the CNS, wherein the container is placed at a sufficient distance that the patient cannot detect the odorant, wherein the patient's other nostril is closed and the patient cannot see the odorant, and wherein the odorant is not capable of detection by trigeminal nerve stimulation;

b) moving the container closer to the nostril of the patient at a consistent rate until the patient detects the odor;

c) measuring the odor detection distance between the patient's nostril and the location of the container where the patient first detected the odor;

d) repeating steps a-c with the other nostril; and

e) comparing the odor detection distance for each nostril, wherein a difference of at least about 5 cm between the detection distance for each nostril or a difference of at least about 10 between the odor detection distance for the patient and the average odor detection distance for a control patient indicates the presence of a neurodegenerative disease.

7. The method of claim 6 wherein the container of pure odorant is moved closer to the test nostril at a rate of about 1 cm/exhale.

8. The method of claim 6, wherein the degenerative CNS disease is Alzheimer's, and wherein the odor detection distance of the left nostril is at least about 5 cm less than the odor detection distance for the right nostril, the patient has a likelihood of Alzheimer's disease.

9. The method of claim 6, wherein the degenerative CNS disease is Parkinson's disease, wherein the odor detection difference between the right and left nostrils is less than or equal to about 3 cm, and wherein the average odor detection distance for both nostrils of the patient is at least about 10 cm less than the average odor detection distance of a control patient, the patient has a likelihood of Parkinson's disease.

10. The method of claim 6, wherein the odorant is peanut butter or the odorant compound in peanut butter.

11. The method of claim 6, wherein the odorant does not contain alcohol.

12. A method of determining the hemisphere of a patient's brain affected with CNS disorder, the method comprising:

a) placing a container containing a pure odorant under a nostril of a patient having a CNS disorder selected from the group consisting of: epilepsy, cerebellar tumor and ataxia, wherein the container is placed at a sufficient distance that the patient cannot detect the odorant, wherein the patient's other nostril is closed and the patient cannot see the odorant, and wherein the odorant is not capable detection by trigeminal nerve stimulation;

b) moving the container closer to the nostril of the patient at a continuous rate until the patent detects the odor;

c) measuring the odor detection distance between the patient's nostril and the location of the container where the patient first detected the odor;

d) repeating steps a-c with the other nostril; and

e) comparing the odor detection distance for each nostril, wherein the identity of the more impaired nostril indicates the hemisphere affected by the CNS disorder.

13. The method of claim 12 wherein the container of pure odorant is moved closer to the test nostril at a rate of about 1 cm/exhale.

14. The method of claim 12, wherein the more impaired nostril indicates the ipsilateral hemisphere as the hemisphere of seizure origin in patients with temporal lobe epilepsy.

15. The method of claim 12, wherein the more impaired nostril indicates the contralateral cerebellum as the more effected by ataxia or by a cerebellar tumor.

16. The method of claim 12, wherein the odorant is peanut butter or the odorant compound in peanut butter.

17. The method of claim 12, wherein the odorant does not contain alcohol.

18. A kit for testing or diagnosing a degenerative disease of the central nervous system (CNS) in a patient, the kit comprising:

a sealed container including a pure odorant that is not capable of detection by trigeminal nerve stimulation, and

instructions for use including the following steps:

a) instructing a patient having a CNS disorder to seal one nostril or sealing the patient's nostril with a device, while leaving the other nostril open.

b) placing the container containing the pure odorant under the open nostril of the patient, wherein the container is placed at a sufficient distance that the patient cannot detect the odorant, and wherein the patient cannot see the odorant;

c) moving the container closer to the open nostril of the patient at a continuous rate until the patent detects the odor;

d) measuring the odor detection distance between the patient's nostril and the location of the container where the patient first detected the odor;

e) repeating steps a-d with the other nostril; and

f) comparing the odor detection distance for each nostril and calculating an odor detection difference for the patient, wherein the odor detection distance and odor detection difference can be used to diagnose a degenerative disease of the CNS.

19. The kit of claim 18, further comprising:
an instrument for measuring distance.
an eye-shielding device, and
a device for closing or obstructing one nostril of a patient while leaving the other nostril accessible for odor detection; and
a device for clearing the air of the test space prior to testing each nostril.

20. The kit of claim 18, wherein the disease is Alzheimer's disease.

21. The kit of claim 18, wherein the odorant is peanut butter or the odorant compound in peanut butter.

22. A system for testing or diagnosing a degenerative disease of the central nervous system (CNS) in a patient, the system comprising:
a device capable of being mounted on a subject's head, wherein the device comprises:
a portion that removably secures the device to the subject's head;
a nose plug for closing one nostril of a subject at a time;
a distance-measuring device; and
a receptacle coupled to the distance-measuring device, wherein the receptacle is adapted to hold a disposable container of odorant material, and wherein the receptacle can be moved along the distance-measuring device to measure the distance of the odorant container to an open nostril of the subject.

23. The system of claim 22, wherein the disease is Alzheimer's disease.
24. The system of claim 22, wherein the odorant is peanut butter or the odorant compound in peanut butter.

25. The system of claim 22, wherein the odorant is selected from the group consisting of: coffee grounds and chocolate.

26. The system of claim 22, wherein the nose plug comprises a disposable nostril contacting portion that can be replaced after each use.

27. The system of claim 22, wherein the distance-measuring device is a ruler.

28. The system of claim wherein the receptacle is coupled to the ruler via a slide configured to enable the receptacle to be moved along the distance-measuring device.

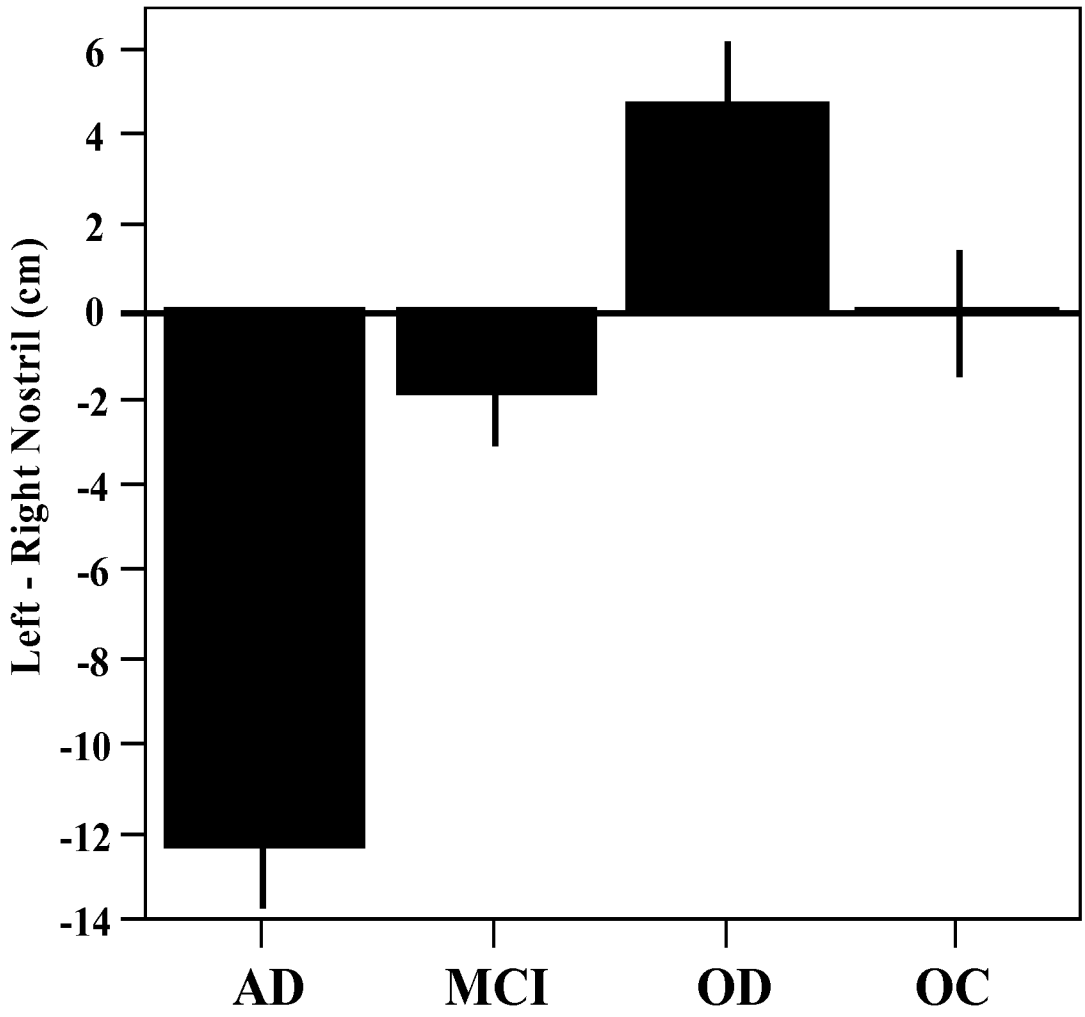

FIG. 1

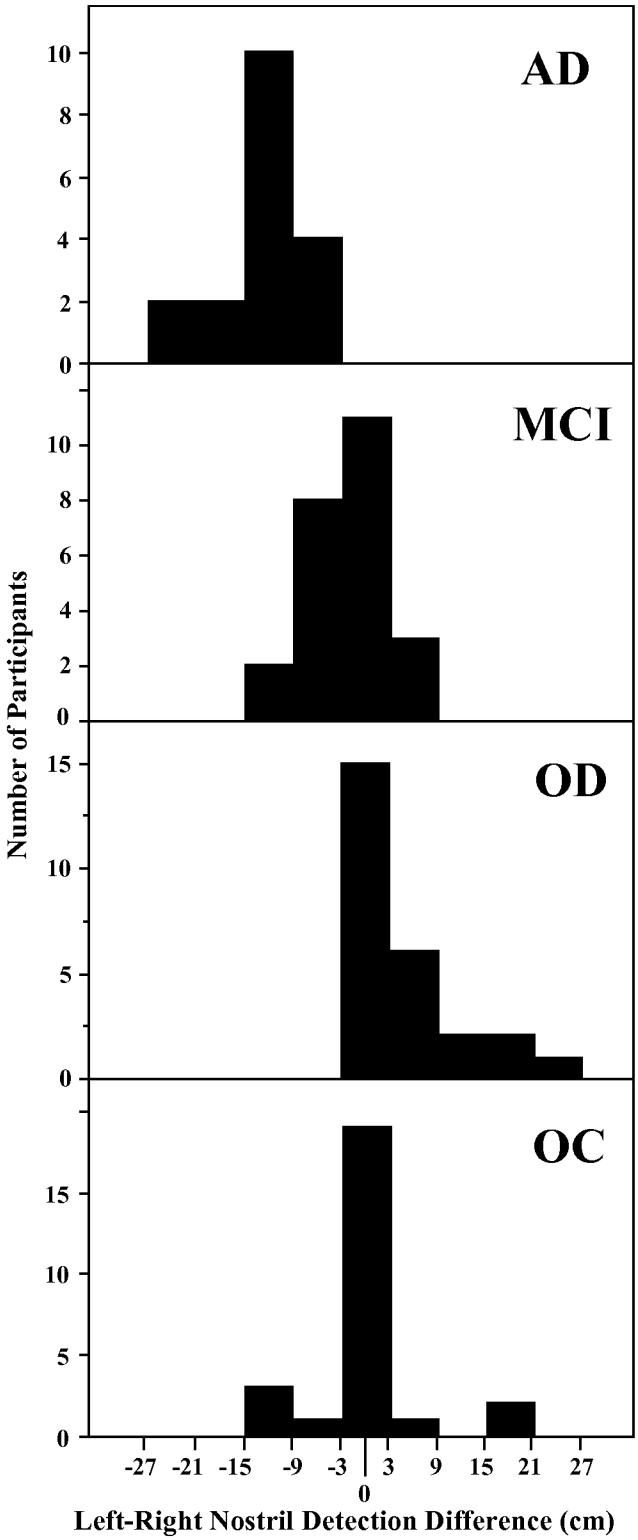
AD
MCI
OD
OC
Number of Participants
Left-Right Nostril Detection Difference (cm)
-27 -21 -15 -9 -3 0 3 9 15 21 27

FIG. 2

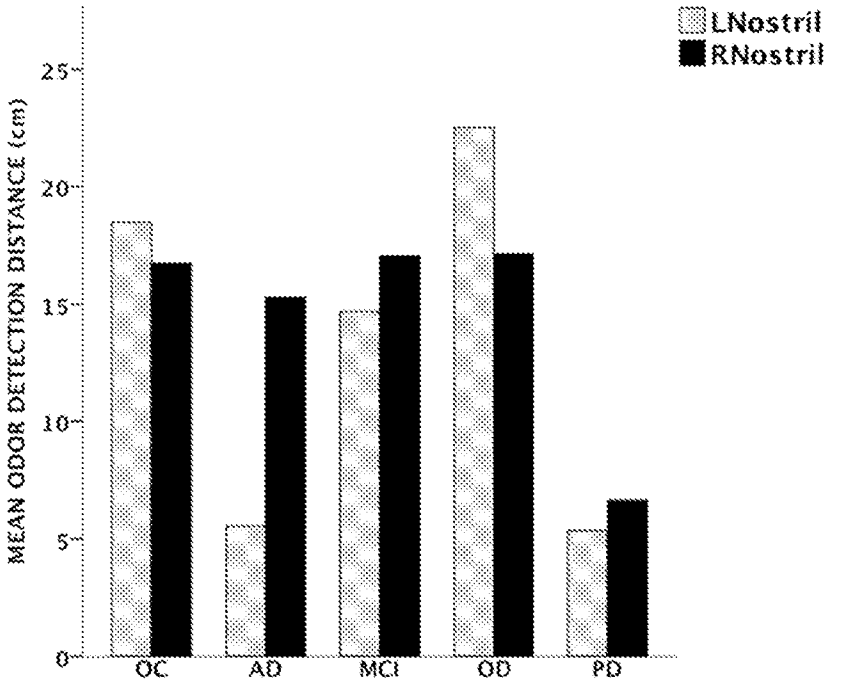
LNostril
RNostril
MEAN ODOR DETECTION DISTANCE (cm)
25
20
15
10
5
0
OC
AD
MCI
OD
PD

FIG. 3

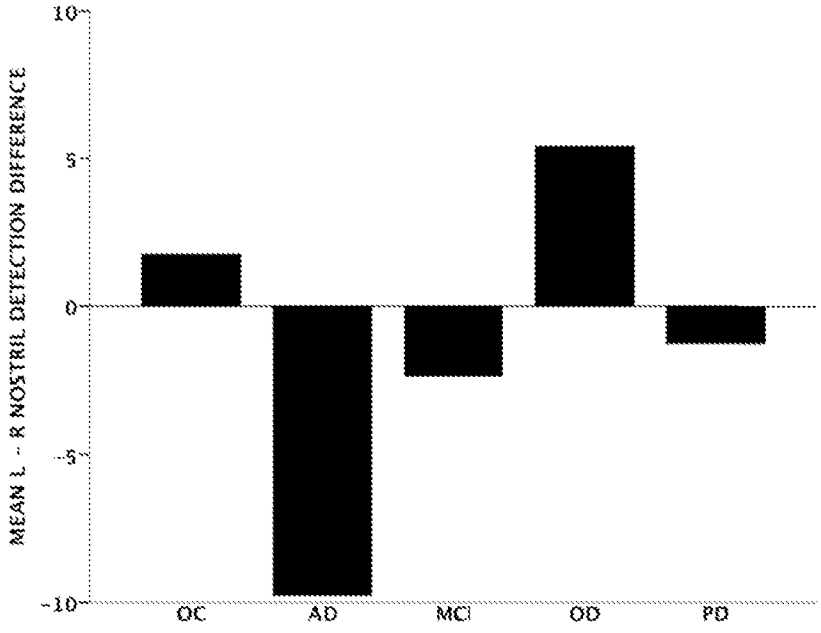
MEAN L - R NOSTRIL DETECTION DIFFERENCE
10
5
0
-5
-10
OC
AD
MCI
OD
PD

FIG. 4

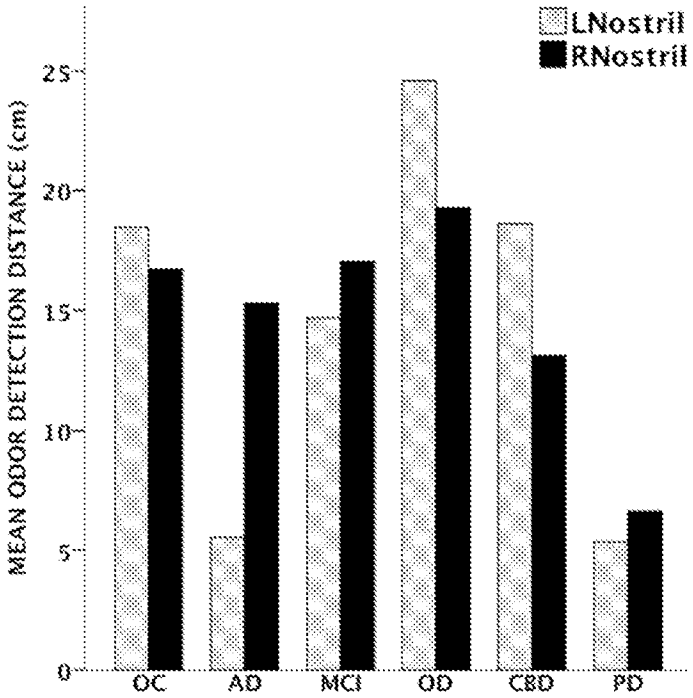
LNostril
RNostril
MEAN ODOR DETECTION DISTANCE (cm)
25
20
15
10
5
0
OC
AD
MCI
OD
CBD
PD

FIG. 5A

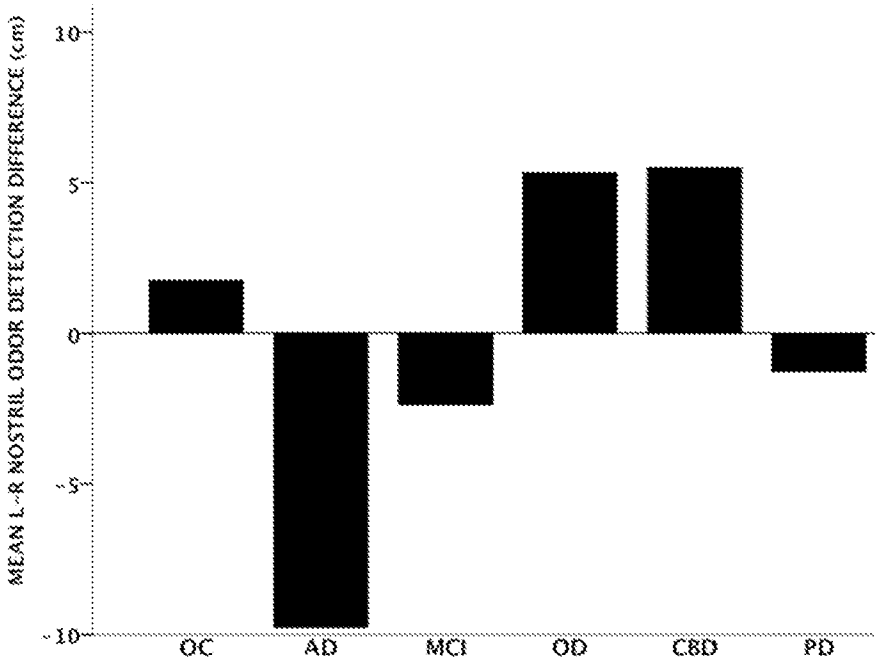
MEAN L-R NOSTRIL ODOR DETECTION DIFFERENCE (cm)
10
5
0
-5
-10
OC
AD
MCI
OD
CBD
PD

FIG. 5B

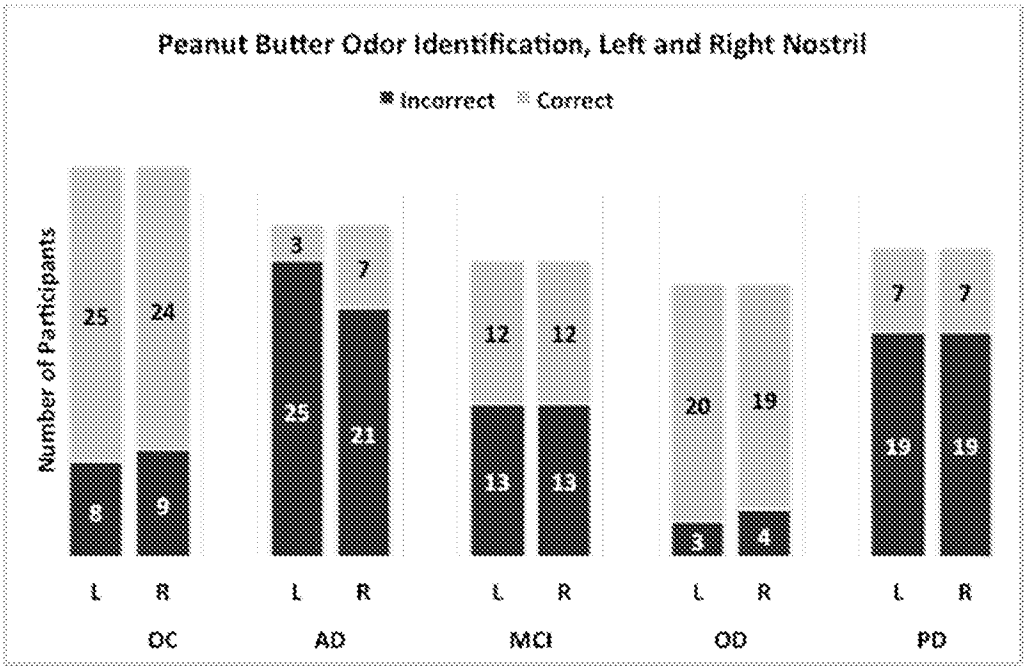
Peanut Butter Odor Identification, Left and Right Nostril
Incorrect
Correct
Number of Participants
25
24
8
9
3
7
25
21
12
12
13
13
20
19
5
4
7
7
19
19
L
R
OC
AD
MCI
OD
PD

FIG. 6A

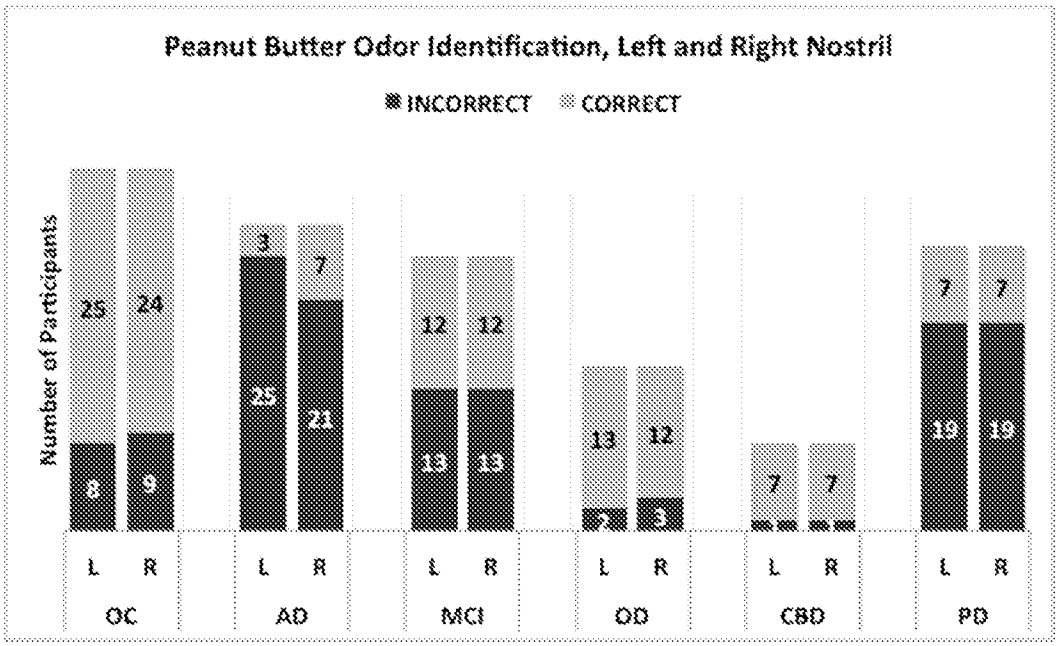
Peanut Butter Odor Identification, Left and Right Nostril
INCORRECT
CORRECT
Number of Participants
25
24
8
9
3
7
25
21
12
12
13
13
13
12
7
5
7
7
7
7
19
19
L
R
OC
AD
MCI
OD
CBD
PD

FIG. 6B

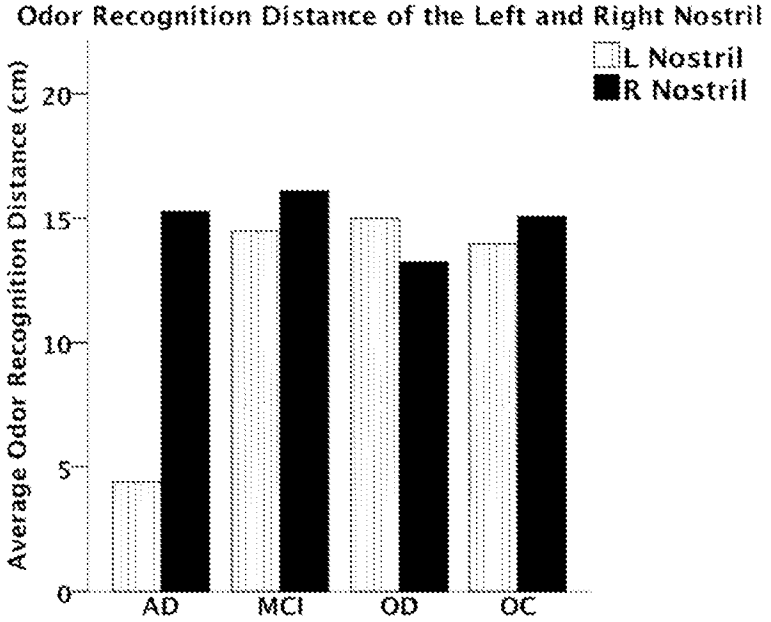
Odor Recognition Distance of the Left and Right Nostril
L Nostril
R Nostril
Average Odor Recognition Distance (cm)
0
5
10
15
20
AD
MCI
OD
OC

FIG. 7A

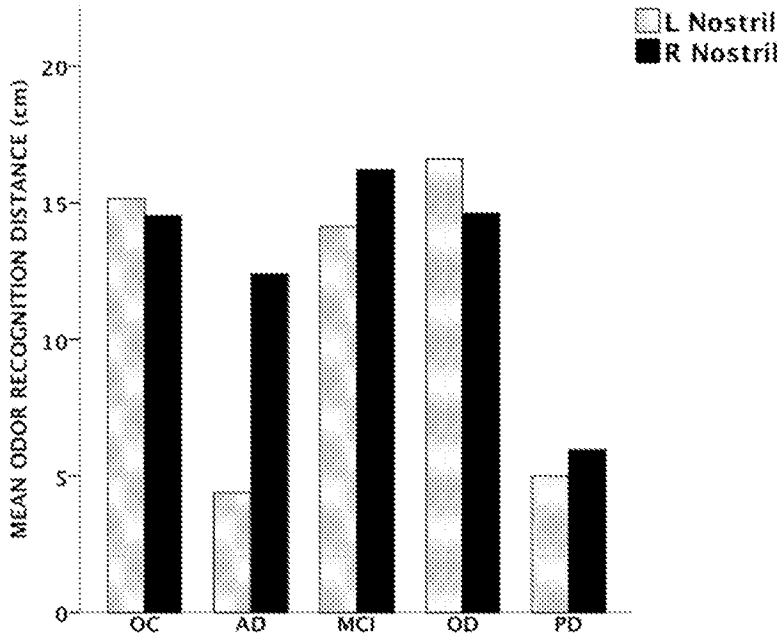
L Nostril
R Nostril
MEAN ODOR RECOGNITION DISTANCE (cm)
0
5
10
15
20
OC
AD
MCI
OD
PD

FIG. 7B

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2014/012002

A. CLASSIFICATION OF SUBJECT MATTER

A61B 5/103(2006.01)i, A61B 5/08(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61B 5/103; A61K 49/00; G09B 7/00; A61B 5/02; G09B 3/00; A61B 5/00; A61B 5/08

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean utility models and applications for utility models
Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
eKOMPASS(KIPO internal) & Keywords: odor, smell, test, nostril, difference, distance, degenerative, disorder, diagnose

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2003-0113701 A1 (WILLIAM GARTNER et al.) 19 June 2003 See abstract, paragraphs [0014]-[0031], claims 1-37 and figures 1-7D.	18-28
A	CN 202568210 U (MA ZAICHEN) 05 December 2012 See abstract, paragraphs [0002]-[0008], claim 1 and figure 1.	18-28
A	US 2007-0077204 A1 (DAVANGERE P. DEVANAND et al.) 05 April 2007 See abstract, paragraphs [0033]-[0041] and claims 1-26.	18-28
A	US 2003-0225335 A1 (PHILIP CHIDI NJEMANZE) 04 December 2003 See abstract, paragraphs [0045]-[0057], claims 1-10 and figures 1-5.	18-28
A	US 3885550 A (PATRICK MACLEOD) 27 May 1975 See abstract, claims 1-3 and figures 1-2.	18-28

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 May 2014 (15.05.2014)	**16 May 2014 (16.05.2014)**

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2014/012002

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 1-17
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 1-17 pertain to diagnostic methods of human body, and thus relate to a subject matter which this International Searching Authority is not required to search under PCT Article 17(2)(a)(i) and PCT Rule 39.1(iv).

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required addtional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of any additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/US2014/012002

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2003-0113701 A1	19/06/2003	AU 2002-353133 A1	30/06/2003
		US 6957038 B1	18/10/2005
		WO 03-051177 A2	26/06/2003
		WO 03-051177 A3	25/09/2003
		WO 03-051177 B1	30/10/2003
US 2007-0077204 A1	05/04/2007	None	
US 2003-0225335 A1	04/12/2003	US 6663571 B1	16/12/2003
US 3885550 A	27/05/1975	None	