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Original Article

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Comparison of Olfactory Identification Patterns among Parkinson's Disease Patients from Different Countries

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Abstract

Olfactory function assessment is an important screening tool and also may differentiate Parkinson's disease (PD) patients from other parkinsonisms, including nondegenerative ones, such as, normal pressure hydrocephalus, vascular, drug induced, or infectious parkinsonism. Several authors in different countries have reported various sets of odors that best differentiate between these conditions. It is debated if distinctive patterns of "restrictive" or "selective" hyposmia in PD may be affected by cultural aspects. To compare the olfactory identification function in PD across different countries, we analyzed Sniffin' Sticks identification task results between 112 PD patients from Argentina and previously reported data of PD patients from Brazil (106 patients), the Netherlands (400 patients), Germany (40 patients), China (110 patients), and Sri Lanka (89 patients). Categorical principal component analysis (CATPCA) was performed to find components reflecting groups of odors similarly perceived across subjects. CATPCA analysis found 2 components for each group which shared 10 out of 16 odors amongst each other. We found that only the shared items of component 2 (orange, mint, banana, garlic, coffee, cloves, and fish) showed uniform results across all of the included countries, whereas variations in component 1 (licorice, turpentine, and apple) were attributed mostly to differences across control groups.

Key words: cultural variation, olfactory dysfunction, Parkinson's disease

Introduction

Parkinson's disease (PD) is a neurodegenerative disorder mainly recognized by its motor symptoms such as bradykinesia, rigidity, and resting tremor. It is also characterized by a variety of nonmotor symptoms, including psychiatric disorders, autonomic disturbances, gastrointestinal problems, and olfactory dysfunction, among many others (Poewe 2008).

Olfactory dysfunction (OD) in particular, is present in up to 90% of PD patients and can precede the onset of motor symptoms for many years (Doty et al. 1988; Haehner et al. 2009). Its presence showed to be one of the best methods to differentiate early PD from healthy subjects (Diederich et al. 2010). The importance of an accurate diagnosis at early stages lies in that the rate of misdiagnosis of

PD ranges from 15% to 36% by relying on clinical criteria, and even among movement disorders specialists, there is up to a 9% of misdiagnosis of PD (Rajput et al. 1991; Hughes et al. 1992; Hughes et al. 2002; Schrag et al. 2002).

OD can be evaluated with several tests that can assess different modalities, such as olfactory threshold (the lowest concentration of a certain odor the patient is able to detect), discrimination (the ability to differentiate between various odors), and identification (the ability to correctly name an odor that is being presented). The most commonly tests used are Sniffin' Sticks Test (SST) (Hummel et al. 1997) and the University of Pennsylvania Smell Identification Test (UPSIT) (Doty et al. 1984a). OD in PD is characterized mainly by an impairment of the identification modality of olfaction accompanied by a different degree of threshold and discrimination, which at first glance seem to show no correlation between each other (Tissingh et al. 2001; Boesveldt et al. 2009a, 2009b). However, this could be a reflection of operational elements pertaining to the specific method involved or further involvement of cognitive processes in the patients studied (Doty 2012). In the routine clinical setting, only the identification task is usually performed due to its easy and less time consuming administration than the others, while maintaining acceptable sensitivity and specificity (Boesveldt et al. 2009a). OD can also be evaluated with the Hyposmia Rating Scale (HRS), a recently self-administered rating scale developed by our group and validated against the SST. It consists of 6-Likert type questions referring to the frequency with which certain odors are perceived, including flowers, gas (mercaptans), sewage/garbage, perfume, perspiration or stuffiness, and home-cooked food (Millar Vernetti et al. 2012). Although being even less time consuming, it has a comparable sensitivity and specificity to the Sniffin' Sticks identification task (SSI) in some countries (Antsov et al. 2014.)

Several authors reported that certain odors better differentiate healthy subjects from PD patients, describing this phenomenon as "restrictive" or "selective" hyposmia, even though these combinations of odors differ from study to study (Hawkes and Shephard 1993; Daum et al. 2000; Double et al. 2003; Silveira-Moriyama et al. 2005; Bohnen et al. 2007; Lötsch et al. 2008). Nonetheless, recent data showed that the pattern of olfactory identification in PD patients and those with hyposmia from other causes does not differ, suggesting that this is not due to specific aspects of the patient's pathology, but may be influenced by the environment and culture (Hähner et al. 2013). These factors might be involved in odor recognition through prior experience and exposure to odors, as well as the presence of genetic polymorphisms (Knaapila et al. 2008; Keller et al. 2012) and can be hindered by air pollution and smoking habits (Katotomichelakis et al. 2007; Guarneros et al. 2009; Calderón-Garcidueñas et al. 2010).

As a product of these variations, olfactory tests, especially SST, were validated in several countries. Adapted versions contain reduced items due to lack of familiarity to certain odors (Silveira-Moriyama et al. 2009; Chen et al. 2012), and the names of distractor odors in the identification task may be changed to more familiar ones to emphasize the correct answer (Fornazieri et al. 2015). This can be easily noted comparing the results across different countries. In China, orange, lemon, apple, and cloves odors failed to differentiate PD from controls (Chen et al. 2012), whereas in Sri Lanka, lemon, banana, and cinnamon, were the best odor suitable for this purpose. In Brazil, cloves, mint, and anise were also the best odors to differentiate PD from controls (Silveira-Moriyama et al. 2008). In Mexico, the accuracy of the 3 olfactory tests that were evaluated was lower in comparison to other published reports which might be due to cultural biases and smell familiarity (Rodríguez-Violante et al. 2014). Moreover, specific tests in different countries may be designed to bridge these differences, such as the Scandinavian Odour Identification Test validated both in Sweden and Finland (Nordin et al. 2002). In line with this, when testing the Odor Stick Identification Test for the Japanese (OSIT-J), significantly lower scores were found in American compared with Japanese subjects, with higher familiarity rates for the OSIT-J in the latter (Kobayashi et al. 2006), with perfume, roasted garlic, curry, and fermented soybeans being the best odors to differentiate PD from controls (Iijima et al. 2008), as were mothball, chocolate, Turkish coffee, and soap in an identification test used in a study performed in Turkey (Altinayar et al. 2012).

To go further into the issue of "restrictive" or "selective" hyposmia in PD that may be affected by cultural aspects, we aim to compare the olfactory identification function in PD patients across different countries. Based on previously published studies and our own population, we investigated if there were subsets of odors that better differentiate between PD patients and healthy controls irrespectively of any country or culture.

Materials and methods

We evaluated the olfactory function of 112 PD patients with the SSI. The study complied with the Declaration of Helsinki, was reviewed and approved by the local IRB and written informed consent was given prior to the evaluation. The SSI consists of a series of 16 felt tip markers filled with odorant substances that are released when uncapped, which the patient tries to identify making a forced choice among 4 given descriptors, one being the target odor, and the rest distracters. The target odors are composed by orange, lemon, banana, pineapple, apple, cinnamon, cloves, anise, licorice, coffee, mint, roses, garlic, fish, leather, and turpentine (Hummel et al. 1997).

A comprehensive search was performed by 2 independent reviewers (PM and MR), updated up to March 2014, by using the search terms "Parkinson's disease AND Sniffin' Sticks" on the PubMed search engine for the MEDLINE database, without article type or language restrictions, and thus encompassing all publications that mentioned PD and the use of this tool. A 2-step sequence was applied to review all retrieved articles, in which firstly, potentially relevant publications were screened by their titles and abstracts. Afterwards, the selected publications were surveyed to assess their suitability and inclusion for analysis. To be included, articles had to evaluate PD and healthy controls with the SSI and had to provide the outcomes for each specific item for both groups. Thus, articles that did not analyze both PD patients and healthy controls were excluded, as well as those without numerical information on the amount of correct or failed answers in a form of absolute or relative count, for each item of the SSI (i.e., the sum of correct responses to each individual item of the SSI represented either as the sum of all correct responses or the percentage of correct responses over total responses given for each specific item).

SSI results were compared between 112 PD patients from Argentina and previously reported data of PD patients from Brazil (106 patients), the Netherlands (404 patients), Germany (40 patients), China (110 patients), and Sri Lanka (89 patients). Chi-square analysis with Bonferroni adjustment was performed.

Categorical principal component analysis (CATPCA) was conducted to find components reflecting groups of odors similarly perceived across subjects from different countries. CATPCA is a data reduction method similar to the usual Factor Analysis, but which can be used on categorical data (Linting et al. 2007). The primary benefit of using CATPCA rather than traditional factor analysis is the lack of assumptions associated with CATPCA, mainly linear relationships among numeric data or multivariate normal data. Notwithstanding,

as with factor analysis, variables are grouped in 2 or more "components" of "factors," which reflects common variance. Components with eigenvalues higher than 1 were selected for further analysis. Unlike the typical factor analysis, rotation of components is not possible. Therefore, "components" were defined based on their scores in a bidimensional surface. For each of the components found by CATPCA, a total score was obtained by summing up positive answer for each one of the odors contained within the component. Comparisons across countries were done by 1-way ANOVA.

Results

The systematic search provided 46 possible articles. After title and abstract screening, 14 articles included SSI data from PD patients and healthy control subjects, of which full text review rendered 7 publications that included specific data on individual items (6 full-text articles and 1 brief report; 6 in English and 1 in German). These studies were carried out in Brazil (Silveira-Moriyama et al. 2008; Santin et al. 2010), China (Chen et al. 2012), Germany (Daum et al. 2000; Casjens et al. 2013), the Netherlands (Boesveldt et al. 2008), and Sri Lanka (Silveira-Moriyama et al. 2009). To reduce the potential confounding factor of possible variations within cities of a same country, only the first published study of Brazil and Germany were included (Daum et al. 2000; Silveira-Moriyama et al. 2008). Studies from Brazil, Sri Lanka, and China included current smokers and patients with history of tobacco use, which did not affect SSI score. Demographics are shown in Table 1. The validation SSI study performed in Sri Lanka (Silveira-Moriyama et al. 2009), removed 4 items (apple, leather, turpentine, and licorice) because less than 50% of the control population was able to correctly identify them. Likewise, in China (Chen et al. 2012) another different 4 items subset (orange, lemon, apple, and cloves) were removed, as it showed no significant difference between control subjects and PD patients.

CATPCA analysis found 2 components in each group with eigenvalues higher than 1. In controls, the first component accounted for 55% of variance and the second one for 10%. A bootstrap resampling method confirmed the stability of the solution. In PD patients, they accounted for 73% and 10% of variable. Figure 1 depicts the bidimensional distribution of variables in controls and PD patients. Two distinct groups of variables can be observed in each one, corresponding to the 2 components. Notwithstanding, in controls, cinnamon, pineapple, and lemon scored close to 0 in the second dimension, meaning that they didn't belong to any component.

Out of 16 odors, 10 were distributed similarly in both groups, 3 of these odors belonged to C1 (licorice, turpentine, and apple) and 7 to C2 (orange, mint, banana, garlic, coffee, cloves, and fish) (Table 2). ANOVA for the scores of shared odors between groups found significant differences according to country ($P < 0.001$) and patient group ($P < 0.001$) for component 1 (except for Sri Lanka, which showed no differences for patient group) and only according to patient group ($P < 0.001$) for component 2 (Figure 2).

Discussion

This study compared the ability of PD patients and healthy control subjects in different countries to identify the odors presented on the SSI. Main findings were that odors could be grouped in 2 components in both groups, with a similar pairing in 10 out of 16 of the items, and that shared odors from component 2 showed a significant difference between groups, meaning they are useful for discriminating between PD patients and controls. Even more, these differences do not vary significantly across countries, meaning that perception of these odors is more or less "universal" for both PD patients and healthy control subjects. For component 1, even though there were significant differences for patient group (except for Sri Lanka), these were mostly attributed to variations in the control group, as PD patients had low scores in general.

The SST has been validated in various countries for its use in PD patients (Daum et al. 2000; Silveira-Moriyama et al. 2008; Silveira-Moriyama et al. 2009; Santin et al. 2010; Chen et al. 2012) with a good clinical performance. Further reduction of the test according to local outcomes resulted in shorter, less time consuming evaluations without a loss, or even a gain, in diagnostic accuracy. In line with this, Casjens et al. (2013) used a statistical approach to select only 3 items to be used as a quick test, noting that their results contained similar odors than previous publications, although there was always some variation, as can be seen in Table 1. Of the 3 parts of the SST, the SSI task was found to be the single most useful one to differentiate PD patients from healthy subjects. Also, the use of a 16 or 32 item version had no significant difference in diagnostic accuracy (Boesveldt et al. 2009a). A further reduction in the number of items, thus creating a specific regional subset of items, can be performed to augment its local usefulness and provide a better tool to support the diagnosis of PD.

Regarding the source of the observed phenomenon in the investigated populations, we hereafter address several factors involved in olfactory perception that may have been responsible for the encountered outcomes. Smoking might be a factor that could affect olfactory testing. In otherwise healthy subjects, olfaction is reduced in smokers compared with nonsmokers, but only to a minor extent and not comparable to the degree of hyposmia found in PD patients. This deficit is dependent of the daily dose and total exposure to tobacco smoke and reversible after smoking cessation (Katotomichelakis et al. 2007). Nevertheless, smoking does not produce a further olfactory alteration in PD patients (Moccia et al. 2014). Moreover, a recent study failed to find differences in olfaction between smokers and nonsmokers in healthy controls, whereas PD patients that smoked, showed better olfactory function in comparison to nonsmokers PD patients (Sharer et al. 2014).

Air pollution in major cities could also have a detrimental effect on olfaction, and when comparing olfactory function of young healthy subjects in a heavily polluted city with those of considerably less polluted ones, Calderón-Garcidueñas found that up to 25% of

Table 1. Demographics of different countries populations

Country	*n*	Age (year)	Male	Top 3 odors	Reference
Germany	40	63.63 (SD 8.84)	28 (70%)	Licorice, pineapple, anise	Daum et al. (2000)
Argentina	112	65.47 (SD 9.62)	66 (59%)	Roses, licorice, anise	Own population
Brazil	106	61.3 (SD 11)	71 (67%)	Mint, anise, cloves	Silveira-Moriyama et al. (2008)
China	110	64.6 (SD 7.1)	66 (60%)	Fish, leather and pineapple	Chen et al. (2012)
The Netherlands	404	61.5 (range 40–90)	251 (63%)	Anise, cinnamon and licorice	Boesveldt et al. (2008)
Sri Lanka	89	60.4 (SD 8.8)	50 (56%)	Lemon, banana and cinnamon	Silveira-Moriyama et al. (2009)

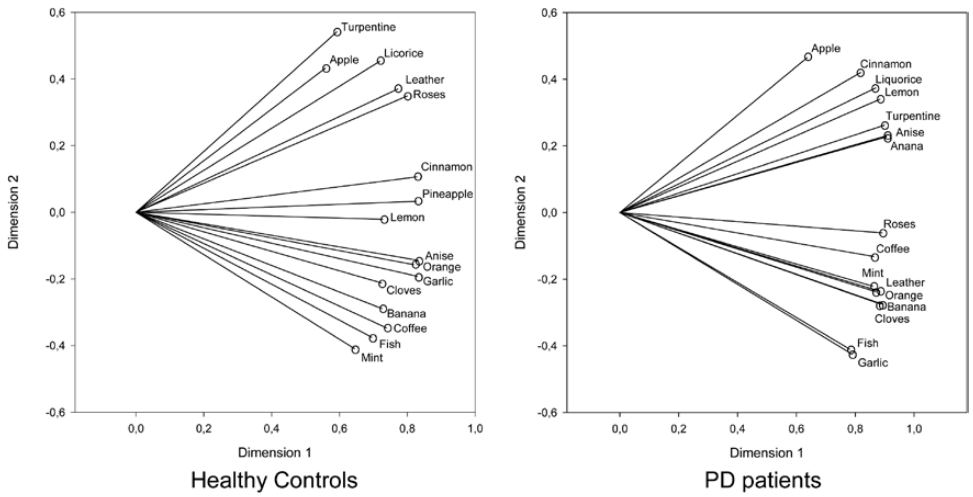

Figure 1. CATPCA saturation graphs in control and PD samples.

Table 2. Distribution of odors into the 2 components as per CATPCA in controls and PD patients

	Control	PD
Orange	**2**	**2**
Leather	1	2
Cinnamon	2	1
Mint	**2**	**2**
Banana	**2**	**2**
Lemon	2	1
Licorice	**1**	**1**
Turpentine	**1**	**1**
Garlic	**2**	**2**
Coffee	**2**	**2**
Apple	**1**	**1**
Cloves	**2**	**2**
Pineapple	2	1
Roses	1	2
Anise	2	1
Fish	**2**	**2**

Shared odors for the same components among groups are shown in bold.

subjects living in a highly polluted city presented mild microsmia, and a 9% with moderate to severe microsmia, compared with a 12% of mild microsmia when using the UPSIT (Calderón-Garcidueñas et al. 2010). In line with these findings, while investigating workers involved in the aftermath of the World Trade Center events on 11 September 2001, a decreased ability in olfactory identification was found, attributed to the short-term exposure of a highly polluted environment (Altman et al. 2011). Nevertheless, there was no significant difference in a study using the SSI in a similar geographic and demographic setting, although a significant alteration of detection thresholds and odor discrimination was observed (Guarneros et al. 2009). Head trauma, recent or chronic upper respiratory infections, or allergic rhinitis are known to potentially alter olfaction (Henkin et al. 2013), but as such, patients with a previous history of these conditions were not included in these studies. Fourthly, sex differences in the different studies may account for some of the variations, as women tend to outperform men both in the general population as in PD patients (Doty et al. 1984b; Stern et al. 1994).Genetic factors may also account for different odor function among cultures. Odor perception depends on interaction of a myriad of molecules with an equally diverse array of olfactory receptors, which due to sequencing or structural variations create an almost a unique combination of olfactory receptors for any given individual (Menashe et al. 2003; Hasin et al. 2008). It must also be noted that in the case of missing receptors as a result of genetics, the remaining ones would probably be able to provide sufficient information for the correct perception of at least some smells (Wilson and Stevenson 2006). Moreover, genotypic variations not necessarily related to olfactory receptors may account for the lower detection rates that some people have toward androstenone, a compound present in human perspiration and pork meat, and the variability of the evoked responses by this substance, which those who are able to, may describe the smell as either pleasant (sweet, floral) or unpleasant (urine-like, sweaty) (Griffiths and Patterson 1970; Knaapila et al. 2012). Perceived intensity to androstenone, galaxolide (musk), pentadecalactone (musk), paint thinner, and isovaleric acid (sweaty) is determined by genetic factors (Whissell-Buechy and Amoore 1973; Wysocki and Beauchamp 1984; Gross-Isseroff et al. 1992; Knaapila et al. 2007; Menashe et al. 2007; Knaapila et al. 2012), but not others such as isoamyl-acetate (banana), eugenol (cloves) or rose, or mercaptans (Knaapila et al. 2012). By contrast, studies with monozygotic and dizygotic twins in different countries showed that variation in odor ratings of cinnamon, turpentine (chocolate and isovaleric acid, is mostly determined by nonshared environmental effects rather than genetic differences (Knaapila et al. 2008). Some of the previously mentioned odors are included in the SSI, even though their actual chemical composition may vary, and be composed by a combination of different odorants. Lastly, previous experience and exposure to odorants could account for some of the variations in sensitivity to odors not explained by genetic factors (Keller et al. 2012) and repeated exposure can augment an individual's perceptions of this smell, as in the case of androstenone, where after repeated exposure subjects show higher identification rates (Wysocki et al. 1989), or the use of "olfactory" to regain olfactory function in patients suffering from postinfectious hyposmia (Damm et al. 2014). As a matter of fact, when applying the discrimination task of the SST to a population of native Amazonians of the Bolivian rainforest (rarely exposed to the synthetically made odorants), even when they had lower olfactory thresholds than subjects from a German industrialized city, their performance was significantly lower than their European counterparts (Sorokowska et al. 2014) Furthermore, the perceived intensity of a smell for

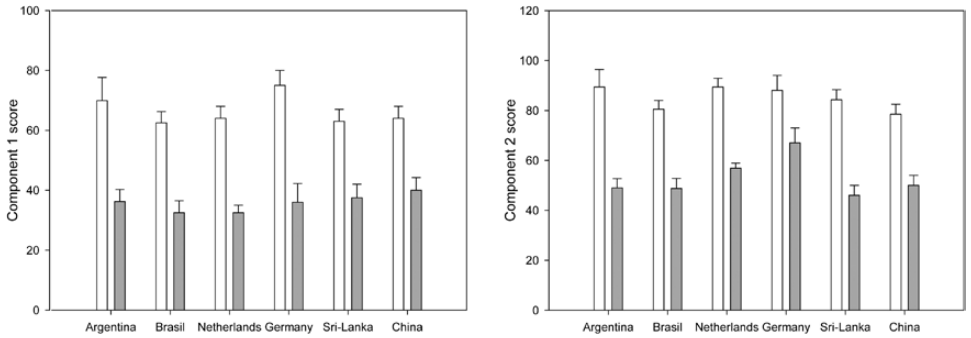

Figure 2. CATPCA components scores in controls and PD samples in the countries assessed. ANOVA found significant differences according to country ($P < 0.001$) and patient group ($P < 0.001$) for component 1 and only according to patient group ($P < 0.001$) for component 2. $^{**}P < 0.01$ versus controls (*t*-test).

different odorants varies across geographical regions and is correlated with odorant familiarity (Ayabe-Kanamura et al. 1998) and even though there is some genetic involvement in phenotypic variation of smell perception, nonshared environmental features account for a more significant part of this phenomenon (Knaapila et al. 2008). Moreover, even though there are high heritability coefficients in olfactory identification, they decrease with ageing, suggesting that genetic traits are influenced during lifetime by environmental and possibly other noninherited factors (Doty et al. 2011).

Interestingly, in a study evaluating 300 Hispanic and non-Hispanic white adults of 40 years of age and above from counties around the Texas-New Mexico border using the B-SIT (a test composed of 12 items taken from the UPSIT familiar to North American, European, South American, and Asian cultures; Doty et al. 1996), neither ethnicity nor years of education affected the subject's performance (Menon et al. 2013). Meanwhile, in a larger Brazilian study comprising over 1800 subjects from the city of Sao Paulo, UPSIT scores showed both a slight difference between white and black Brazilians, as well as a moderate positive correlation with years of education (Fornazieri et al. 2015).

The studied populations come from different ethnical backgrounds and cultures that can account for both genetic and environmental influences in olfaction. Particularly cuisine and eating habits, as 14 out of 16 items of the SSI consist of food related odors. As an example of this, Latin American cuisine shares more items with East Asian cuisine than they both do with western European, which could explain the consistency of the sensitivity to garlic, a commonly shared ingredient in different cuisines (Ahn et al. 2011)

In conclusion, we have found a set of "universal" SSI items consisting of orange, mint, banana, garlic, coffee, cloves, and fish that has a uniform response across the different countries included in this study. Nevertheless, this does not mean that this is the best combination of items to achieve an optimal sensitivity and specificity for each case, furthermore it is worth taking into account that the odors mentioned for the SSI are a description for the compounds used in this test, and different chemical formulations in different tests may be described using the same denominators. Taking this into account, due to the variations in identification capability across different countries with the use of the SSI, we recommend local validations to be made thus allowing the use of a reduced number of items while reducing time of application without compromising on diagnostic accuracy.

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