Anosmia in neurodegenerative disorders

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Abstract

Since the discovery of olfactory dysfunction in Parkinson's disease (PD) and Alzheimer's disease (AD) just over three decades ago, research into olfactory dysfunction in PD and AD has grown vastly. It appeared that olfactory dysfunction is similar in PD and AD. However, recent studies show that the severity of olfactory dysfunction differs between PD and AD.

Olfactory dysfunction in PD appears to be stable during disease progression and severity except for odour discrimination. In AD however, olfactory dysfunction in identification, discrimination and threshold is associated with severity and the degree of dementia. It has been found that both PD an AD are preceded at approximately five years by olfactory dysfunction before the presence of typical symptoms. Typical symptoms for PD are bradykinesia, rest tremor and rigidity. For AD typical symptoms are cognitive impairment and memory deficits. Also, olfactory dysfunction can identify future PD or AD developers from an at risk group. However, the predictive value of olfactory dysfunction in a general population is unknown.

Another difference can be found in treatment response. Olfactory dysfunction improves in AD with acetylcholinesterase inhibitors (ChEI), where in PD, olfaction is unaffected by typical dopaminergic treatment. There are a number of explanations for this difference, among which is that the underlying mechanism in PD is more complex and comprises multiple system, e.g. dopaminergic system and acetylcholinesterase (AChE) activity. It has recently been suggested that the AChE is more important in olfactory dysfunction in PD than the dopaminergic system.

Olfactory testing appears very useful in early detection and differential diagnosis and could be very useful in clinical settings, but further research is needed to investigate the underlying mechanisms and possibilities for inclusion in treatment. Also, further research could focus on the link between movement and olfaction as seen in animals. Another possible line of research is that of olfaction and emotion or lack thereof as seen in both PD and AD.

Introduction

Over the past few decades there has been an increase in research in olfactory dysfunction in a variety of disorders, including psychiatric and neurodegenerative disorders. The most commonly researched disorders at the moment are Parkinson's disease (PD), Alzheimer's disease (AD), mood disorders (depression) and schizophrenia [2,14,15,31,50,51,53,55,81,86], whereas the first two have received most attention. Due to the believed resemblances between the PD and AD [50] and the importance of PD and AD in ageing societies, this review will only focus on these two neurodegenerative diseases.

The first mention of olfactory dysfunction in PD was made in 1975 by Ansari and Johnson [1]. They showed that olfactory dysfunction was prevalent in 45-49% of patients. However, data of prevalence studies of olfactory dysfunction in PD shows large differences possibly due to sample size, olfactory tests used and age distribution [28]. Hawkes and colleagues show a prevalence of olfactory dysfunction between 70% and 90% [33]. Doty and colleagues report prevalence data up to 90% [17]. With data showing olfactory dysfunction in up to 90% of patients, olfactory dysfunction is more common than one of the cardinal symptoms, tremor, occurring in ~70% of patients [17,24,33].

The first observation of olfactory dysfunction in AD was made around the same time as in PD by Waldton [84]. This led to an increase in research into olfactory dysfunction in AD. Research in olfactory dysfunction in AD has grown vast in over three decades [e.g., 19,56,69,72], making olfactory dysfunction best researched in AD and PD. Data on olfactory dysfunction in AD show that prevalence of olfactory dysfunction is similar to that in PD and occurs in ~85-90 % of patients [15,16].

Although research has vastly increased over the past few decades, still little is known about the exact pathology and underlying mechanisms of olfactory dysfunction. However, research focussing on early detection has yielded interesting results. This is because the prevalence of PD and AD is high and will be increasing with the ageing of the western society. Approximately 1% of people between 65 to 69 years of age, increasing to 40%-50% of people over 95 years of age are affected by AD [39]. Prevalence is somewhat lower in PD, where 0.5-1% is affected in the elderly population and in subjects above 80 years of age 3% is affected [60]. It is therefore important to better understand the meaning of olfactory dysfunction in AD and PD and to explore the possibilities of olfactory dysfunction in early and differential diagnosis to optimize treatment.

In this review, olfactory dysfunction in PD and AD will be compared in the light of new evidence, e.g. what are the differences and similarities between olfactory dysfunction in PD and AD and what do they mean. More specifically, this review will try and answer the following questions. If possible, how can olfactory dysfunction in PD and AD be of use in early detection and treatment response, e.g. using olfaction as a marker, and what are the supposed underlying mechanisms? And what possible future research could be suggested by the current findings in olfactory dysfunction in PD and AD?

Odour tests and measures

Before investigating recent studies, it is important to know what olfactory dysfunction can consist of and how it is measured. There are a variety of olfactory measures which may or may not be independently affected in disease and may show different behaviour over the course of the disease.

Odour detection threshold

The detection threshold is the minimum concentration that is needed for a certain stimulus to be detected reliably, i.e. evoke a sensation. A forced choice paradigm is commonly used where there are two different samples, one of which is 'odourless', e.g. water. Then the subject has to identify which of the samples contains an odour. The odour only needs to be detected and not recognized [44]

Different approaches exist on determining the threshold. One of the more used methods is the staircase method [21,43], or the up-and-down method. Threshold is determined by averaging the reversal points. Another procedure is the ascending method of limits (AML), where two samples are presented sequentially from a low to a high concentration. The point where the subject is able to detect and identify the right sample is seen as the detection threshold. The single staircase method is more reliable and also more often used than the AML.

Odour identification

There are numerous different odour identification tests [25]. The most widely used are the University of Pennsylvania Smell Identification Test (UPSIT) [21] and the "Sniffin' Sticks" (SS) [43].

All tests assess odour identification in a similar way. Subjects are given one odour at suprathreshold level to smell and then need to identify this odour using forced multiple choice

with a list of odour names. If subject are unable to identify the odour they still have to make a choice.

Furthermore, odour identification tests correlate well with threshold and discrimination tests and are therefore, besides its easy and rapid use, the preferred test for most researchers. Other tests are however necessary for multiple reasons, e.g. to assess other olfactory functions, or if cognitive impairment is suspected.

Odour discrimination

The capacity for odour discrimination is based on a measure of a subject's ability to differentiate between odours. There are different ways of doing this. The simplest form is to present a subject with two odours and ask whether or not the two odours are identical. A more complex form of this task is to present a subject with an array of odours (usually three samples) and ask the subject to pick the odd one out. To perform this task only acuity is required, subject do not need to name, i.e. identify, the odours presented [49].

Odour recognition (odour memory)

Memory for odours is a lesser researched olfactory function then the ones described above. Odour recognition is tested using conventional recognition paradigms. Therefore it is suggested that this may not be an accurate measure of olfactory function but also of memory and might thus be influenced by subtle memory deficits [52]. The possible contamination of this task by memory deficits makes it a less useful technique to measure olfactory function.

Odour change detection

It is thought that the olfactory system constantly monitors the environment for odours. Odours change detection is a measure to see if subjects react when suddenly a train of a certain odour is altered, without paying attention to the odours. Subjects receive specific instructions to perform a different task. Using electroencephalography (EEG) a mismatch negativity (MMN) can be found when a odour train is interrupted by a different odour [46]. Because this test is not as easy or as quick to administer as the above described measurements, this test is not often used.

Besides these different olfactory measures, there are two commonly used tests. It is important to investigate the tests used in studies when comparing different studies, thus knowing whether different findings might be attributed to different tests.

University of Pennsylvania Smell Identification Test (UPSIT)

The first widely tested and validated olfactory test is the UPSIT and is developed in north America [20,21]. The UPSIT contains 4 booklets each comprising 10 scratch-and-sniff items.

A shorter (and faster) variant has been developed, namely the Cross-Cultural Smell Identification Test (CC-SIT), also known as the Brief Smell Identification Test (B-SIT) [18]. The CC-SIT contains only 12. The UPSIT and its altered forms solely measure odour identification.

"Sniffin' Sticks" (SS)

The second, often used, task is the SS, developed and introduced in Germany [38,43]. Where the UPSIT only measures identification, the SS measures threshold (T), discrimination (D) and identification (I). The identification subtest contains 16 odours for which subjects have to choose the right answer from 4 choices. The discrimination subtest uses 16 triplets where one of the sticks had a different smell. An extended version of the SS has been made, which contains 32 odours. The extended version has higher test-retest reliability but is also more time consuming [30].

Before investigating the olfactory dysfunction in both PD and AD, it is vital to know which areas are involved in and responsible for olfactory functioning.

Neural correlates of olfaction

From the olfactory bulb cell axons are sprouting to synapse on structures included in the primary olfactory cortex. Among these structures are the anterior olfactory nucleus (AON), the piriform cortex, the anterior cortical nucleus of the amygdala, the periamygdaloid complex and the rostral entorhinal cortex [15]. From there connections to the secondary olfactory cortex pass by the dorsal medial thalamus, whereas in other sensory systems fibres are synapsing on the thalamus before reaching any cortical regions. Also, it is unique for the olfactory area of the entorhinal cortex to directly receive olfactory sensory input, whereas other sensory areas of the entorhinal cortex receive their information via a relay in cortical association areas near the hippocampus [40].

Furthermore, using positron emission tomography (PET) it has been found that the primary olfactory cortex is located bilaterally at the temporal and inferior frontal lobes (piriform cortex). However the secondary olfactory cortex appears to be only present in the right orbitofrontal cortex [87].

The representation for odour quality, identity and familiarity (recognition) is found to be located in the piriform cortex. This area is associated with learning and remembering of odours [26]. Intensity of pleasant and unpleasant odours is associated with amygdala activity,

which appears to be its only function in olfaction. The entorhinal cortex is involved in learning and memory by preprocessing information before it enters the hippocampus [26].

Odour detection is associated with caudal orbitofrontal cortex activation. Short- and long-term odour recognition is related to more rostral regions of the orbitofrontal cortex [26].

Although intensity of pleasant and unpleasant odours is related to amygdala activity, pleasantness of odours itself is associated with different areas. A lateral-medial dissociation in prefrontal and orbitofrontal cortices has been found for pleasant and unpleasant odours [27].

In addition, using functional magnetic resonance imaging (fMRI) the act of smelling itself (i.e. sniffing), which enhances odour detection, has been shown to activate the piriform and orbital frontal cortices [75].

Before assumptions can be made about which areas are affected in PD and AD, it is necessary to review olfactory functioning in these disorders, or more specifically olfactory dysfunction.

Olfactory dysfunction in PD and AD

It is well established that olfactory dysfunction is present in PD. Prevalence data shows that olfactory dysfunction is present in up to 90% of PD patients [17,28,33]. Doty and colleagues established that olfactory dysfunction is independent of duration and severity of motor and cognitive functions [17]. These findings were replicated by Hawkes and colleagues [33], who also showed that PD patients have specific anosmia for certain odours, including pizza and wintergreen. Specific anosmia is therefore suggested to be a specific marker for PD.

In a later study it was found that olfactory dysfunction was bilateral and asymmetries found were similar to asymmetries found in healthy controls and were not related to the side where major motor dysfunction was found [22]. In their study, Doty and colleagues [22] also showed that olfactory dysfunction was similar in treated and untreated patients and was unrelated to duration or severity of the disease. In this study they used the UPSIT, meaning that only odour identification was measured.

Although most studies show no difference between treated and untreated patients using psychophysical measures, an olfactory event-related potential (OERP) study shows that anti-parkinsonian medication actually leads to a prolonged latency in PD patients compared to controls [3]. In this study untreated patients only showed a tendency towards prolonged latency compared to controls. However, it is not known whether this difference might be related to disease severity or disease stage or age difference between the treated and untreated

patients. Lack of this information makes it difficult to determine the value of these findings. In addition, this study revealed there is no trigeminal dysfunction in both treated and untreated PD, i.e. the trigeminal system appears to be unaffected in PD.

More recent studies have shown that, although UPSIT scores appear to be unrelated to disease severity, odour discrimination actually is related to disease severity [80]. A study by Boesveldt and colleagues [5] has confirmed that odour discrimination is actually correlated with disease duration, but not disease stage.

Herting and colleagues [34] confirmed earlier findings that olfactory dysfunction is not related to disease duration or severity. They, however, did not rely on cross-sectional studies and conducted a longitudinal study in PD patients. As they used the SS, they tested the full range of olfactory function and used the composite TDI score to compare results. Their findings are in accordance with a large number of studies on identification and threshold. They also found some other, remarkable results, namely that some patients improved from being functionally anosmic to hyposmic. A possible explanation they offer is that of an increase in dopaminergic neurons in the olfactory bulb, found by Huisman and colleagues [36].

A different recent finding shows that odour recognition (odour memory), a less studied olfactory measure, may not be impaired in PD, when corrected for detection scores [4]. Few previous studies testing recognition where inconclusive and a review actually suggested that odour recognition was impaired [50]. The finding that recognition is not impaired might also be expected in non-demented PD patients, as they have no cognitive impairment. The explanation that odour recognition deficits might be due to detection deficits thus seems plausible.

Although odour discrimination appears to be related to disease duration, and might therefore be argued to be more important than other odour measures, as it is more unique to PD, odour identification actually allows for better discrimination between PD patients and controls [5]. In patients odour identification deficits and odour discrimination deficits were present in 65% and 42.1% respectively.

Several studies identified certain odours to be more sensitive for PD. However, most of these studies report different odours. Bohnen and colleagues [6] showed that banana, liquorice and dill pickle. Hawkes and Shephard [32] previously showed pizza and winter green to be most sensitive in PD. Yet another study by Daum and colleagues [11] showed aniseed, pineapple, apple, turpentine and banana to be most sensitive. Boesveldt and colleagues [5] showed that aniseed, cinnamon and liquorice best discriminated between PD and controls.

Possible reasons for these differences can be found in cultural preference for certain odours or (cultural) familiarity or different threshold values in odour identification tasks such as the UPSIT.

In AD, Doty and colleagues [19] showed that patients had significantly lower scores on odour identification and higher threshold scores compared to their controls. They did not find any significant relation between olfactory dysfunction and disease stage. In this study they also noted that less than 10% of the patients were aware of their olfactory problems. However, studies on odour threshold were still inconclusive. Murphy and colleagues [56] partially replicated these results, but also showed that odour threshold was correlated with disease severity. They therefore suggest that the previous inconclusive findings might be due to comparison of patients with different disease severity, i.e. mixed patient groups. Furthermore, the stimulus used in this study was chosen to only stimulate the olfactory nerve and not the trigeminal nerve (cranial nerve V), which is involved in sensory aspects such as temperature, pain or chemical thresholds in the facial area (mouth and nose).

Morgan and colleagues [54] conducted one of the first well controlled studies with AD patients where they compared odour identification (UPSIT) with picture identification (PIT) and showed that olfactory dysfunction was more pronounced. In addition they performed a non-verbal (picture-based) odour identification task and showed that eliminating the verbal factor did not alter odour identification scores. Also, they performed a detection test, showing that AD patients had significantly higher thresholds than controls. Because threshold did not correlate with identification scores, identification can not solely be attributed to a detection deficit, but also involves higher levels of processing. So, controlling for both non-olfactory identification tasks and verbal performance and detection threshold showed that odour identification is a deficit per se.

Dysfunctions of memory or recognition do not seem to be specific for odour in AD patients [58]. Poor recognition was also found in visual tasks, suggesting a perhaps more subtle memory deficit. This finding however is in contrast with an earlier finding by Moberg and colleagues [52] showing greater odour memory deficits compared to verbal and visual memory.

Moberg and colleagues [51] conducted a study investigating odour identification. They replicated earlier findings in olfactory dysfunction and analyses showed that olfactory dysfunction, odour identification, was unaffected by medication.

To investigate whether odour identification deficits were not merely cognitively based, Morgan and Murphy [53] tested AD patients using OERP. They compared OERP with auditory ERP to exclude a possible overall sensory dysfunction. They found that OERP peak latencies were significantly longer in AD than in controls. Also OERP was significantly correlated with severity of dementia. This indicates that olfactory dysfunction is not merely a result of cognitive impairment and tasks might not be well-understood by subjects. Differentiation of AD from controls was better using OERP measures compared to auditory ERP. They furthermore showed that OERP correctly classified 92% of AD patients and in combination with odour identification scores classification was 100%.

It is furthermore noteworthy that some studies have shown that patients are usually not aware of their olfactory dysfunction [17,19,31]. Nordin and colleagues [57] showed that 74% of AD patients were unaware of their olfactory dysfunction, which was similar to the 77% of normal elderly presenting with smell loss, even though thresholds in patients with AD was approximately nine times higher than in normal elderly subjects. In contrast, for example only 8% of patients suffering from sinusitis were unaware of their olfactory dysfunction.

For an overview of olfactory dysfunction in PD and AD, see table 1.

Table 1. Summary of olfactory dysfunction in PD and AD

	PD		AD	
	Present	Related to severity or duration	Present	Related to severity or duration
Prevalence	~70 - 90%	Unknown*	~85 - 90%	Unknown*
Identification	Yes	No	Yes	Yes
Threshold	Yes	No	Yes	Yes
Discrimination	Yes	Yes	Yes	Yes
Awareness	Unknown	-	~10 - 25%	Unknown

*Although unknown, it is not likely as olfactory dysfunction is one of the earliest symptoms for AD and PD.

Knowing what olfactory dysfunction consists of in PD and AD, the following question arises: When is olfactory dysfunction present and can it be used as an early marker?

Early detection

The finding that olfactory dysfunction was amongst the first signs in both PD and AD suggests that olfactory dysfunction may be used for early detection of these disorders. Pathological studies have shown that entorhinal areas, involved in olfactory processing, are affected early in AD [8].

Ponsen and colleagues [63] studied the predictive value of olfactory dysfunction in relatives of patients with PD. To do so, they tested identification (adaptation from the CC-SIT), detection and discrimination (developed at University Medical Centre Utrecht). They showed, at a two year follow-up, that 10% of relatives with olfactory dysfunction developed PD and none of the relatives with normal olfaction. In addition, they used SPECT scanning to test for dopaminergic function. The 10% who developed PD showed lower DAT binding in nigrostriatal dopaminergic system than relatives with normal olfaction and the relatives who did not develop PD showed a significantly greater decline in DAT binding compared to relatives with normal olfaction. It should be noted that, due to use of non-standard olfactory tests, it might prove difficult to compare directly with other studies.

A twin study with at risk subjects was done by Marras and colleagues [48] using the UPSIT. At a seven year follow-up interval, olfactory dysfunction was not yet present in twins of PD patients. At follow-up 10% had developed PD and also showed greater reduction in olfaction compared to twins who did not develop PD [48]. They concluded that olfaction is not a sensitive indicator in a group at risk seven years or more before typical PD signs.

Using dopamine transporter (DAT) single photon emission computed tomography (SPECT) scanning, Siderowf and colleagues [73] found that UPSIT scores are correlated with DAT uptake in the striatum. The subjects in this study where all early-stage PD and it is therefore not known if this relation holds when disease progresses. However, since DAT SPECT scanning has been proposed as a diagnostics tool in early stage, this finding is useful, as UPSIT is much more cost efficient and can be used more easily.

Haehner and colleagues [29] found that 7% of subjects with olfactory dysfunction, measured with a composite TDI score from the SS, developed PD symptoms at four years of follow-up. In total, 13% of subjects with olfactory dysfunction showed abnormalities of the motor system. Although olfactory dysfunction doesn't increase over time, the SPECT imaging they performed showed a decline in DAT binding. They thus argue that a combination of techniques might be used to predict PD and that a threshold might be established at which symptoms become noticeable.

The first study not using relatives of PD patients, but a random cohort of healthy elderly people, was done by Ross and colleagues [70]. In this study, consisting entirely of male subjects, they found that olfactory dysfunction may signal PD development up to four years prior to development of typical PD symptoms. Because all subjects were Japanese American, the CC-SIT was used as to limit cultural effects on odour identification. It should be noted

however that the CC-SIT had never been used in a Japanese American population before. This means that the validity of these results could be argued.

A recent study tested over 300 first-degree relatives of PD patients concluding that olfactory dysfunction on odour detection threshold, odour discrimination and odour identification was associated with PD development at five year follow-up [64]. The best predictor of the three olfactory tests was odour discrimination. In this same group, a selection was made of approximately 40 subjects in a normosmic group and 40 subjects in a hyposmic group [65]. This study showed that 12.5% of hyposmic subjects developed PD. All subjects who developed PD demonstrated abnormal striatal DAT binding, whereas none of the hyposmic subjects who did not develop PD demonstrated abnormal striatal DAT binding. This indicates that a combination of olfactory testing followed by DAT SPECT scanning dramatically increases specificity.

Nording and Murphy [59] conducted a study comparing patients with questionable AD (which is different from probable AD) with controls. They found that although odour memory is impaired in healthy ageing individuals it is more pronounced in subjects with questionable AD. Also odour memory appears to be more affected than visual memory in early or preclinical AD (i.e. questionable AD). This study therefore suggests that odour memory tasks could be very useful in use of early detection in patients with impaired cognitive functions but no impairment in everyday functioning (i.e. questionable AD).

Devanand and colleagues [13] found that patients with mild cognitive impairment (MCI) who exhibited olfactory dysfunction measured with the UPSIT and had lack of awareness were more likely to development AD. About 40% of patients with MCI and olfactory dysfunction developed AD whereas none of the patients without olfactory dysfunction developed AD at two year follow-up. Although combining odour identification deficit with lack of awareness decreases sensitivity, it increases specificity. Thus olfactory dysfunction in combination with lack of awareness may provide a useful measure in predicting future AD.

Schiffman and colleagues [71] showed that subjects at risk for familial AD showed poorer performance on both olfactory measures as well as taste tests with memory demands compared to controls. However, they were not judged to have cognitive impairments based on neuropsychological testing. Also, these findings seem to be odour specific. Detection thresholds for menthol for example, which has a large trigeminal component, were unrelated to at-risk status. It is suggested that olfactory measures with a memory component might be

especially useful in identifying at risk subjects for AD. It should be noted that this study did not use standard tests for olfaction and might thus be difficult to compare with other studies.

As stated earlier, there appear to be specific odours that are more affected by AD development than others. Tabert and colleagues [78] used the UPSIT and the CC-SIT to investigate which of these might best be used for early detection of AD. They found a subset of ten items from the UPSIT and CC-SIT which better predicted conversion to AD then the UPSIT as well as the CC-SIT. It should be noted that the CC-SIT is designed for cross-cultural use, whereas the ten items currently investigated were only used in this study in North-America. However, if these ten items are specific for AD and not cultural specific, it does suggest that when testing for AD in clinical settings, this short and quick test might prove very useful in identifying early AD. Even though a previous study [13] showed that outcome was better predicted if patients also lacked awareness of olfactory dysfunction, this study, with a larger sample size and longer follow-up (mean of 42 months), showed that these ten items strongly predicted conversion from MCI to AD.

Devanand and colleagues [12] showed that a combination of UPSIT with other predictors increases the predictive value and sensitivity for conversion from MCI to AD. The best sensitivity was found using UPSIT, Selective Reminding Task (SRT), Pfeffer Functional Activities Questionnaire (FAQ), hippocampal volume and entorhinal cortex volume, namely 85.2%. Using only the Mini-Mental State Examination (MMSE) and age (the two commonly used indicators) in combination with UPSIT, SRT and FAQ led to a sensitivity of 81.3 %. Although adding MRI data yields slightly better results, it is more practical and cost-efficient to use multiple tests and questionnaires that are easily administrable. This includes olfactory function testing using the UPSIT.

In a large healthy group of elderly people, Wilson and colleagues [86] found that olfaction is related to AD post mortem pathology, e.g. neurofibrillary tangles in especially entorhinal cortex and hippocampal regions, and also to risk of developing MCI. This is the first study testing a random group of people not indicated to be at risk and although they show there is a relation between olfaction and AD pathology and development, no notion is made of specificity or sensitivity. Therefore it is difficult to say if subjects with olfactory dysfunction might be at risk for different disorders, such as PD.

In short, olfactory dysfunction precedes both PD and AD at approximately five years. In PD this is confirmed by research using identification, TDI composite and DAT binding. In AD, predictive research is mostly done using identification tests. So far, it is known that people with olfactory dysfunction at risk for developing PD or AD are very likely to develop

PD or AD respectively. It remains unclear what the predictive value of olfactory dysfunction is in a healthy cohort.

Having clarified what olfactory dysfunction in PD and AD consists of and what the onset of olfactory dysfunction is, the next question should be answered before trying to reveal the underlying mechanisms responsible for the olfactory dysfunction. Can olfactory dysfunction be used as a treatment response marker?

Treatment response marker

Doty and colleagues [22] were the first to report on the effects of anti-Parkinsonian medication on olfactory function. They found that anti-Parkinsonian treatment had no effect on olfactory dysfunction.

A later study by Tissingh and colleagues [80] confirmed this finding. No difference in olfactory dysfunction was found on odour identification and threshold. However, they did find a difference in treated and untreated (early) PD with regard to odour discrimination, where treated patients perform significantly worse. This might be explained by severity of the disease, as it appears that odour discrimination is effected by PD severity. This suggests that odour discrimination could be used to test disease severity in PD patients who receive treatment, where severity of symptoms might be obscured by the effects of medication.

It is argued by Huisman and colleagues [37] that PD treatment with for example L-dopa does not alleviate olfactory function because of an increase in dopaminergic neurons in the olfactory bulb. The increase of dopaminergic neurons in the olfactory bulb is over 100% and is known to inhibit olfactory transmission.

Kranick and Duda [45] hypothesize that the neural population was so early in the disease that no response was possible after anti-parkinsonian medication. Another explanation, according to Bohnen and colleagues [6], is that the opposing effect of D_1 and D_2 receptors stimulation on olfactory functioning is the reason why L-dopa has no effect on olfactory functioning.

Velayudhan and Lovestone [83] conducted the first study investigating the use of olfactory function as a treatment response marker in AD. They studied olfactory function in subjects receiving acetylcholinesterase inhibitor (ChEI) treatment (donepezil), which is a standard pharmacological treatment for AD. Their results show that olfactory improvement is correlated with the Clinician Interview Based Impression of Change plus caregiver input

(CIBIC-plus), which is a validated scale used for testing donepezil outcome. It should however be noted that this was a study with small sample size and was uncontrolled and not blind.

The next question to answer after covering olfactory dysfunction, early detection (or onset) and response to treatment is what the underlying mechanisms of olfactory dysfunction in PD and AD are.

Underlying mechanism

Although research into olfaction in both PD and AD has been growing vastly over the past few decades, the exact underlying mechanisms of this symptom are still poorly understood.

Pearce and colleagues [62] found that atrophy of the AON is related to disease duration, though it is still unknown what the precise function of the AON is in humans.

The notion of increase of olfactory neurons in the olfactory bulb, which have an inhibitory effect on olfaction, may point towards the dopaminergic system as the underlying cause. This is also implied by the notion that olfactory scores are related to DAT uptake in the striatum [73], creating strong circumstantial evidence for the contribution of the dopaminergic system in olfactory dysfunction.

Furthermore it has been shown that selective hyposmia, i.e. certain odours that are especially poorly identified, in PD is associated with hippocampal dopaminergic denervation. This correlation is higher than for general odour identification scores [6]. In a more recent study by Bohnen and colleagues [7], it is found that odour identification scores in PD correlate positively with acetylcholinesterase (AChE) activity in the hippocampal formation, the amygdala and the neocortex. It is even stated that this relation is more robust than the earlier found relation of odour identification with striatal dopaminergic denervation. This suggests that a more complex mechanisms of both the dopaminergic system and AChE activity is affecting olfactory dysfunction in PD.

In AD it has been shown that ChEI treatment improves olfactory functioning, suggesting that AChE activity might be an important part of the underlying mechanism for olfactory dysfunction [83]. Other findings only comprise the presence of neurofibrillary tangles and Tau pathology in areas associated with olfaction processing.

Discussion

In this review, the olfactory dysfunction in both PD and AD has been discussed extensively. Both similarities and differences have been evaluated as to uncover what olfactory dysfunction consists of in PD and AD. After that, the following questions were investigated and reviewed. How can olfactory dysfunction in PD and AD be of use in early detection and treatment response? What are the supposed underlying mechanisms? And what possible future research could be suggested by the current findings in olfactory dysfunction in PD and AD?

Although it was long thought that PD and AD showed similar olfactory deficits [47,50], such as severity of olfactory dysfunction and preclinical duration of olfactory dysfunction, new studies indicate clear differences. It has now been shown that in PD only odour discrimination appears to be related to disease duration and the other olfactory deficits stay unchanged over time, whereas for AD all measures of olfaction are related to disease severity and duration.

Another clear distinction between PD and AD can be found in treatment response. PD treatment does not result in any improvement in olfactory function, whereas for AD, conventional medication (AChEI) shows improvement which is related to general improvement according to CIBIC-plus scores. There are a number of explanations for this. In PD, olfactory dysfunction has multiple underlying mechanisms, e.g. dopaminergic system and AChE activity. Also the increase of dopaminergic neurons in the olfactory bulb and the contradictory effects of D_1 and D_2 are possible explanations for non-response to medication.

One of the more interesting findings is that in about 80-90% of PD patients olfactory deficits can be found, where diagnosis accuracy is just over 80% [35]. However, it is not yet known whether the patients exhibiting normal olfaction, are those who have the wrong diagnosis. Though it is suggested that if PD patients exhibit normal olfaction, diagnosis should be reviewed and for example progressive supranuclear palsy (PSP) is a more likely diagnosis. The same goes for olfaction in AD, where diagnostic accuracy is just over 90% [67] and olfactory dysfunction has a similar prevalence to that in PD. In this case too, it is unknown whether the patients who don’t show olfactory dysfunction are those who are wrongly diagnosed. This indicates that in future research the tested subjects should preferably undergo post-mortem examination for either PD or AD pathology and see if those without olfactory dysfunction are incorrectly diagnosed. This is of great importance, because some dementias for example are reversible. To sum up, prevalence of olfactory dysfunction is very

high in PD and AD, but it is unclear if those who exhibit normal olfaction are those who are misdiagnosed as proven by autopsy.

Besides the importance of the right diagnosis and treatment, it is also highly desirable that diagnosis is made as early as possible, because early intervention or medication might improve outcome, emphasizing the need of a marker for early detection. It is believed that olfactory dysfunction is such an early marker for both PD and AD, preceding the main symptoms by up to five years. Studies in at risk groups for both PD and AD show that olfactory dysfunction has a high predictive value and sensitivity. The main problem is that these are groups containing at risk subjects, whereas it would be preferable to use in a generalized population. Only a few cohort studies have been done, all with limitations, such as sensitivity of olfaction measures. Olfactory dysfunction has been shown to predict PD or AD development in at risk groups, but what is the predictive value in the general population and how specific is it, i.e. what does olfactory dysfunction predict in not at risk people? It is therefore argued that olfactory testing is a diagnostic tool which might contribute much, but is more effective when combined with other markers or cognitive tests. Because of the high prevalence of olfactory dysfunction in PD and AD, it could be argued that olfactory testing should become standard in yearly check-ups, as it is quick and inexpensive, especially when only the CC-SIT is used, which only takes a few minutes and is self-administrable. If scores are below cut-off and have no clear cause, further investigation is warranted. In short, olfactory dysfunction is very accurate in predicting PD and AD in at risk group, but its significance in a general population is unknown.

Although the predictive value of olfactory dysfunction has been widely tested, it is still unclear what the underlying mechanism is exactly. All current evidence is circumstantial. Olfactory dysfunction in PD has long been described to be related to dopaminergic denervation in the hippocampal region and DAT uptake in the striatum. However, new evidence suggests that the underlying system might be multi-component and that the AChE activity might even be the most important contributor to olfactory dysfunction in PD, which appears to be similar to AD. However, in PD, no medication appears useful for improving olfactory dysfunction, i.e. both L-dopa and ChEI do not results in olfactory improvement. Though, in AD typical ChEI treatment does improve olfactory dysfunction. Non-effects of medication on olfaction in PD have been hypothesized to be due to contradictory effects of D_1 and D_2, or to increase of dopaminergic neurons in olfactory bulb, thus having an inhibitory effect on olfaction, or even severity of olfactory damage, i.e. olfactory dysfunction is beyond repair. The addition of AChE makes this much more complicated and demands research into

the complexity of the underlying cause for olfactory dysfunction in PD. In conclusion, olfactory dysfunction in PD is believed to have complex and not fully understood underlying mechanisms, whereas olfactory dysfunction in AD appears to be mostly due to the AChE system.

Besides, while olfactory testing is quick and cost efficient, and growing in clinical use, it is still not standard in practice or clinical settings for (early) diagnosis and differential diagnosis. Although a very useful tool, there might be another reason for including olfaction in PD and AD in clinical settings. For example, it is known that decreased appetite and subsequent weight loss might be attributable to olfactory dysfunction [85], however very few studies actually suggest this should be considered by clinicians and adopted into treatment plans. Especially in AD this would very useful as malnutrition is associated with development of AD [e.g., 61]. It would thus be advisable to include olfaction and subsequent nutrition problems in diagnosis and even treatment plan, since neuroprotective agents have also been found in nutrition [41]. Another reason for inclusion of olfactory dysfunction in both PD and AD is the danger of subjects being unable to smell certain dangerous odours such as gas and smoke or rotten food [79]. It is notable that this is the case for every patient with olfactory dysfunction, whether or not they have PD or AD.

It is widely known that in PD and AD there is a high co-morbidity of apathy [9,23] and depression [68,82]. Recently, it was found that there is a correlation between apathy and olfaction in PD [10]. Combining this information with the olfactory bulbectomy model of depression in rats [76] and the finding that olfactory bulbectomy alters cholinergic receptors [74] and with the recent finding by Bohnen and colleagues [7] suggesting that AChE is more important than the dopaminergic system in olfactory dysfunction in PD, it could be argued that AChE in PD is more important for olfaction and emotional dysfunction than previously expected. Furthermore, it is found that AChE plays a significant role in PD and in modulating dopamine release in striatal regions as well [66]. It may therefore be valuable and desirable to investigate the AChE mechanism more thoroughly with regard to olfactory dysfunction amongst others.

Where humans are thought to be less dependent of their sense of smell than most animals, which use olfaction to find food, suitable mates and their homes, humans use the olfactory system to identify edible foods, dangerous odours and potential mates [77]. Humans mostly use olfaction for identification, but animals rely on smell to navigate and coordinate their movements. Even though it is well known that most animals, e.g. rodents, have a more sophisticated and complex olfactory system than humans, it has only recently been found that

rodents can localize odours by ipsinostral excitation and contranostral inhibition in the AON [42]. Although the role of human olfaction in movement has never been proven, this strong link between olfaction and movement in animals might prove to be a useful analogy for investigating the link between olfaction and motor symptoms in PD.

In conclusion, olfactory dysfunction follows a different course in PD than in AD. Differences lie in severity and change, i.e. worsening, of olfactory scores, during disease progression. Also it appears the underlying mechanism of olfactory dysfunction in PD is more complex, although evidence is merely circumstantial. Therefore, further research is warranted to investigate the underlying mechanism of olfactory dysfunction, both in PD as well as in AD. Further research is also needed to examine the predictive value of olfactory dysfunction outside at risk groups, i.e. in a cohort. A similarity found between PD and AD is that olfactory dysfunction appears to be present up to five years before typical signs of PD or AD. Finally, olfactory dysfunction could be very useful in clinical settings in both (early) diagnosis and treatment.

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