Impaired olfactory function: Loss of smell and insight into neurodegenerative disorders

Jia Prasad

A dissertation submitted to

Auckland University of Technology

on partial fulfilment of the requirements for the degree of

Bachelor of Health Science (Honours)

2022

School of Health and Environmental Sciences

Primary Supervisor: Dr Mangor Pederson

Table of Contents

ACKNOWLEDGMENTS....4

ATTESTATION OF AUTHORSHIP....5

ABSTRACT....6

Keywords....6

INTRODUCTION....7

Rationale and olfactory testing....11

Olfactory function and memory....14

Causes of Age-Related olfactory impairment....17

LITERATURE REVIEW....19

METHODS....31

RESULTS....34

DISCUSSION....51

Limitations....56

Future Research....58

Conclusion....59

REFERENCES....61

Acknowledgements

It has been a very difficult, yet enlightening experience completing this dissertation in a very uncertain time of lockdown and quarantine. First and foremost, I would like to thank my supervisor Dr Mangor Pederson, who guided me throughout and always steered me in the right direction with information and advice. I will never forget the kindness and support you showed me during troubling times, thank you for always being on my side and believing in me, even when I was doubting myself. Secondly, I would love to say a huge thank you to my friends, who encouraged and joined me in many fun adventures that helped me to enjoy my honours year with a little less stress. Finally, thank you to everyone and anyone who wished me the best, and always had faith in me.

Attestation of Authorship

"I hereby declare that this submission is my own work and that, to the best of my knowledge and belief, it contains no material previously published or written by another person (except where explicitly defined in the acknowledgements), nor material which to a substantial extent has been submitted for the award of any other degree or diploma of a university or other institution of higher learning."

Signed: _____ Date: 02/02/2022

Abstract:

This study aims to investigate the possible association between olfactory function (‘sense of smell’) impairment in neurodegenerative disorders such as Alzheimer's disease and Parkinson’s disease, through a systematic review of relevant medical academia. Findings were overall consistent among research articles, and suggest that early stages neurodegenerative diseases could be identified through a poor sense of smell, which was simultaneously linked to lower volumes of the olfactory bulb. Implications suggest that inexpensive and noninvasive olfactory function assessments would be excellent biomarkers to aid in clinical diagnosis.

Keywords:

Human olfactory system; Olfaction; Olfactory receptor neurons; Olfactory assessment; Smell; Tau; Neurofibrillary tangles; Odour identification; Temporal information; Alzheimer's disease; Parkinson’s disease; neurodegenerative disorders.

Introduction:

Neurological disorders affect both the central nervous system (CNS); comprised of the brain and the spinal cord and the peripheral nervous systems (PNS), which includes the 12 cranial nerves attached to the brain and connect with the body's neck head and trunk, and the 31 pairs of spinal nerves which send the CNS information. The first two cranial nerves, the optic and olfactory nerves control the seeing and smelling functions respectively.

Due to its location at the front of the brain, the frontal lobe (responsible for higher executive function and emotional regulation) is reported as the most commonly damaged lobe and may result in partial (paresis) or complete (paralysis) loss of bodily movement (Hoffmann, 2013). Neurodegeneration may also cause changes to an individual's personality in terms of engaging in social behaviour or concern or interest (apathy). Aversi-Ferreira et al., (2019) state that deterioration of the temporal lobe (processes non-physical sensory information, including understanding language and memory recollection) may lead to issues with communication or memory and information recalling, whereas damage to the parietal lobe (responsible for processing sensory information) can result in issues with the five primary senses, including having difficulty identifying the location of sensations on the body (heat, cold, touch) (Ambron et al., 2018). Finally, impairment of the occipital lobe (processes visual information) could potentially lead to impairment in the processing of visual information, including difficulty in seeing objects in motion and the inability to recognize and see words (Tordesillas-Gutierrez et al., 2018). There have been recent studies by Null et al., (2016) noting the development of neurological disorders through malnutrition.

Global statistics pin neurological disorders in 2016 as the main perpetrator of disability-adjusted life years (DALYs) (276 million) and secondary cause of deaths (90 million) (Feigin et al., 2019). During the years between 1990 and 2016, the total number of documented deaths due to neurological disorders increased by 39% and DALYs increased by 15%. Common examples of these disorders include Alzheimer's disease (AD), Parkinson's disease (PD), epilepsy and other dementias, which are caused by damage to the brain, it may also manifest in cerebrovascular diseases such as strokes or migraines, and other headache disorders, or as multiple sclerosis, neuroinfections, brain tumours, as traumatic nervous system disorders caused by head trauma.

Both AD and PD are classified as dementia, which is an overall general term given to the loss of cognitive functioning, in which individuals will struggle with tasks often relating to independent function on a daily basis, the most severe cases requiring a daily aid for individuals to complete even basic and essential daily functions and activities including using the lavatory or feeding oneself. Diagnostic and Statistical Manual of Mental Disorders (5th ed.; DSM–5; American Psychiatric Association, 2013) classifies 6 areas as individuals being regularly affected in; complex attention (involves sustaining focus and processing), executive ability (such as decision making), learning and memory (recalling past events), perceptual-motor skills (such as handling or picking up objects), social cognition (such as regulation of emotions), which also links with language (involving expression through words). Dementia may progressively worsen and is more likely to develop in old age (60), though it is not guaranteed, and many elderly individuals lead dementia-free lives. Despite the fact that

dementia has no true cure, in current times there are many medications and therapies that help to alleviate symptoms, and in some cases, certain causes may be reversible (Scott and Barrett, 2007).

AD accounts for the majority (60-70%) of all dementia diagnoses and frequently manifests as a progressive loss of episodic memory and cognitive function, resulting in the language (difficulty participating in long conversations and understanding the meaning of words) and visuospatial skill declines (difficulty drawing, buttoning up own shirt, poor distance perception) which are also regularly accompanied by behavioural disorders such as aggression, depression and apathy (Weller and Budson, 2018). PD is the most frequently diagnosed case of parkinsonism and similarly manifests as a progressive nervous system disorder that causes loss of movement and muscular function (resulting in stiffness, slow movement, difficulty maintaining balance and coordination) due to the lack of dopamine in the brain. PD may develop into PD dementia, which involves further cognitive decline, including having difficulty focusing and recalling memories (DeMaagd and Philip, 2015)

The healthy brain emphasises functional brain activity and response and can perform normal levels of language, learning and recalling accurate information, alongside judgement and cognition. Its importance is not understated in scientific literature, the complex system structures that connect to control the body and receive and process information is frequently noted. Olfactory bulb (OB) projections are then directly sent to the piriform cortex; a key aspect of the brain that focuses on the processing, collecting and coding of olfactory information (Markopoulos et al., 2012). This first begins when odour molecules enter the

respiratory system, either through the mouth commonly during the tasting of food, or through the nasal cavity through inhalation of scents. Sharma et al., (2019) state that olfactory receptors are stimulated when interacting with passing odour molecules, and in response produce cyclic AMP (cAMP), leading ion channels, which are proteins that selectively permit specific ions to move through its channel and towards receptors. This promotes information passing between neurons through electrical signals.

A decrease in olfactory function in patients with AD or idiopathic Parkinson's disease (IPD) is well documented. Recently published research has indicated that odour processing and identification is greatly impaired for patients with AD (Growdon et al., 2015). The natural process of ageing has also been established as impacting various brain functions and motor skills, including the sense of smell (Murphy et al., 1990). Neurodegenerative changes appear early in areas associated with the OB, often physically by reducing the cell count inside the OB itself, also hindering the prepiriform cortex, amygdala, entorhinal cortex and hippocampus, which are all aspects of olfactory function and processing (Murphy, 2018).

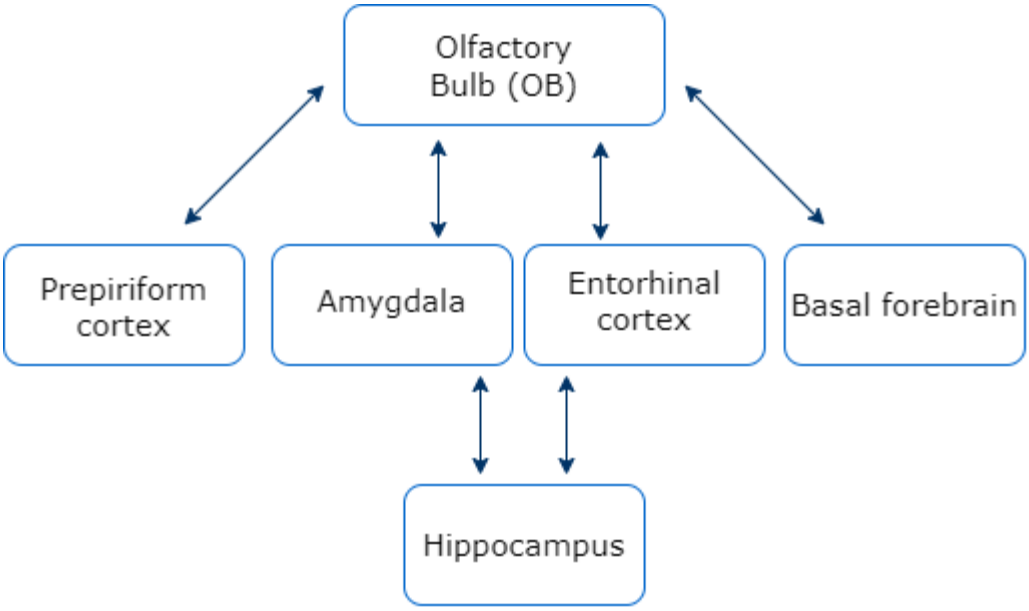

Figure 1. Brain Function. This figure demonstrates the regions of the brain are connected with one another.

Rationale and olfactory testing

Decreased olfactory function was found to be present in >50% of individuals aged between 65 - 80 years and in 62-80% of those >80 years of age (Attems et al., 2015). Olfaction and odour identification impairment has been shown to predict mortality, as the sense of smell is also very crucial to identifying gas leaks and unsafe situations (fires), and testing unsafe foods through acknowledgement of foul or unordinary odour, all of which may impact mortality rate by aiding in avoiding potentially harmful situations (Santos et al., 2004).

Dysfunctional olfactory function caused specifically by age was most commonly detected through olfactory assessment tools measuring odour detection, identification and ability to discriminate between smells (Yahiaoui-Doktor et al., 2019). Tools used to assess these areas are predominantly used on the elderly (aged 60 years and older) as many structural changes

occur in the nose of an aged individual; mucosal blood flow is decreased, airflow fluctuates, the mucociliary function is impaired, etc which may contribute to the loss in sense of smell (Doty and Kamath, 2014). Similarly, the volume of brain regions, including the OB has been established to deteriorate with age suggesting potential impacts to the efficiency of olfactory processing.

Not only has this been widely established in the literature, but is also commonly acknowledged in the medical field and by the general public, and therefore was consistent across all studies. Lower scores in olfactory assessments across studies suggested a direct relation to the impact of an ageing body and brain, (Olofsson et al., 2021) commenting that diminished olfactory system efficiency was due to age-related reductions.

In modern times, with greater technological advancements standardised tests rating an individual's odour identification ability have become available for purchase and usage. The measurements provided may be a useful tool as an accurate predictor for cognitive decline, AD, and mortality in senior adults (65+). It has been widely researched that decreased olfactory function also impacts nutritional status as well as everyday safety and is associated with increased mortality and overall quality of life (Boesveldt and Parma, 2021).

Current neurobiological markers are both expensive and invasive therefore to counter this, new clinical trials are both less invasive and are available at a much cheaper cost, both of which are seen as important factors for testing the general population. One example of these newer testing kits is the 'UPSIT': (The University of Pennsylvania Smell Identification Test) which is a book comprised of 40 pages, each of which has an odour microencapsulated within

a rectangle on the page (Morley et al., 2018). Individuals are asked to scratch with a pencil which causes the release of an odour and is then asked to correctly identify the scent amongst four given written choices. Correct identification leads to a score of 1, whereas incorrect identification leads to a score of 0, the total score ranges from the lowest score of 0 (no correct answers) to the highest of 40 (all correct answers). The process is relatively simple and is completely non-invasive, additionally due to its small size when compared to the complex and heavy machinery (structural imaging - MRI scans), it is comparatively less expensive to manufacture and could be replaced on a massive scale for easy purchasing.

"Sniffin' Sticks" are another common olfactory assessment tool that measures nasal chemosensory performance (Rumeau et al., 2016). It is a tubular device that dispenses various odours that test for odour threshold (n-butanol), odour discrimination (16 pairs of odourants, forced-choice questioning) and odour identification (16 common everyday odourants, forced-choice questioning) to establish the level of olfactory function. Each tube contains both an antibacterial agent, and 4 mL of odorant fluid or odorant material in propylene glycol, and individuals will be asked to correctly identify the odourant, without the visual aid of the pens. The total score is the sum of all correctly identified odours, and scores will range from 0 (no correct answers) to 16 (all correct answers).

The importance of olfactory function cannot be understated, with recent research suggesting a link between early stages of neurodegenerative diseases and dysfunctional olfactory function resulting in observable smell loss, the possible implications of this information and potential

of earlier AD and PD detection are crucial information contributing towards aiding the clinical health field

Olfactory function and memory

A proper olfactory function that provides the ability to smell and distinguish odours has many real-world applications often overlooked in favour of generally more easily observed abilities but it is still a factor considered very impactful to human health and function.
The smell is one of the five senses (sight, touch, hearing, taste and smell) that are integral to human function, and greatly affects the overall quality of life, commonly in aspects not immediately understood to be crucial. These include being an early alert of dangers such as spoiled or perished foods or goods, and gas leaks or fires.

The importance of smell on tasting and experiencing food is often understated, though the tongue can distinguish different qualities from understanding when a certain meal is sweet, salty, sour, bitter or umami, the smell provides a dominant influence on how we perceive what we are eating. This is more so evident when we are unable to taste as strongly due to the blockage of the nose, or similar illnesses, demonstrating how strongly our sense of smell changes how we recognise and regard food.

The sense of smell is also strongly linked with memory, due to the closeness of the olfactory processing system and the memory processing system. This linkage is so powerful that specific smells can trigger a memory vividly. Due to the closeness of the OB and the memory,

many significant experiences are tied to our sense of smell, this may include a favourite homemade dish, to the smell of a well-loved toy. The association between memories and smell is powerful and well established, particularly in schemas relating to food (such as salivation as a response) or simply the identification and recognition of scents.

The limbic system receives olfactory signals from the brain very soon after a scent is detected, Dalton and Maute (2018) demonstrate this by conducting an observation regarding how well participants were able to recognize and recall faces. These findings suggest that participants were more likely to recall faces when the same odour was also present when participants were first exposed to the faces, indicating how recalling information may be strengthened with the presence of odours.

Despite not having the most complex or sensitive noses, humans can recognise, identify and distinguish an extremely broad range of thousands of different smells.
Sense of smell is important to how we interact with our environment. We often wear perfumes and deodorants to become more appealing to others, but also uncomfortable when too many fragrances or particularly strong scents are exposed to our senses. The ability to identify fear through smell has been noted in scientific literature and has been suggested to have been linked with human evolutionary fight or flight reactions, suggesting that the olfactory system has previously played a role in humans learning fear (Taylor et al., 2020).

The evidence for olfactory dysfunction as an impact of neurological diseases is widely supported and olfactory training itself is effective in combating olfactory disorders.

Additionally, olfactory dysfunction has recently been receiving more attention in the scientific and medical communities which have greatly contributed to possible treatments and breakthroughs. Olfactory assessments have demonstrated some promise as an effective tool for assisting in early diagnosis, as a biomarker for identification and recognition of the progression of dementia.

At some point in human life, almost all individuals will experience some form of disruption of olfactory perception, often being noted as a common side effect for infections, particularly relating to sinuses leading to inflamed nasal cavities, runny noses and nasal congestion all of which greatly inhibit the sense of smell.

Dementia can be potentially reversible if caught early, and once severe not only greatly affects memory and processing for the individual but is also very painful for loved ones to endure. Because of the severity and seriousness of the condition, knowledge surrounding dementia is valuable to both scientific research and medical application societies. Due to the nature of this current study's focus surrounding the early stages of neurodegenerative disorders, possible findings could be greatly beneficial for strengthening arguments for the sense of smell and olfactory function as biomarkers.

Research conducted by Dintica et al., (2019) added to knowledge surrounding olfactory dysfunction and its possible association with further cognitive decline and neurodegeneration. They assessed the olfactory function of 380 older participants (mean age of 78 years), who did not currently have any form of dementia. The authors used the Brief Smell Identification Test

(B-SIT) at baseline to categorise normal olfactory function, anosmia (total loss of olfactory function) and hyposmia (impaired olfactory function); participants were followed up for 15 years and had cognitive function annually assessed with 21 tests. Results show that both anosmia and hyposmia were associated with a faster rate of cognitive decline when compared to normal olfactory function. This was also reflected in MRI scans which revealed impaired olfaction was additionally associated with a smaller volume of the hippocampus, entorhinal, fusiform and middle temporal cortices. This suggests that it is possible to predict future cognitive decline even before the development of dementia.

Causes of Age-Related olfactory impairment

When commenting on past research Yang and Pinto (2016) state findings that suggest olfactory issues may be relatively common in the overall population (24.5%) and is significantly more frequent in the elderly community (up to 70%). They further report that AD is among the first and earliest olfactory impacting neurodegenerative diseases that begin to develop, and its influence is therefore so widely established in research.

Tau is proteins found in brain neurons that aid in maintaining stabilisation of microtubules that regulate and protect cell cytoskeleton and can accumulate insoluble clumps due to over increased activity of tau kinases. Serrano-Pozo et al., (2011) report the significance of neurofibrillary tangles (NFTs) inside the OB and its correlation to AD in ageing individuals. NFTs are abnormal formations of tau which collect within the neuron and may subsequently cause neuron death, and has been known to be found in patients with dementia, and

specifically with AD. The volume of NFTs (abnormal tau) is directly linked with the stage and severity of dementia.

Arnold et al., (2009) comment that early studies into AD found pathological phosphorylated tau filaments within the olfactory epithelium, and in turn gave birth to the potential of diagnosing AD through the use of biopsy of the olfactory epithelium, however, these results were unable to be repeated in subsequent studies. Alzheimer-type changes such as senile plaques and NFTs appear in the brain during ageing Lim et al., (2013) and report that approximately 86% of subjects aged 74.3 ± 1.75 years have NFTs in their OB, whereas approximately 33% of them show the presence of amyloid deposition, which are central neuropathological abnormalities.

O'Brien et al., (2011) and report on the significance of the OB, which is one of the earliest areas in which changes caused by AD begin to appear, and maybe contribute to age-related olfactory dysfunction. Diverted olfactory fibres that enter deeper areas of the OB and ectopic glomeruli (glomeruli formed outside of glomerular layer) can both be seen in AD and may damage olfactory processing by altering the synaptic organisation which ordinarily would aid the formation of connections between neurons and in turn the transmission and processing of neural information (Hoogland et al., 2003).

Literature Review

Though a decrease in olfactory function has been widely researched in regards to individuals with neurological issues, Al Aïn et al., (2019), notes that olfactory training on the healthy population is not as extensively established. To further investigate the nature of the olfactory function and if it could be improved, the researchers conducted a well-controlled, 6-week olfactory training programme on 36 healthy participants who were then split into three groups, each containing 12 participants. The first group of participants experienced daily 20-minute training that included an odour intensity classification task, odour quality classification task and a target odour detection task. The second group of participants simply underwent an equivalent visual control training, and the third group did not undergo any olfactory training to serve as a control group. Findings suggest that participants in the first group did see improvements in olfactory function, and in particular in odour identification, which further aligns with the structural magnetic resonance imaging (MRI) used to showcase an increase in cortical thickness in the right inferior frontal gyrus, the bilateral fusiform gyrus and the right entorhinal cortex. This research proposes that training an individual's olfactory function may show an improvement in identifying odours and smells, and similarly but may cause a change in the physical difference in the brain's structure.

Murphey (1999) comments that patients with AD do show neuropathological changes in areas significantly linked to olfactory function, demonstrating the importance of using assessment tools to investigate any olfactory changes within patients. Murphy also states the similarities in neuropathological changes seen in individuals with Down's Syndrome over 40. The author

investigates assessing olfactory processing and function by testing the olfactory threshold, odour identification, odour similarity judgements, odour recognition memory, odour recall, and odour fluency of both patients with AD and individuals with Down's Syndrome. Findings show a significant decrease in olfactory function in both patients with AD and individuals with Down's Syndrome, also suggesting that certain areas were more heavily affected than others within the early stages of the neurological process. This indicates that decreased function would continue to occur over time, in correlation to later stages of the process, and demonstrate an association with falling DRS scores. The author also mentions that when comparing these results to those obtained from patients with Huntington's Disease, while also showing some olfactory function impairment, the degree of which decreased impact differed from individuals with cortical dementias concerning the assessment tasks.

Kondo et al. (2020) comment that as humans grow older, functions in our body and brain begin to deteriorate, including sensory systems and taste, smell, hearing, and eyesight. The authors reflect on previous epidemiological studies which found that olfactory function naturally begins to decrease rapidly at the age of 60, additionally, they note that frequently males are more greatly affected than females, and unhealthy habits such as smoking and heavy alcohol use, as well as sinonasal diseases have also played a large part in the impairment of the olfactory function. The authors state that when investigating research on animals, though studies have established that the peripheral and central olfactory nervous systems are affected with older age, the pathophysiology surrounding decreased olfactory function in humans is not as widely researched. What has been studied and found, is both the loss of mature olfactory neurons and basal cell proliferation within the olfactory neuroepithelium that resides in the

nasal cavity of aged individuals. Similarly, there is also a decrease in the turnover of interneurons within the OB and decreased activity within the olfactory cortex where olfactory stimulation is found. The authors state that though no evidence-based pharmacotherapy has been established to help improve age-related decrease in olfactory function, current findings may suggest that olfactory training using odorants may be beneficial in the improvement of certain aspects of olfactory impairment.

Luzzi et al., (2007) studied the three major aspects of olfactory testing; odour discrimination, naming, and matching, and compared these in individuals with four distinct types of neurodegenerative disorders; semantic dementia, frontotemporal dementia, dementia caused by AD, and corticobasal degeneration. Findings suggest that despite having normal levels of discrimination, individuals with semantic dementia were considered to also have severe olfactory identification impairment, whereas the poor odour discrimination in individuals with AD was suggested to be due to a perceptual impairment. Both frontotemporal dementia and corticobasal degeneration individuals were found to have mild impairments in odour identification which were expected with their generalised executive dysfunction. The authors conclude by suggesting olfactory dysfunction can occur at a semantic or a perceptual level with associative (inability to recognize due to perceptual processing) or apperceptive (inability to recognize not due to perceptual processing) forms of visual and auditory deficiency.

Kovács et al., (2001) propose that the most heavily impacted areas of hyposmia and anosmia within neurodegenerative disorders are majorly interconnected with the central olfactory system rather than being majorly interconnected with sensory regions that lack olfactory

connections. Despite the knowledge, OB is the olfactory pathway's first synaptic relay, and the authors state the inconsistent results of prior studies in AD. By analysing 15 individuals with AD and comparing the findings to 15 healthy controls, the authors found developed NFTs in both groups, whereas amyloid deposition was primarily found in individuals with AD. Furthermore, amyloid immunoreactivity was detected in the compact, primitive, classical and diffuse deposits in individuals with AD, compared to their control group counterparts which were contained in mainly difficult deposits. Final results not only suggest that earlier pathology in the OB provides a source of early NFT development, but added that the emergence of more than 10 NFTs can be potentially compatible with an approximately 93.3% accuracy in an AD diagnosis.

Gudziol et al., (2013) further researched the effect of traumatic brain injury (TBI) on olfactory function and found that TBI can cause olfactory dysfunction and loss. The authors carefully studied the prevalence of olfactory loss in 110 patients with TBI within the first 3 months after trauma, who were divided into two groups. The first group, consisting of 81 patients had both their odour threshold and odour identification tested through the use of validated "Sniffin' Sticks", the second group consisting of the remaining 36 patients had their prospective change of olfactory function tested through discrimination, validated odour threshold and identification tests. Findings demonstrate that olfactory function was significantly poorer in patients with TBI II° and TBI III° when compared to patients with TBI I. Additionally, 36% of patients were found to show clinically significant olfactory function improvement, most commonly shown during the first 6 months after trauma, and in a median follow-up interval of approximately 21 months, suggesting that the window of opportunity for olfactory recovery

lies in the first 6-month window. Though TBI was not found to cause any overall major effect on the patient's olfactory function, both TBII° and TBIII° were found to decrease the sense of smell in patients by 57%.

Olfactory ability deterioration has been shown to correlate with the early stages of neurodegenerative diseases, and in particular patients with PD and AD do begin to demonstrate losing the ability to smell prior to diagnosis (Dibattista et al., 2020). Research conducted by Dibattista et al. (2020), may suggest that olfactory neurons found in both the brain and nose may provide a greater understanding of brain physiology and pathophysiology, leading to better insight into how neurodegenerative diseases develop within our brains. The authors state that due to nasal olfactory receptors allowing for regeneration, these internal cellular systems could be mutated and changed during the development of AD. Such mutations may include the weakening and dysfunction of the odorant receptors (being unable to carry information), the olfactory epithelium (unable to correctly transfer information), axonal targeting to the OB (mistargeting leads to misinformation about odour smelled) and the formation of new neurons within the OB. The findings suggest that the olfactory system is highly vulnerable to the changes caused by neurodegenerative diseases, the most severe changes falling within the early stages of AD. The research proposes concepts around using olfactory dysfunction as a tool to gain better insight into how internal cellular systems are involved in causing and affecting AD.

Buschhüter et al., (2008) investigated the correlation between OB volume and olfactory functions of odour identification, odour discrimination and odour thresholds by conducting an

experiment involving 125 randomly selected healthy participants, with no history of loss of smell and of which were aged ranged from 19 to 79 years. Participants underwent an MRI scan to measure specific volumes of areas of the brain, a cognitive screen to ensure functional performance, and olfactory assessments specialised to one specific side of the brain at a time. Manual segmentation of the coronal slices was used as a volumetric assessment for the right and left OBs. Results show a significant association between OB volume and strength of olfactory function, as well as another significant correlation between a decrease in OB volume and participant age, thus aligning with and strengthening evidence provided by previous research. The authors note that the link between olfactory volume and olfactory function was independent of age, suggesting that though volume loss can be observed, even at an older age participants with greater volume continued to demonstrate a superior sense of smell.

Hawkes, (2006) also refers to observations made through reviewing previously published studies, and uniquely comments that the process of olfactory deterioration first begins at the approximate age of 36 in both males and females, and will continually accelerate during the ageing process, first beginning with the loss of identifying pleasant odours. Their findings demonstrate the universal nature of olfactory dysfunction, being apparent in IPD and AD and developing before other movement or cognitive disorders. The author states that diagnosis of IPD should often be prompt, as normal and healthy odour identification in the disease is often rare and unusual, with exceptions being found in female individuals who suffer from a tremor-dominant disease, commenting that it is highly unlikely patients with corticobasal degeneration or supranuclear palsy to have anosmia. These results indicate the genetic risk of the dominant ApoE4 allele and its role in developing AD (approximately 5 times as likely),

and that dysfunctional olfactory function may be seen in potential individuals with at least approximately 50% of developing PD, and in individuals with hyposmia unexplained by other means. The authors state that there is little clinical value in finding abnormalities through HC and MND smell testing as non-specific changes in AD and IPD through the removal of olfactory nasal neurons do not appear to aid in diagnosis.

Rothermel and Wachowiak, (2014) uniquely used genetically-encoded calcium sensors (GCaMPs) to observe feedback projections that were targeting the OB and in particular, found anterior olfactory nucleus (AON) projections were a major source of information guided towards the OB. Through observation, it was found that the OB is provided continuous feedback by the AON, which not only serves as a multifunction cortical area but also as a relay for the other neuromodulatory systems (regulates and modifies diverse neurons and cell activity via use of chemicals or electrical agents). Results suggest feedback was stronger while awake, but odorants were found to evoke major signals in both states of wakefulness.

Li et al., (2019) comment on this further by stating that the task of generating accurate odour information whilst under different states of brain and behaviour is the single most important responsibility of the olfactory system. They describe the importance of the OB in the initial processing stage of odour information as managing the representation of odours, and the encoding of the odour's unique identity, intensity and timing. The authors comment that currently, there have been two proposed strategies for odour representation in the OB, spatial coding and temporal coding. Spatial coding refers to specific glomeruli, the small connection of blood vessels that filter waste and additional fluids from blood, which have been observed

to form spatial maps once activated by particular and familiar odours, this has been shown to correlate to both strength of odour and the intensity of the perceived glomeruli pattern, and the process is replicated throughout many species. Temporal coding instead focuses on the particular timing which mitral cells (that carry olfactory information from the OB towards the rest of the brain) and tufted cells (processes the odour signals within the glomerulus) fire in response to odours. The importance of latency related to the first spike in response, as well as local field potential (referring to the electrical potential of neurons), neural oscillation (repetitive motion of moving backwards and forwards) in the brain and firing pattern of the mitral and tufted cells were all linked to the accuracy of the representation of odour identification and strength. The authors state that both strategies share similar weaknesses in the fact that odour representation is state-dependent, due to being sensitive to minor changes in the brain state as seen in previous studies demonstrating the significant weakening of the firing rate while under anaesthesia, and therefore showing greater consistency when completely awake. They comment that this is most likely due to the weakened concentration of feedback and centrifugal projections (the process of axons moving from ‘higher brain’ to ‘lower brain’ to the OB, however, this has not been widely researched.

Ubeda-Bañon et al., (2020) delve further into research surrounding AD and PD stating that they share similarities in their idiopathic nature and cause both cognitive and motor dysfunction. The authors continue this comparison by commenting that both are neurodegenerative disorders that become active when normal proteins (tau protein in AD and Lewy bodies in PD) become abnormally aggregated and change in size, precipitate and self-associate and in areas of the brain and the nervous system in an accumulative manner with

six distinctive stages of spread, the first of which has been demonstrated to be within the primary olfactory cortex and OB. The highly sensitive OB changes can be seen by a significant decrease in both overall volumes and the anterior olfactory nucleus' total cell count. This is further evident as it is also stated that during previous research, it was found that increased tau protein concentration in the brain was correlated with poorer odour identification scores. The authors also recall the findings of additional studies suggesting that odour identification is superior to even verbal episodic memory loss in the ability to predict future cognitive decline, further reinforcing the importance of clinical trials surrounding smell loss.

Hummel et al., (1997) conducted a study involving a group of 104 healthy participants (52 females and 52 males, mean age 49.5 years, range 18-84 years) in order to demonstrate test-retest reliability and compare 'Sniffin' Sticks' to an established measure of olfactory performance (the Connecticut Chemosensory Clinical Research Center Test, CCCRC). 'Sniffin' Sticks' are pen-like odour dispensing devices that involve 3 nasal chemosensory performance tests: smell threshold (n-butanol, testing through a single staircase), odour discrimination (16 pairs of odorants, triple forced-choice), and odour identification (16 common odorants, multiple forced-choice from four verbal items per test odorant). Correlation coefficients were 0.61 for thresholds, 0.54 for discrimination, and 0.73 for identification between sessions 1 and 2. Additionally, the test-retest reliability for CCCRC thresholds was 0.36, whereas it was 0.60 for odour identification. Results obtained from CCCRC suggest that butanol thresholds increased as a function of age, but similar results were not found for the CCCRC odour identification task. Findings suggest that the increased age of the participants

correlated with decreased performance ($p < 0.001$), and the authors conclude that 'Sniffin' Sticks' may be useful to routinely evaluate olfactory performance in a clinical setting.

To investigate the application of Sniffin' Sticks as a worldwide olfactory performance assessment tool, Mahlknecht et al., (2016) conducted a systematic review and meta-analysis of relevant data between the performance of PD patients and healthy controls in multiple countries to see whether additional cofactors may impact the test's accuracy or findings. A country subgroup analysis was carried out, as well as a meta-regression using age, gender, and air pollution as factors. Among the 66 publications included in the meta-analysis, results found that patients with PD significantly performed worse on the Sniffin' Sticks test than their healthy counterparts. The residual heterogeneity and intra-country heterogeneity were both considered to be high and was not significantly reduced following subgroup analysis by nation, indicating that cultural influence may have some form of impact on the Sniffin' Sticks findings. The authors suggest this may be due to the disparity in age and air pollution amongst the countries, which were shown to have significance in a few subtests, and are factors that can impair olfactory performance.

In neurodegenerative disorders such as AD and PD, the six levels of Braak staging, ranging from I through VI and are distinguished by their distinct distribution pattern, are used to classify the spread and position of neurofibrillary tangles in the brain (Burke et al., 2008). Neurofibrillary tangles (NFTs) are confined to the transentorhinal area of the brain in stages I and II and are established as the early stages of Braak, indicating minor and less severe changes that begin at the lower brainstem that manifest in non-motor symptoms. NFTs appearing in the limbic areas, which include the hippocampus, signify stages III and IV and

are known as the mid-pathologic stages, where prominent changes in both the transentorhinal area and the proper entorhinal cortex appear, at which time dementia becomes clinically evident and diagnosable. Finally, NFTs that have spread to the neocortical areas of the brain stages V and VI is referred to as the advanced stage and signify the loss of all isocortical association regions, leading to further difficulty making connections between sensory information. With severe neuron and cell death, these final stages are the most fatal.

AD and PD are notably common neurodegenerative diseases, with PD affecting at least 1% of all individuals aged 60 and older (Reeve et al., 2014). A defining factor in both these diseases includes dementia, which greatly reduces the brain's cognitive abilities to a degree in which it impacts daily life and activities. The severity of dementia's symptoms reflects the stage of progression. but are established to often include significant decreases in visual perception, judgement, attention, comprehension, reasoning, and most commonly memory loss. Dementia also occurs more frequently in the over 65 age group but has shown to start developing as early as 45 years old, demonstrating its wide and common prevalence in the general population, and adding to the seriousness of the disorder. These diseases may be unnoticeable for many years, with individuals noticing and discovering them in many later stages, therefore preventing an early or timely diagnosis, in turn affecting the treatment success rate and severity of the issue. Currently, there are a few different clinical measures for the testing of these neurodegenerative diseases, such as structural imaging through computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography (PET), however, they sustain high expenses, can often become a lengthy process and are assessed at a very invasive level to the individual.

We expect results to further strengthen knowledge already previously published which have laid the groundwork into establishing the link between the OB, olfactory function, sense of smell and the changes made to these aspects during neurodegenerative diseases. We expect these results as scientific literature has already established the importance of the OB volume, and its correlation with the dysfunction of olfactory function. Due to the sense of smell decreasing in strength and function as a direct consequence of the impact and overall volume loss of the OB, the sense of smell, therefore, becomes important as a potential early detector. Because the olfactory system is directly responsible for the sense of smell and is highly sensitive to neurological changes in the brain, the importance of the OB is evident. Due to this understanding in volume correlation, an increase in this volume would then allow for greater olfactory function, and as some studies have suggested, the sense of smell could be improved by training, and in turn increase the olfactory volume through the use of trials and tools, helping to combat olfactory loss.

Recent diseases and viruses, such as SARS-CoR-2 (Covid-19) inhibit a loss in taste and smell, and by understanding why these may be the case, we can create more tools for the early detection of new viruses in individuals. This also serves as a demonstration of how future diseases may also benefit greatly from the knowledge researched in this paper.

Methods

The preferred reporting items of systematic reviews and meta-analyses (PRISMA) guidelines (Moher et al., 2009) were used as protocol markers for conducting the systematic review. This begins with a search of eligible literature, followed by the assessment of the quality of the literature, and data collection. Finally, the study findings are analysed and interpreted and recommendations for future and further research is considered.

Published scientific literature and past research were gathered and selected to be analysed and reviewed. To determine the eligibility of each academic journal, publications were chosen on their focus and theme around olfactory function, neurodegenerative diseases/disorders, sense of smell and dementia. Publications were excluded if research was not peer-reviewed, or not conducted in the past 10 years to avoid outdated or disproven information. No country of article publication was excluded; however, literature must be published in the English language.

To assist in finding relevant literature, the tag search on article publisher sites and engines (PubMed, Google Scholar, Medline) were used to input keywords. Different literature methodology was considered to ensure that observational studies that may assess new olfactory testing methods, and literature studies that would provide stable and conclusive evidence were both included.

To break down the total of (25) studies analysed, (14) were observational studies involving consenting participants, the remaining (11) were literature reviews that used data from existing materials similar to the current study's methodology. Out of the 14 observational studies, 7 centred around using Cognitive assessments in the forms of various MRI scans of the volumetric measures of the brain regions, 5 focused around using olfactory assessment tools to judge the sense of smell and neurodegeneration process, 2 used cell count analysis to study the protein depositions in post-mortem human brains which would not be ethically viable if subjects were alive. Out of the 11 literature reviews, 7 focused on olfactory function as a predictor, 2 researched PD discrimination, 1 centred on brain scans as predictors and 1 focused around the spread of NFTs and Lewy bodies in the brain as a measure of neurodegeneration.

Two major themes that were prevalent in exclusion were research articles that were considered outdated, or research that focused on non-human brains (typically research in rodent models). Though commonly, behaviour in animals will be generalised to the human population, and although similar findings were suggested in animals that suffered from olfactory dysfunction as suggested in the literature review, due to the sensitive and unique nature of the makeup of

the human brain, data was specifically collected from human participants. Because the link between neurodegenerative diseases and olfactory function has primarily been recently established and researched in the scientific community, it became apparent that only studies from the past 10 years would need to be considered, as often before the previous decade, information is more speculative, and very outdated due to low engagement on the topic by the scientific community.

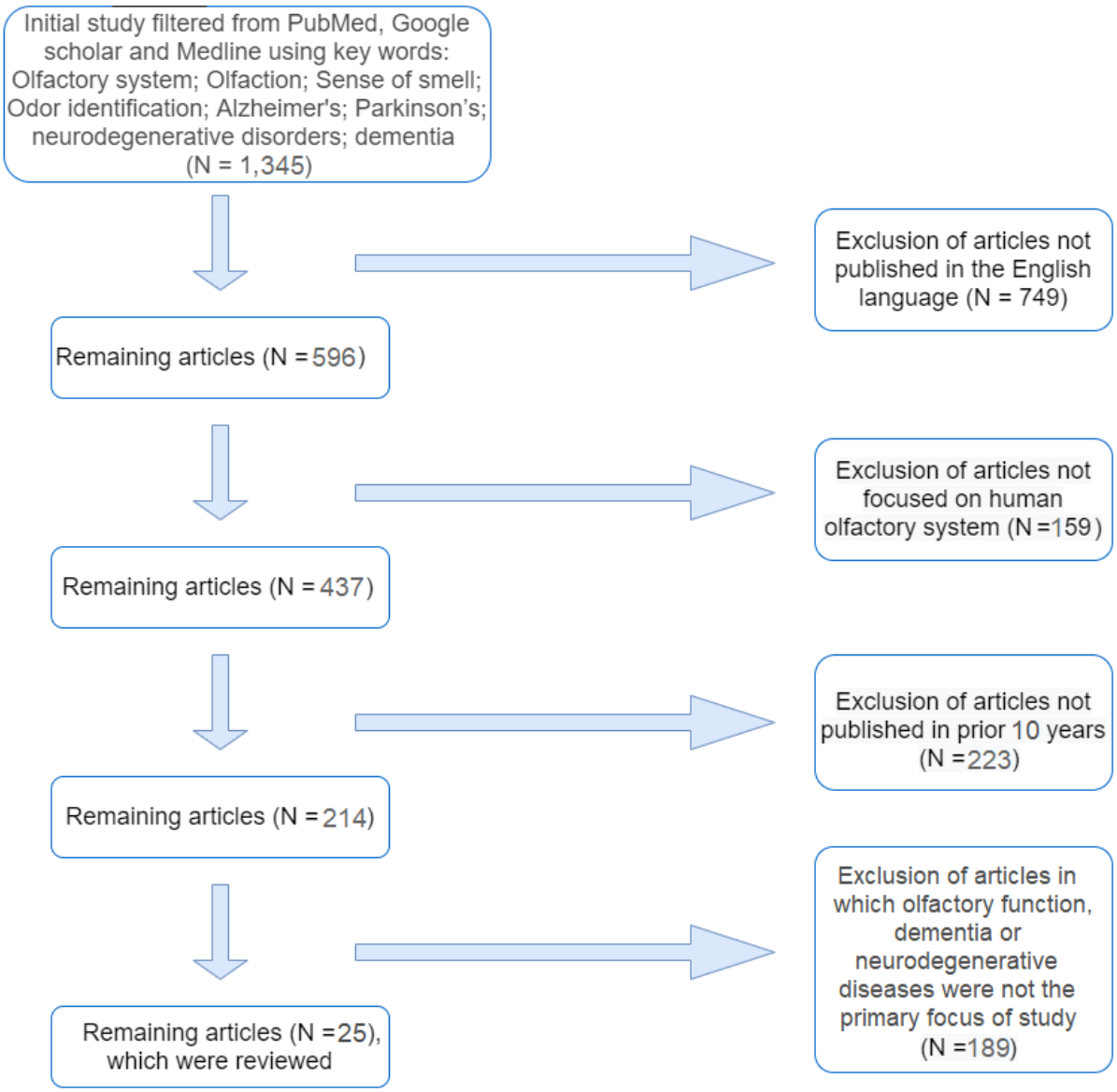

Figure 2. Exclusion Criteria. This figure demonstrates the exclusion criteria performed in the current study.

Results

To assess olfactory function tests. Yu et al., (2018) compared olfactory dysfunction (OD) ratings from self-report, the Hyposmia Rating Scale (HRS), and the Sniffin' Sticks test. 60 patients with AD dementia, 37 patients with moderate cognitive impairment related to AD (MCI), and 30 healthy controls were recruited to investigate the association between OD and clinical symptoms of AD and were categorised into AD with OD (AD-OD) and AD without OD (AD-NOD) groups. The frequency of OD based on self-report in the control, MCI, and AD dementia groups was 10.0%, 13.5%, and 18.3%, respectively, whereas based on HRS they were; 6.7%, 24.3%, and 48.3%, respectively. Finally based on the Sniffin' Sticks test they were; and 3.3%, 13.5%, and 65.0%, respectively. The diagnostic coincidence rates of OD by HRS in individuals with MCI and AD dementia were 89.2% and 66.7%, respectively, when compared to the findings of the Sniffin' Sticks test. When compared to the AD-NOD group, the scores for attention, visuospatial ability, cognition and memory were all lower ($p<0.05$), whereas apathy ($p<0.05$) and activities of daily living were both higher ($p<0.01$). Though the prevalence and accuracy of OD by self-report are both low, these findings suggest that HRS has the potential to be used as an olfaction test in individuals with MCI caused by AD, and similarly that the Sniffin' Sticks test shows promise in validating OD in AD patients due to their overall decrease in olfactory threshold, discrimination and identification abilities.

Hummel et al., (2011) investigated the link between OB volume and olfactory processes such as odour threshold, odour discrimination, and odour identification in children and adolescents to further explore the volumetric growth of the OB. MRI scans and lateralized olfactory testing was conducted on 87 participants ranging in age from 1 to 17 years old (with an average age of 8 years) and manual segmentation of coronal slices across the OB yielded volumetric measurements of the right and left OB. Results indicate that no participants presented any evidence of olfactory decline or impaired sense of smell, though a significant relationship between OB volumes and olfactory function was found. Although the correlation between structure and function was not mediated by the participants' age, both OB volumes and olfactory function increased with age, suggesting that the link between OB volume and olfactory functions does also present in children.

To study PD, Wang et al., (2011) similarly used MR imaging, but uniquely combined their methodology with Japanese T&T olfactometer threshold testing (Saiki et al., 1994) to perform morphometric analyses. Patients and their healthy counterparts both had their olfactory structure evaluated with an olfactometer threshold test, which revealed olfactory recognition thresholds were significantly greater in patients with PD when compared to healthy controls, and like olfactory atrophy causing reductions in the depth of the olfactory system along with the volume of the OB was only found in the patients with PD, and not amongst the control group. Results found indicate both groups follow the established correlations between the OB volume and the strength of the olfactory function. Finally, amongst both groups, no significant

correlation between olfactory system depth and ability to carry out olfactory function was found.

Similar results were also found in the Attems et al., (2015) study, which also reported that the likelihood of dysfunctional olfactory would increase the older the individual would age. This was stated after the identifying research suggesting more than half the population of individuals aged between 65 - 80 is likely to be suffering from decreased function, and an approximate range of 62-80% of individuals aged over 80 beings also likely to suffer from the same dysfunction. They continue to suggest that memory loss and weakening of cognitive abilities have some association with impaired odour identification, which supports the potential of using the sense of smell as early and crucial warnings indicating neurodegenerative disorders, which have been shown to impact the brain and damage olfactory function. Neurodegenerative disorders that lead to dementia such as AD and PD were found to be warranted as potential early identifiers in particular, as both dementia and a decrease in cognitive abilities are common symptoms that continuously worsens as the disease develops. Findings very conclusively point to the decreased quality of life suffered by individuals with impaired olfactory function, and results also may suggest that decreased olfactory function may quicken the progression of dementia in the brain of individuals with AD and PD who already suffer from mild cognitive impairment.

MRI scanning was similarly used in Al Aïn et al., (2019) to observe any potential changes in the cortical thickness and tissue density in participants who were exposed to repeated intensive odour identification training for 6 weeks. In a similar fashion to previous studies, MR imaging

was successful in finding notable differences, in particular, the authors found that following the training, the cortical thickness was increased in the right inferior frontal gyrus, the right entorhinal cortex and the bilateral fusiform gyrus regions of the brain. Participants also were observed to have significantly greater olfactory sensitivity further emphasising the association between olfactory function and structural changes in areas of the brain that correlate to olfactory processing.

Barresi et al., (2012)'s findings focus on the new instrumental approaches to diagnosing PD and AD, commenting that though the inability to discriminate and identify odours has been noted to be a potential early manifestation, it may still not be diagnosed in time to prevent late-stage development. Through the support of the olfactometer (an instrument used for measuring the sensitivity and intensity of odours) psychophysical testing has entered new potential in the form of functional magnetic resonance imaging (fMRI) and olfactory event-related potentials (OERPs), which uses electrophysiological methods to observe changes in olfactory function, via activation of brain areas including the regions of the temporal lobe, the amygdala and mid-OFC and insular cortex. Results show that this is highly effective and allows analysis of subjects without inherent individual response bias, and aids investigation when individuals have difficulty responding. Both show promise as potential candidates as clinical tools for early-stage diagnosis in neurological diseases.

Attems et al., (2014)'s research findings suggest that the major factors of neurodegenerative associated olfactory dysfunction are the olfactory tract, OB and the primary olfactory cortex, which is responsible for the learning and recalling of odours. They state the primary factors of

olfactory dysfunction as linked to pathological proteins, including the neurofilament, tau and α-synuclein proteins, further commencing that neuroinflammation induced by changes in the molecular process, often will lead to cell death caused when the cellular process is disrupted, these brain changes are often heavily associated with severe anosmia. Findings from investigating pathophysiological modifications in the brain in individuals suffering from common neurodegenerative disorders (AD) (mean age 81.3) reveal that severity in neuropathological changes in the olfactory tract and bulb were significantly ($p < 0.001$) correlated with increased neuritic Braak stages (classifiers to distinguish stages of AD and PD), with later stages being established as having a greater spread of the disease within the brain. The Braak stages additionally signalled greater Lewy body and tau protein pathology.

Kotecha et al., (2018) comment on the continuously increasing average global life expectancy, suggesting that the likelihood of AD may become more prevalent due to more individuals living to their senior years, evident by the increasing number of global AD cases in the ageing population. They state the urgency of administering effective interventions as early as possible and carried out a meta-analysis to analyse the credibility of preclinical testing olfactory function in the diagnosis of AD by contrasting individuals with AD and mild cognitive impairment (MCI) with healthy controls. The authors were able to identify that as MCI develops into AD, and that olfactory dysfunction in patients reflects this by progressively becoming worse, which showcases the ability to accurately test and recognize declined olfactory function, thus supporting the potential of using dysfunctional olfactory ability as an early identifier of preclinical AD.

To evaluate the odour identification ability of Sniffin' Sticks and determine whether the tool would reliably and accurately be able to identify PD, Mahlknecht et al., (2016) conducted a study involving 646 PD patients and 606 controls alongside 75 patients with atypical parkinsonism or essential tremors and 24 patients with idiopathic rapid eye movement sleep behaviour disorder. Findings show that in all cohorts, olfactory performance was inferior in PD patients compared to controls and non-PD patients ($p < 0.001$). The findings from Sniffin' Sticks were able to very easily discriminate performance from the PD and their healthy control counterparts, and this remained unchanged when individuals with a disease duration of more than three years were eliminated from the study, indicating a strong association between PD and impaired sense of smell. The authors conclude by stating that odour identification testing has a high diagnostic accuracy in distinguishing PD patients from controls and diagnostic mimics (atypical parkinsonian), and has the potential to become a cheap, quick and consistent tool to identify PD.

Carnemolla et al., (2020) conducted a systematic review to investigate the possible linkage between olfactory function and Frontotemporal dementia (FTD), which the authors state is often difficult to diagnose due to symptomatic overlap with other psychiatric disorders. The authors examined 74 papers to explore the changes in olfactory dysfunction patterns, with a focus on the most prevalent smell measures: odour identification and discrimination. Results show that FTD patients were significantly impaired in scent identification but not in discrimination; in contrast, other psychiatric disorders showed (such as depression) showed no olfactory abnormalities, or a distinctively different olfactory pattern (impaired in discrimination, but not in identification). Due to the high incidence of scent identification

defects in FTD, and further support in the evidence that smell dysfunction predicts neurodegeneration in other illnesses, the authors conclude by suggesting that olfactory testing does appear to be a viable route for supporting an earlier FTD diagnosis, and in particular aiding in discriminating against other psychiatric disorders.

Velayudhan, (2015) reviewed articles to confirm the notable impairment in olfactory function in individuals with AD when compared to their healthy control counterparts and additionally found research suggesting that poor olfactory function could serve as a marker for the progression from MCI to the development of AD. This potential is noted due to findings suggesting that severity of AD, both structural and functional MRI measures and non-cognitive neuropsychiatric symptoms are all associated with the strength of the odour identification function. Finally, this study also comments on the interaction between the apolipoprotein E genotype (APOE), and its potential risk factor in developing both dementia and AD by stating an association is present.

Brodoehl et al., (2012) comments on the neuropathological similarities in the dysfunction olfactory system among affected individuals with PD and states that MRI has not been a consistently accurate method in PD volumetric loss of the OB. To remedy this, the authors use a 3.0-Tesla MRI constructive interference to evaluate potential volumetric loss in individuals with PD to compare against a healthy control group. Results found a significant loss of OB volume in patients with PD when compared to the control group, the findings consistently note in particular that an observable decreased height was routinely found within the left OB

showcasing a consistent and observable difference, suggesting a potentially reliable parameter for clinical investigation in patients with IPD.

Velayudhan et al., (2015) additionally tested olfactory assessment tools as a potentially useful diagnostic aid for AD, focusing on determining the pattern of the type of odour affected in individuals with AD, to improve clinical applicability. Using UPSIT, 54 outpatients aged 40 years and older that suffered from mild to moderate AD were tested against gender-matched healthy controls, data was then analysed to determine the most optimized subset of UPSIT that could accurately distinguish AD outpatients from healthy non-demented controls. A total of 12 UPSIT components were found using a Random Forest with a backwards elimination method that reliably and consistently discriminated between AD outpatients from healthy controls (sensitivity, 0.89 and specificity, 0.83, positive predictive value of 0.889, and negative predictive value of 0.833). The authors state that these 12 smells that were shown to be most affected within AD outpatients reflect traits such as food and safety, which are frequently known to be affected in people with AD, and may disrupt daily tasks, but could potentially be used to create a quick scale for detecting AD in clinical settings.

Wesson et al., (2011) comments that abnormal odour investigation, odour discrimination and odour habituation (short-term memory), are major aspects of olfactory impairment, connecting to previously established studies, which used olfactory testing tools aimed at assessing these areas. Findings suggest that amyloid deposition occurs firstly in the OB, and then is followed by developing in the olfactory cortex and finally hippocampus. These imply that amyloid deposition in these areas may play a role in olfactory impairment in both early and later stages

of life. The authors comment on the significant prevalence of anosmia in other dementias, including PD, frontotemporal dementia, and Lewy body disorder, suggesting that through olfactory impairment alone current measures are insufficient as a specific diagnostic for AD. However, if combined with other potential markers, olfactory screening for AD could improve diagnostic sensitivity, because they are noninvasive and reflect accurate functioning of brain regions affected in the early stages of the disease.

Links have also been found between dementia and hearing, vision and taste (Behrman et al., 2014), and results found by Behrman et al. through review of established literature suggest that individuals suffering from dementia have more trouble recognising and identifying odours than they do detecting them, hinting at a relationship with higher cognitive function. The authors further state that with approximately 85.2% sensitivity, olfactory function impairment has been found to predict development from moderate cognitive impairment to the progression of AD. They conclude by stating that to aid in the care of individuals with dementia, sensory considerations should be expected to play a larger role in the future.

Recent findings by Haehner et al., (2014) through the usage of published research suggest that approximately 90% of individuals with PD struggle with significant olfactory loss, due to its bilateral and widespread nature in PD that affects all olfactory regions. The authors state the unique factors of olfactory loss in PD as being clinically measured to be independent of both disease duration and severity, though this is countered somewhat due to the authors' acknowledgements of imaging that demonstrate olfactory impairment progressing in early phases of motor development. Because these may occur before clinical symptoms appear, they

therefore may potentially be used as a predictor of the likelihood of developing PD in otherwise asymptomatic observed individuals. Findings suggest that olfactory probes show significant value in aiding early and differential diagnosis as olfactory alterations specifically found in PD may be beneficial in discriminating the disease from other potential dementia causing disorders.

Tarakad and Jankovic, (2017) comments on the established knowledge of Anosmia as a frequently appearing non-motor symptom of PD, remarking on its relation to the more under-researched linkage to ageusia (loss taste) and PD. Findings suggest that the olfactory tract is intertwined with early stages of PD, and the authors refer to evidence demonstrating occurrences of hyposmia and anosmia manifesting potentially years before motor symptoms. Additionally, autopsy studies suggest pathology in both the anterior olfactory nucleus and olfactory tract at the first stages of PD. Consistent evidence points to the strong link between olfactory loss and cognitive status, though associations with other PD features or specific PD phenotypes remain unconfirmed, but heavily debated in the scientific community. Finally, results also suggest the linkage between hyposmia, and the severity of PD, manifesting more frequently in individuals with severe cases of the PD than typically any other Parkinsonian syndromes, opening up suggestions on being used as a potential biomarker

Mundiñano et al., (2011) comment on olfactory dysfunction, stating that though typical in both AD and PD, it is considered rare in individuals with frontotemporal dementia (FTD). Mechanisms involving early protein deposition in the OB result in smell impairments, similar to what is commonly demonstrated in clinical analysis within AD and PD patients. The

authors compared the deposits of amyloid, alpha-synuclein and tau in the OB of 41 patients with a historical diagnosis of FTD (n = 11), AD (n = 24) and PD (n = 6) with the OBs of 15 healthy individuals. Findings reveal that regardless of diagnosis, tau pathology was found in the OB of all patients, whereas -amyloid and -synuclein protein deposits were predominantly present in AD and PD. Additionally, a greater number of dopaminergic periglomerular neurons (the central source of dopamine in the central nervous system) was observed in the OB of FTD, AD and PD individuals through the use of stereological techniques. Results found through volumetric measures of the OB demonstrate that only individuals with AD show a substantial decline, whereas, in FTD and PD patients, OB volume was measured to be identical to controls. The authors conclude that changes resulting in increased dopaminergic tone may be a compensatory mechanism caused by early degradation of the neurotransmitter systems, leading to the possibility of olfactory impairment in patients suffering from neurodegenerative disorders.

To investigate the links between ageing, cognitive function, and olfaction in patients with olfactory impairment, Suzuki et al., (2021) conducted a study that included 141 participants that suffered from olfactory deterioration and were diagnosed with dementia, age-related hyposmia, postviral olfactory dysfunction (PVOD) or MCI. To assess cognitive and olfactory impairment, a self-administered odour questionnaire (SAOQ), visual analogue scale (VAS), and a Mini-Mental State Examination and T&T olfactometry assessment were all performed on the patients. The T&T measures odour thresholds through the amount of odorous substance required to elicit a response, the lowest concentration amount is scored at -2, and the greatest concentration amount is scored at 6. The results indicate that T&T odour recognition

thresholds decreased with both age ($p < 0.01$) and cognitive impairment ($p < 0.08$). Patients with dementia required the greatest average T&T concentration threshold at 5.1 ($p < 0.05$), whereas for patients with MCI, PVOD, and age-related hyposmia the average recognition thresholds were 4.6, 3.7 and 4.2, respectively. Additionally, the greatest average differences between detection and recognition thresholds were also found amongst dementia patients at 3.7 ($p < 0.05$), whereas in patients with MCI, PVOD and age-related hyposmia, the average differences were 2.8, 2.3, and 2.0 respectively. When compared to the other groups' averages, hyposmia with dementia had the highest SAOQ and VAS scores ($p < 0.05$). With greater differences between the T&T detection and recognition thresholds indicating greater olfactory impairment, the authors conclude that patients with hyposmia should be analysed for dementia, including those who scored high SAOQ and VAS averages.

Devanand et al., (2014) analysed the predictability of AD and future cognitive impairment through assessing the odour identification abilities in 1,037 participants with the UPSIT, follow ups were also carried out at 2 and 4 years post the initial assessment. Results indicate That lower baseline UPSIT scores were correlated with cognitive decline in logistic regression analyses (relative risk 1.067 per point interval; 95% confidence interval [CI] 1.040, 1.095; $p < 0.0001$), and remained significant after covariates were included (relative risk 1.065 per point interval; 95% CI 1.034, 1.095; $p < 0.0001$). The authors state the strength of UPSIT's ability to predict cognitive decline in participants, which did not require baseline cognitive impairment, and was reflected in the follow-up assessments, finding 101 participants having transitioned from poor cognitive ability to an AD diagnosis. Lower baseline UPSIT scores were additionally correlated with AD transition (hazard ratio 1.099 per point interval; 95% CI

1.067, 1.131; $p < 0.0001$), and remained highly significant after functional, demographic and cognitive covariates were included (hazard ratio 1.072 per point interval; 95% CI 1.036, 1.109; $p < 0.0001$). These findings suggest that in cognitively healthy adults, impairment in olfactory identification showed greater predictability of cognitive deterioration than deficiencies in verbal episodic memory, supporting the potential of using relatively inexpensive odour identification assessments as biomarkers of the development of dementia and cognitive impairment.

Voegels et al., (2014) state that the majority of patients with AD and PD are unaware of their olfactory loss prior to doing an olfactory test, and reveal that 85 - 90% of patients in the early stages have an olfactory impairment. These olfactory abnormalities are generally accompanied by neuropathologic changes (NFTs) in olfaction-related brain areas in AD such as the OB, olfactory tract, transentorhinal and entorhinal cortex, anterior olfactory nucleus, and amygdala. The amount of NFTs reflects the severity of dementia and has been linked to reduced olfaction at the time of death even in individuals who neither had dementia nor MCIs. Due to the association between the sense of smell and dementia, the authors conclude by suggesting that otolaryngologists should remember the necessities of olfaction assessment in aiding diagnosis, and in general, all physicians should consider the use and benefits of olfactory screening tests.

To compare selective olfactory dysfunction and OB volume Altinayar et al., (2014) conducted a study on 41 patients diagnosed with IPD and 19 healthy age and gender-matched controls, IPD patients were classified as either tremor dominant (TDPD) (65.9%) or non-tremor dominant (NTDPD) (34.1%), and all participants completed neurological, ear, nose, and throat

exams, as well as orthonasal olfaction tests.OB volume was measured through MRI and results found that the IPD group had significantly decreased scores in the olfactory identification tests, in particular having difficulty distinguishing between the aromas of mothballs, chocolate, Turkish coffee, and soap. The OB volume levels were not significantly different between the TDPD patients and the control group, however, it was determined that the NTDPD patients OB volumes were lower than the control groups. However, when compared to their healthy counterparts, TDPD individuals showed a decreased odour detection ability. The authors state that the most common non-motor symptom of IPD is olfactory impairment and findings suggest that OBV values in all PD patients did not alter with age, duration of the disease, age at beginning of the disease, or Unified Parkinson's Disease Rating Scale motor scores (UPDRS-m). This suggests that olfactory function is a complicated process that involves both olfactory and cerebral components and therefore changes in OBV alone do not appear to be directly connected to olfactory impairment in IPD.

To investigate the link between amyloid-related depression and the development of AD, Qiu et al., (2016) conducted an observational study including 223 participants who did not have a dementia diagnosis at the start of the study, and were all given a second cognitive examination for incident AD. The genotype of Apolipoprotein E (ApoE) was established, and Non-amyloid (NAD) vs. amyloid-associated depression (AAD) was classified by having a low vs. high plasma amyloid-peptide 40 (A40)/A42 ratio, and any antidepressant use was noted. After an average of 6.2 years of follow-up, 15 participants (7% of the total count) developed AD, whereas no patients with NAS developed AD, on the other hand, 20 (9%) patients with AAD did develop AD. Additionally, ApoE4 carriers had a greater risk of AD than ApoE4

non-carriers (40% vs. 4%, $p = 0.06$) among individuals with AAD. In comparison, only 17 (8%) of individuals who did not have depression at the start of the study developed AD, although results indicate that there was no difference in AD risk between ApoE4 carriers and non-carriers. After controlling for age, the interaction between ApoE4 and AAD ($\beta = +0.113$, $SE = 0.047$, $p < 0.02$) was linked with the risk of developing AD, suggesting that AAD may be a precursor to AD, particularly when also in the presence of ApoE4.

Jobin et al., (2020) conducted a systematic review to summarise the existing understanding of the volume and cortical thickness of olfactory brain areas throughout the progression of AD. 12 papers were able to meet the strict criteria that included needing participants to already have a diagnosis of AD or MCI, a control group of the same age, the use of MRI scans to calculate cortical volume or thickness, and finally an assessment of olfactory capacities. Results were consistent, as all papers reported decreased olfactory capacities in patients (AD or MCI). Among these individuals, 8 studies found lower hippocampus volume, while 9 studies linked olfactory capabilities to hippocampal volume. The main olfactory cortex yielded similar results, although the volumes of the amygdala and entorhinal cortex are similarly changed, results on their association to olfactory ability remains inconclusive. Among the 12 papers, only a single one examined the link between OB volume and found no significant results. Olfactory measures were also linked to the volume of the pre-central gyrus, ventricles, and neocortex, suggesting that the olfactory deterioration seen in the early stages of AD may be reflecting damage already present in these stages, particularly to the hippocampus and primary olfactory cortex. The authors conclude by stating that olfactory deterioration might be an early indicator of AD.

Servello et al., (2011) investigated the role of the volume of the hippocampus and the ability of olfactory tests to predict the development of MCI into AD. The study involved using Sniffin' Sticks to evaluate the olfactory function of 18 patients with amnestic MCI (mean age 68.05 years) who were divided into normosmic, hyposmic, and anosmic groups, all of which had hippocampus volumes measured by MRI brain scans. Results found that during the one-year follow-up period, 5 MCI patients had developed AD, with an annual conversion rate of 27.7%. 4 patients (22.2%) were normosmic, 12 (66.6%) were classified as hyposmic, and 2 were found to be anosmic (11.1%). 4 out of 5 MCI patients who had developed AD showed considerable bilateral hippocampus volume loss ($1.3cm^3$), which was found to be related with poorer threshold, discrimination, and identification scores when compared to patients who did not develop AD. Findings suggest there was a statistically significant connection between MCI and hippocampus volume reduction ($p < 0.05$), additionally, 8 MCI patients (46%) had olfactory deficits in addition to hippocampus volume loss, 6 MCI patients (34%) suffered hippocampal volume loss, 1 MCI patient (3%)had an olfactory impairment only, and finally 3 MCI patients (17%) had both normal olfactory function and hippocampal volume. These findings suggest that in MCI patients who progressed to AD, there were significant olfactory threshold, discrimination, and identification abnormalities, as well as cognitive and MRI hippocampus volume reduction, implying that olfactory testing and the measuring of hippocampus volumes may be useful in the early diagnosis of AD.

Vasavada et al., (2015) conducted an observational study to investigate if structural degeneration of the primary olfactory cortex (POC) would be observable in both AD and MCI

patients through functional magnetic resonance imaging (fMRI) scans. The process involved 27 cognitively normal (CN), 21 MCI, and 15 AD participants, who all had their total structural volumes, volumes of their POC and hippocampus, as well as olfactory and cognitive behavioural functions, evaluated. Results found that both AS and MCI patient groups had significant atrophy in the POC and hippocampus. Behavioural and volumetric assessments revealed a steady deterioration from CN through MCI to AD, however, the MCI group demonstrated a quicker decline in the olfactory activation volume in the POC and hippocampus when compared to similar tissue volume in the AD group. The authors conclude by stating that the decline in olfactory activity was associated with the structural deterioration of the POC in AD patients and that within MCI patients there was a greater impairment in olfactory activity than in behavioural and tissue volume. These results indicate the potential of fMRI to produce a sensitive marker of functional neurodegeneration in patients with MCI and AD.

Discussion

The hypothesis declared at the beginning of the current study stated that a link between AD and PD development, OB volume and olfactory function (sense of smell) was expected. Findings were fairly consistent across all studies, and the main findings of the results do support this prediction as overall with (23) out of (25) studies confirming and therefore strengthening knowledge on the link between sense of smell and OB deterioration caused by neurodegenerative disorders. Additionally, there was evidence supporting the ApoE4 gene and its role in the development of neurodegenerative disorders and AD in particular. Studies that delved into the assessment of neurodegenerative disorders have provided a strong case of why olfactory testing kits should be taken under consideration when screening for dementia in higher-risk individuals, and showcased its usefulness in accurately assisting in pinpointing the stage of degeneration due to its correlation inability to discriminate and identify odours.

Our main findings suggest that olfactory function was directly correlated with the development of neurodegenerative disorders, supported by all 25 studies. During the development of these dementias, the brain will begin to deteriorate, losing many memory and olfactory functions due to the location of tau and Lewy bodies first appearing in the amygdala

and hippocampus, which are each responsible for recalling and processing memories, and the sense of smell, respectively. This is supported by findings from Jobin et al., (2020) indicating that the volume of the pre-central gyrus, ventricles, and neocortex was correlated to olfactory performance in AD patients, proposing that the deterioration of the primary olfactory cortex and hippocampus would directly reflect the severity of AD and impaired olfactory function. Attems et al., (2015) additionally comment that not only does an impaired sense of smell affect the quality of life in individuals, but may quicken the progression of the stage of dementia in AD and PD patients who also have a form of MCI. This suggestion is also supported by findings from Kotecha et al., (2018), which indicates that olfactory impairment progressively worsens as MCI develops into AD. This aligns with findings from Behrman et al., (2014) which imply that an individual's olfactory performance is able to predict their potential transition from MCI to AD with an approximately 85.2% sensitivity, showcasing the reliability and accuracy of using impaired olfactory function as a biomarker for the development for AD. This is also true for FTD, as findings by Carnemolla et al., (2020) showcases individuals diagnosed with FTD also possessing greater instances of odour identification defects. Additionally, this was also evident with patients suffering from PD as evident by results from Tarakad and Jankovic, (2017) and Suzuki et al., (2021) indicating that hyposmia would manifest more frequently in patients diagnosed with more severe cases of PD, and therefore individuals with loss of smell should also be assessed for dementia.

The correlation found between the sense of smell and neurodegeneration further highlight our results indicating the potential of using olfactory ability testing as an early identifier of neurodegenerative diseases, this is reinforced by results from the Mahlknecht et al., (2016)

study, which demonstrates the strength of Sniffin' Sticks as a highly accurate, fast and inexpensive tool that is able to identity PD due to the strong association between PD and impaired olfactory function. This aligns with findings suggested by Devanand et al., (2014) which reveal that even in adults with normal cognitive ability, the UPSIT was able to predict cognitive deterioration more effectively and accurately than impaired verbal episodic memory, as the UPSIT scores were directly correlated to MCI to AD transition 2-4 years prior to diagnosis, indicating the strength and potential of odour identification measurements as early biomarkers of cognitive decline and dementia. The potential of the UPSIT is additionally reinforced by results found by Velayudhan et al., (2015) which indicate that the test was able to pick up on the 12 odours which affected AD patients the most, and therefore could be used for a rapid clinical scale for AD detection due to the frequency and effect of these scents on individuals who have or are developing the disease. Findings by Haehner et al., (2014) strongly imply that due to the olfactory abnormalities specific to PD being an early indicator of the disease, olfactory assessments are highly useful in distinguishing the disease from other dementia-causing conditions and aiding early and differential diagnosis. Results found by Wesson et al., (2011) supports using olfactory impairment tests, which possess both accurate readings of brain function and high diagnostic sensitivity for AD in combination with other markers to create an accurate measurement of other dementias, and reflects on the noninvasive nature as beneficial and less threatening for many patients.

The findings surrounding OB volume somewhat imply a relation to neurodegenerative disorders, however, findings from Altinayar et al., (2014) suggests that OB volumes do not appear to correlate with IPD, as individuals with NTDPD had an observable volumetric loss,

but did not perform significantly differently from the control group, whereas individuals with TDPD demonstrated a weaker performance, but no difference in OB, additionally OB volume did not significantly change during the duration of IPD or age of the patients. Wang et al., (2011) report that both reductions in both the depth of the OB volume and system were found in patients with PD and that a correlation between the OB volume and the strength of the olfactory function was found. These support findings by Buschhüter et al., (2008) implying that a greater sense of smell was observable in individuals with greater OB, additionally a significant correlation between age and decreased OB volumes was found, which may suggest why the elderly have a poorer sense of smell. This is supported by Barresi et al., (2012)'s findings, which show excellent potential in brain scans and OERPs as highly effective early-stage clinical tools due to its lack of inherent response bias and its benefit to patients who have difficulty speaking or communicating, allowing for subject analysis in many situations. Findings by Al Aïn et al., (2019) suggest similar claims, as results demonstrate that the cortical thickness of the right inferior frontal gyrus, the bilateral fusiform gyrus and the right entorhinal cortex, which receives direct input from the OB, was significantly correlated to olfactory function. This was seen through results indicating that olfactory training would improve the cortical thickness, which in turn would allow better olfactory performance in individuals. To add to this, Brodoehl et al., (2012) state that studies using MRI were not consistently providing conclusive answers on the relation between volumetric loss of the OB and PD, which may imply why results from Altinayar et al., (2014) did not align with other studied reviewed. By choosing to use a 3.0-Tesla MRI constructive interference, the authors were able to find significant and observable height decline in the left OB. This may suggest that the differences in the tool of measurement affected the imaging of the brain, and therefore

differences were only observable when particular tools or tool settings were utilised, however, at this time results surrounding PD, in particular, remain somewhat implied.

However, regarding AD and its link to diminished OB volume and olfactory function, on the other hand, was very conclusive as Servello et al., (2011) report significant hippocampus volume loss in patients which transitioned from MCI to an AD diagnosis, this important to note as the OB is directly connected to the hippocampus, suggesting a possible linkage. This similarly reflects findings by Vasavada et al., (2015), which state that deterioration of the POC in MCI and AD patients are not only observable but can be used as a potential market for neurodegeneration in MCI and AD patients, also suggesting that AD patients, in particular, showed an observable volumetric loss. This is further evident by Mundiñano et al., (2011)'s findings, which found a significant decline of the OB volume in AD patients only, whereas, in patients that suffered from PD or FTD, OB volumes did not show significant differences when compared to controls. This is completely in line with results found by Attems et al., (2012), which suggest that changes in the OB and olfactory tract in patients with AD were directly correlated with Braak stages, indicating that lower volume was linked with greater Lewy bodies and tau proteins signalling greater AD progression, linking with evidence found by Ubeda-Bañon et al., (2020). This reflects the findings of Kovács et al., (2001) suggesting that NFT spread causes further AD progression, and therefore measuring the OB, where NFTs will be found, can be a suitable measure of AD in individuals. This is also supported by Voegels et al., (2014)'s results which suggested that the number of NFTs in the OB, olfactory tract, olfactory nucleus, amygdala and other olfactory-related areas in the brain is associated with

diminished olfaction at the time of death, particularly in patients with AD but are found even in cognitive impairment and dementia-free individuals.

Finally, this current study found evidence suggesting a link between ApoE as a potential risk factor in AD patients due to its ability to influence receptors, the binding of lipids and amyloid-β (Aβ), which aggregates in plaques within the brain, causing the formation of NFTs. This is supported by results by Velayudhan, (2015) who found an association between the gene and the development of AD and dementia, linking back to Burke et al., (2008) who suggested that the spread of NFTs were directly linked to the progression of AD and Braak stages. Findings by Qiu et al., (2016) further supports this by revealing AD was much more likely to develop in individuals with ADD who were also carriers of the ApoE4 gene than individuals who were not, suggesting that the presence of ApoE4 may manifest as transitioning from ADD to AD. This is supported by Hawkes (2006)'s results, which found that individuals carrying the ApoE4 allele would be approximately 5 times at risk to develop AD, though this does not necessarily mean that it is guaranteed, it does account for genetic risk in AD.

Limitations

A major prevalent limitation of the current review includes the general nature of the methodology, in which evidence was only as strong as the studies that were chosen, and a large majority of the studies that investigated OB volume through volumetric scans included a low participant count. Though understandable that the population available for research is very slim and niche as they are generally much older (60+), and often must be diagnosed with a

form of dementia, studies with lower participant count may be considered as having weaker evidence.

Potential bias may be introduced in studies assessing olfactory function testing tools, such as the UPSIT or the Sniffin' Sticks tests. Coffee is a very frequent scent in these tests, and for instance, might be more easily identifiable to individuals from Brazil and the United States of America which are countries more readily exposed to the scent of coffee (Czarniecka-Skubina et al., 2021), serving as a partial advantage due to familiarity of odours. Additionally, Stafford, & Orgill, (2020) comments that drinking coffee before the assessment may enhance odour (threshold) sensitivity but reduce odour identification, possibly giving a potential advantage to certain individuals in some test areas.

MRI scans which measure the nasal cavity, piriform cortex and olfactory bulb are located deep in the brain, where MRI may be affected by noisy signals (magnetic artefacts), which could potentially adversely influence the detectability and reproducibility of the scans leading to inaccurate information that may compromise the strength of the research (Lu et al., 2018).

Recent studies surrounding ApoE were difficult to find due to the majority of research surrounding non-human subjects, often due to ethical reasons, or being considered as outdated. The frequency of studies that were used in this current research based on the topic was not equal, as the majority of studies surrounding MRI scans favoured discussion of AD rather than PD. Due to the nature of these observational (quantitative) studies, lived experiences of the elderly community's olfactory dysfunction was not stated nor collected here, which would

have given a deeper insight into how this affects daily life on a personal level, rather than simply understanding and acknowledging how this creates non-personal quality of life changes.

Observational studies are prone to a common limitation of lacking the ability to control the environment. Though most studies did include the use of control groups to represent the alternative of the independent variables, in research which simply aimed to view the differences between the healthy and dementia affected brains, they are unable to account for possible other variables and therefore it becomes more difficult to determine causation.

Future Research

Future studies may aid in contributing to other currently unexplored links between sense of smell and neurodegenerative disorders by investigating and finding more conclusive evidence around the association between additional PD symptoms and phenotypes, olfactory function, and olfactory bulb, which was implied but may not be strongly suggested. Research with the 3.0-Tesla MRI may prove to show more conclusive findings, and consistent data due to its stronger imaging power, and in particular, could be used to further analyse the spread of NFTs and Lewy bodies in the brains of AD and PD patients. Additionally, deeper studying into the ApoE genes and how it affects the development of AD in humans and how it is activated could be beneficial to discriminate between the gene variants and plan future treatments. Further research may also look into comparing olfactory testing with new emerging blood testing, which recent evidence suggests may have high accuracy in identifying neurodegenerative

disorders before key symptoms identifiers, and has been noted as a potential biomarker for AD in particular (Kim et al., 2021).

This current study focused on articles primarily heavily centred around AD and PD, and though aligning with the purpose of the current study, additional research into less common types of dementia and neurodegenerative disorders may also have provided some benefit to a deeper understanding of how other forms of disorders may have associations with olfactory function. Future research may also investigate relations between new viruses (SARS-CoR-2) and the link between ageusia (loss of taste) and loss of smell.

Overall, deeper and larger research involving further observational testing could prove to improve research in this field.

Conclusion

The clear evidence of olfactory function as a measurement of dementia supports the use of olfactory testing as an early identifier of preclinical dementia. Specific regions of the brain impacted by dementia (hippocampus and amygdala) are directly connected to the olfactory system, and therefore an impaired sense of smell could signal the spread of NFTs and Lewy bodies in these regions, indicating the development of AD and PD. Furthermore, the use of UPSIT as a predictor of MCI transitioning into AD is significant, due to showing greater promise than verbal episodic memory loss which is a key factor in AD development. Some

research indicating training of olfactory functions may help as a preventive measure against volumetric loss of the OB, particularly in healthy individuals, which is connected to the strength in one's sense of smell.

The new variety of assessment tools that all directly (through brain scans) or indirectly (through olfactory function) measure the structure of the brain and the volume of the OB shine a light on the bright future for earlier detection of neurodegenerative disorders. Though this study does not recommend one specific olfactory test over another, the use of these assessments serves as an inexpensive and quick tool that may cut down the time of neurodegeneration detection, leading to an earlier diagnosis and therefore earlier treatment being administered helping improve outcomes for individuals with dementia.

References

Aarsland, D., Andersen, K., Larsen, J. P., Perry, R., Wentzel-Larsen, T., Lolk, A., & Kragh-Sørensen, P. (2004). The rate of cognitive decline in Parkinson's disease. Archives of Neurology, 61(12). https://doi.org/10.1001/archneur.61.12.1906

Al Aïn, S., Poupon, D., Hétu, S., Mercier, N., Steffener, J., & Frasnelli, J. (2019). Smell training improves olfactory function and alters brain structure. Neuroimage, 189, 45-54. https://doi.org/10.1016/j.neuroimage.2019.01.008

Altinayar, S., Oner, S., Can, S., Kizilay, A., Kamisli, S., & Sarac, K. (2014). Olfactory dysfunction and its relation olfactory bulb volume in Parkinson's disease. European review for medical and pharmacological sciences, 18(23), 3659–3664.PMID: 25535137

Alves, J. (2014). Olfactory dysfunction in dementia. World Journal Of Clinical Cases, 2(11), 661. https://doi.org/10.12998/wjcc.v2.i11.661

Arnold, S. E., Lee, E. B., Moberg, P. J., Stutzbach, L., Kazi, H., Han, L.-Y., Lee, V. M., & Trojanowski, J. Q. (2009). Olfactory epithelium amyloid-β and paired helical filament-tau pathology in Alzheimer's disease. Annals of Neurology, 67(4), 462–469. https://doi.org/10.1002/ana.21910

Ambron, E., Piretti, L., Lunardelli, A., & Coslett, H. B. (2018). Closing-in behavior and parietal lobe deficits: Three single cases exhibiting different manifestations of the same behavior. Frontiers in Psychology, 9. https://doi.org/10.3389/fpsyg.2018.01617

American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders (5th ed.). https://doi.org/10.1176/appi.books.9780890425596

Ashford, J.W. APOE genotype effects on Alzheimer's disease onset and epidemiology. J Mol Neurosci 23, 157–165 (2004). https://doi.org/10.1385/JMN:23:3:157

Attems, J., Walker, L., & Jellinger, K. (2014). Olfactory bulb involvement in neurodegenerative diseases. Acta Neuropathologica, 127(4), 459-475. doi: 10.1007/s00401-014-1261-7

Attems, J., Walker, L., & Jellinger, K. (2015). Olfaction and Aging: A Mini-Review. Gerontology, 61(6), 485-490. https://doi.org/10.1159/000381619

Aversi-Ferreira, T. A., Tamaishi-Watanabe, B. H., Magri, M. P., & Aversi-Ferreira, R. A. G. M. F. (2019). Neuropsychology of the temporal lobe: Luria's and contemporary conceptions. Dementia & Neuropsychologia, 13(3), 251–258. https://doi.org/10.1590/1980-57642018dn13-030001

Bacon Moore, A., Paulsen, J., & Murphy, C. (1999). A Test of Odor Fluency in Patients with Alzheimer's and Huntington's Disease. Journal Of Clinical And Experimental Neuropsychology, 21(3), 341-351. https://doi.org/10.1076/jcen.21.3.341.918

Barresi, M., Ciurleo, R., Giacoppo, S., Foti Cuzzola, V., Celi, D., Bramanti, P., & Marino, S. (2012). Evaluation of olfactory dysfunction in neurodegenerative diseases. Journal of the Neurological Sciences, 323(1-2), 16–24. https://doi.org/10.1016/j.jns.2012.08.028

Behrman, S., Chouliaras, L., & Ebmeier, K. (2014). Considering the senses in the diagnosis and management of dementia. Maturitas, 77(4), 305-310. https://doi.org/10.1016/j.maturitas.2014.01.003

Bergmann, O., Liebl, J., Bernard, S., Alkass, K., Yeung, M. S. Y., Steier, P., Kutschera, W., Johnson, L., Landén, M., Druid, H., Spalding, K. L., & Frisén, J. (2012). The age of olfactory bulb neurons in humans. Neuron, 74(4), 634–639. https://doi.org/10.1016/j.neuron.2012.03.030

Boesveldt, S., & Parma, V. (2021). The importance of the olfactory system in human well-being, through nutrition and Social Behavior. Cell and Tissue Research, 383(1), 559–567. https://doi.org/10.1007/s00441-020-03367-7

Brodoehl, S., Klingner, C., Volk, G., Bitter, T., Witte, O., & Redecker, C. (2012). Decreased olfactory bulb volume in idiopathic Parkinson's disease detected by 3.0-Tesla magnetic resonance imaging. Movement Disorders, 27(8), 1019-1025. doi: 10.1002/mds.25087

Burke, R., Dauer, W., & Vonsattel, J. (2008). A critical evaluation of the Braak staging scheme for Parkinson's disease. Annals Of Neurology, 64(5), 485-491. https://doi.org/10.1002/ana.21541

Buschhüter, D., Smitka, M., Puschmann, S., Gerber, J., Witt, M., Abolmaali, N., & Hummel, T. (2008). Correlation between olfactory bulb volume and olfactory function. Neuroimage, 42(2), 498-502. https://doi.org/10.1016/j.neuroimage.2008.05.004

Carnemolla, S. E., Hsieh, J. W., Sipione, R., Landis, B. N., Kumfor, F., Piguet, O., & Manuel, A. L. (2020). Olfactory dysfunction in frontotemporal dementia and psychiatric disorders: A systematic review. Neuroscience & Biobehavioral Reviews, 118, 588–611. https://doi.org/10.1016/j.neubiorev.2020.08.002

Czarniecka-Skubina, E., Pielak, M., Sałek, P., Korzeniowska-Ginter, R., & Owczarek, T. (2021). Consumer choices and habits related to coffee consumption by Poles. International Journal of Environmental Research and Public Health, 18(8), 3948. https://doi.org/10.3390/ijerph18083948

Dalton, P., & Maute, C. (2018). Odours and incontinence: What does the nose know? Proceedings of the Institution of Mechanical Engineers, Part H: Journal of Engineering in Medicine, 233(1), 127–134. https://doi.org/10.1177/0954411918781409

DeMaagd, G., & Philip, A. (2015). Parkinson's Disease and Its Management: Part 1: Disease Entity, Risk Factors, Pathophysiology, Clinical Presentation, and Diagnosis. P & T: a peer-reviewed journal for formulary management, 40(8), 504–532.

Devanand, D. P., Lee, S., Manly, J., Andrews, H., Schupf, N., Doty, R. L., Stern, Y., Zahodne, L. B., Louis, E. D., & Mayeux, R. (2014). Olfactory deficits predict cognitive decline and Alzheimer dementia in an Urban Community. Neurology, 84(2), 182–189. https://doi.org/10.1212/wnl.0000000000001132

Dibattista, M., Pifferi, S., Menini, A., & Reisert, J. (2020). Alzheimer's Disease: What Can We Learn From the Peripheral Olfactory System?. Frontiers In Neuroscience, 14. https://doi.org/10.3389/fnins.2020.00440

Dintica, C. S., Marseglia, A., Rizzuto, D., Wang, R., Seubert, J., Arfanakis, K., Bennett, D. A., & Xu, W. (2019). Impaired olfaction is associated with cognitive decline and neurodegeneration in the brain. Neurology, 92(7). https://doi.org/10.1212/wnl.0000000000006919

Doty, R. L., & Kamath, V. (2014). The influences of age on olfaction: A Review. Frontiers in Psychology, 5. https://doi.org/10.3389/fpsyg.2014.00020

Feigin, V. L., Stark, B. A., Johnson, C. O., Roth, G. A., Bisignano, C., Abady, G. G., Abbasifard, M., Abbasi-Kangevari, M., Abd-Allah, F., Abedi, V., Abualhasan, A., Abu-Rmeileh, N. M. E., Abushouk, A. I., Adebayo, O. M., Agarwal, G., Agasthi, P., Ahinkorah, B. O., Ahmad, S., Ahmadi, S., … Murray, C. J. (2021). Global, regional, and national burden of stroke and its risk factors, 1990–2019: A systematic analysis for the global

burden of disease study 2019. The Lancet Neurology, 20(10), 795–820. https://doi.org/10.1016/s1474-4422(21)00252-0

Geißler, K., Reimann, H., Gudziol, H., Bitter, T., & Guntinas-Lichius, O. (2013). Olfactory training for patients with olfactory loss after upper respiratory tract infections. European Archives Of Oto-Rhino-Laryngology, 271(6), 1557-1562. https://doi.org/10.1007/s00405-013-2747-y

Growdon, M. E., Schultz, A. P., Dagley, A. S., Amariglio, R. E., Hedden, T., Rentz, D. M., Johnson, K. A., Sperling, R. A., Albers, M. W., & Marshall, G. A. (2015). Odor identification and Alzheimer disease biomarkers in clinically normal elderly. Neurology, 84(21), 2153–2160. https://doi.org/10.1212/wnl.0000000000001614

Gudziol, V., Hoenck, I., Landis, B., Podlesek, D., Bayn, M., & Hummel, T. (2013). The impact and prospect of traumatic brain injury on olfactory function: A cross-sectional and prospective study. European Archives of Oto-Rhino-Laryngology, 271(6), 1533–1540. https://doi.org/10.1007/s00405-013-2687-6

Haehner, A., Hummel, T., & Reichmann, H. (2014). A Clinical Approach Towards Smell Loss in Parkinson's Disease. Journal Of Parkinson's Disease, 4(2), 189-195. https://doi.org/10.3233/jpd-130278

Hawkes, C. (2006). Olfaction in neurodegenerative disorder. Taste and Smell, 133–151. https://doi.org/10.1159/000093759

Hoffmann, M. (2013). The human frontal lobes and frontal network systems: An evolutionary, clinical, and treatment perspective. ISRN Neurology, 2013, 1–34. https://doi.org/10.1155/2013/892459

Hoogland, P. V., Van Den Berg, R., & Huisman, E. (2003). Misrouted olfactory fibres and ectopic olfactory glomeruli in normal humans and in Parkinson and Alzheimer patients.

Neuropathology and Applied Neurobiology, 29(3), 303–311. https://doi.org/10.1046/j.1365-2990.2003.00459.x

Hüttenbrink, K., Hummel, T., Berg, D., Gasser, T., & Hähner, A. (2013). Olfactory Dysfunction. Deutsches Ärzteblatt International. doi: 10.3238/arztebl.2013.0001

Hummel, T., Sekinger, B., Wolf, S. R., Pauli, E., & Kobal, G. (1997). 'sniffin' sticks': Olfactory performance assessed by the combined testing of odour identification, odour discrimination and olfactory threshold. Chemical Senses, 22(1), 39–52. https://doi.org/10.1093/chemse/22.1.39

Hummel, T., Smitka, M., Puschmann, S., Gerber, J. C., Schaal, B., & Buschhüter, D. (2011). Correlation between olfactory bulb volume and olfactory function in children and adolescents. Experimental Brain Research, 214(2), 285–291. https://doi.org/10.1007/s00221-011-2832-7

Husain, M. A., Laurent, B., & Plourde, M. (2021). APOE and Alzheimer's disease: From lipid transport to physiopathology and therapeutics. Frontiers in Neuroscience, 15. https://doi.org/10.3389/fnins.2021.630502

James, B. D., Boyle, P. A., Buchman, A. S., Barnes, L. L., & Bennett, D. A. (2011). Life space and risk of Alzheimer's disease, mild cognitive impairment, and cognitive decline in old age. The American Journal of Geriatric Psychiatry, 19(11), 961–969. https://doi.org/10.1097/jgp.0b013e318211c219

Jobin, B., Frasnelli, J., & Boller, B. (2020). Volumetry and cortical thickness of olfactory‐related structures in Alzheimer's disease: A systematic review and meta‐analysis. Alzheimer's & Dementia, 16(S5). https://doi.org/10.1002/alz.040582

Kim, H. J., Park, J.-C., Jung, K. S., Kim, J., Jang, J. S., Kwon, S., Byun, M. S., Yi, D., Byeon, G., Jung, G., Kim, Y. K., Lee, D. Y., Han, S.-H., & Mook-Jung, I. (2021). The clinical use of blood-test factors for Alzheimer's disease: Improving the prediction of cerebral amyloid

deposition by the QPLEXTM ALZ Plus Assay Kit. Experimental & Molecular Medicine, 53(6), 1046–1054. https://doi.org/10.1038/s12276-021-00638-3

Kondo, K., Kikuta, S., Ueha, R., Suzukawa, K., & Yamasoba, T. (2020). Age-Related Olfactory Dysfunction: Epidemiology, Pathophysiology, and Clinical Management. Frontiers In Aging Neuroscience, 12. https://doi.org/10.3389/fnagi.2020.00208

Kotecha, A., Corrêa, A., Fisher, K., & Rushworth, J. (2018). Olfactory Dysfunction as a Global Biomarker for Sniffing out Alzheimer's Disease: A Meta-Analysis. Biosensors, 8(2), 41. doi: 10.3390/bios8020041

Kovács, T., Cairns, N., & Lantos, P. (2001). Olfactory centres in Alzheimer's disease: olfactory bulb is involved in early Braak's stages. Neuroreport, 12(2), 285-288. doi: 10.1097/00001756-200102120-00021

Li, A., Rao, X., Zhou, Y., & Restrepo, D. (2019). Complex neural representation of odour information in the olfactory bulb. Acta Physiologica, 228(1). https://doi.org/10.1111/apha.13333

Lim, Y. Y., Maruff, P., Pietrzak, R. H., Ames, D., Ellis, K. A., Harrington, K., Lautenschlager, N. T., Szoeke, C., Martins, R. N., Masters, C. L., Villemagne, V. L., & Rowe, C. C. (2013). Effect of amyloid on memory and non-memory decline from preclinical to clinical Alzheimer's disease. Brain, 137(1), 221–231. https://doi.org/10.1093/brain/awt286

Lu, J., Wang, X., Qing, Z., Li, Z., Zhang, W., Liu, Y., Yuan, L., Cheng, L., Li, M., Zhu, B., Zhang, X., Yang, Q. X., & Zhang, B. (2018). Detectability and reproducibility of the olfactory fmri signal under the influence of magnetic susceptibility artifacts in the primary olfactory cortex. NeuroImage, 178, 613–621. https://doi.org/10.1016/j.neuroimage.2018.06.008

Luzzi, S., Snowden, J., Neary, D., Coccia, M., Provinciali, L., & Lambon Ralph, M. (2007). Distinct patterns of olfactory impairment in Alzheimer's disease, semantic dementia,

frontotemporal dementia, and corticobasal degeneration. Neuropsychologia, 45(8), 1823-1831. doi: 10.1016/j.neuropsychologia.2006.12.008

Mahlknecht, P., Pechlaner, R., Boesveldt, S., Volc, D., Pinter, B., Reiter, E., Müller, C., Krismer, F., Berendse, H. W., van Hilten, J. J., Wuschitz, A., Schimetta, W., Högl, B., Djamshidian, A., Nocker, M., Göbel, G., Gasperi, A., Kiechl, S., Willeit, J., … Seppi, K. (2016). Optimizing odor identification testing as quick and accurate diagnostic tool for parkinson's disease. Movement Disorders, 31(9), 1408–1413. https://doi.org/10.1002/mds.26637

Markopoulos, F., Rokni, D., Gire, D. H., & Murthy, V. N. (2012). Functional properties of cortical feedback projections to the olfactory bulb. Neuron, 76(6), 1175–1188. https://doi.org/10.1016/j.neuron.2012.10.028

Mena, M. A., Rodríguez-Navarro, J. A., & de Yébenes, J. G. (2009). The multiple mechanisms of amyloid deposition: The role of parkin. Prion, 3(1), 5–11. https://doi.org/10.4161/pri.3.1.8122

Moher, D., Liberati, A., Tetzlaff, J., & Altman, D. (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ, 339(jul21 1), b2535-b2535. https://doi.org/10.1136/bmj.b2535

Morgan, C. D., Nordin, S., & Murphy, C. (1995). Odor identification as an early marker for Alzheimer's disease: Impact of lexical functioning and detection sensitivity. Journal of Clinical and Experimental Neuropsychology, 17(5), 793–803. https://doi.org/10.1080/01688639508405168

Morley, J. F., Cohen, A., Silveira-Moriyama, L., Lees, A. J., Williams, D. R., Katzenschlager, R., Hawkes, C., Shtraks, J. P., Weintraub, D., Doty, R. L., & Duda, J. E. (2018). Optimizing olfactory testing for the diagnosis of Parkinson's disease: Item analysis of the University of

Pennsylvania Smell Identification Test. Npj Parkinson's Disease, 4(1). https://doi.org/10.1038/s41531-017-0039-8

Mundiñano, I., Caballero, M., Ordóñez, C., Hernandez, M., DiCaudo, C., & Marcilla, I. et al. (2011). Increased dopaminergic cells and protein aggregates in the olfactory bulb of patients with neurodegenerative disorders. Acta Neuropathologica, 122(1), 61-74. https://doi.org/10.1007/s00401-011-0830-2

Murphy, C. (2018). Olfactory and other sensory impairments in Alzheimer disease. Nature Reviews Neurology, 15(1), 11-24. https://doi.org/10.1038/s41582-018-0097-5

Murphy, C., Gilmore, M., Seery, C., Salmon, D., & Lasker, B. (1990). Olfactory thresholds are associated with degree of dementia in Alzheimer's disease. Neurobiology Of Aging, 11(4), 465-469. https://doi.org/10.1016/0197-4580(90)90014-q

Narr, K., Woods, R., Thompson, P., Szeszko, P., Robinson, D., & Dimtcheva, T. et al. (2006). Relationships between IQ and Regional Cortical Gray Matter Thickness in Healthy Adults. Cerebral Cortex, 17(9), 2163-2171. https://doi.org/10.1093/cercor/bhl125

Null, G., Pennesi, L., & Feldman, M. (2016). Nutrition and lifestyle intervention on mood and neurological disorders. Journal of Evidence-Based Complementary & Alternative Medicine, 22(1), 68–74. https://doi.org/10.1177/2156587216637539

O'Brien, R. J., & Wong, P. C. (2011). Amyloid precursor protein processing and Alzheimer's disease. Annual Review of Neuroscience, 34(1), 185–204. https://doi.org/10.1146/annurev-neuro-061010-113613

Olofsson, J. K., Ekström, I., Larsson, M., & Nordin, S. (2021). Olfaction and aging: A review of the current state of research and Future Directions. i-Perception, 12(3), 204166952110203. https://doi.org/10.1177/20416695211020331

Qiu, W. Q., Zhu, H., Dean, M., Liu, Z., Vu, L., Fan, G., Li, H., Mwamburi, M., Steffens, D. C., & Au, R. (2015). Amyloid-associated depression and APOE4 allele: Longitudinal follow-up for the development of Alzheimer's disease. International Journal of Geriatric Psychiatry, 31(3), 316–322. https://doi.org/10.1002/gps.4339

Reeve, A., Simcox, E., & Turnbull, D. (2014). Ageing and Parkinson's disease: Why is advancing age the biggest risk factor?. Ageing Research Reviews, 14, 19-30. https://doi.org/10.1016/j.arr.2014.01.004

Rombaux, P., Potier, H., Markessis, E. et al. Olfactory bulb volume and depth of olfactory sulcus in patients with idiopathic olfactory loss. Eur Arch Otorhinolaryngol 267, 1551–1556 (2010). https://doi.org/10.1007/s00405-010-1230-2

Roses, M.D, A. D. (1996). Apolipoprotein E alleles as risk factors in Alzheimer's disease. Annual Review of Medicine, 47(1), 387–400. https://doi.org/10.1146/annurev.med.47.1.387
Rothermel, M., & Wachowiak, M. (2014). Functional imaging of cortical feedback projections to the olfactory bulb. Frontiers In Neural Circuits, 8. doi: 10.3389/fncir.2014.00073

Rumeau, C., Nguyen, D. T., & Jankowski, R. (2016). How to assess olfactory performance with The sniffin' sticks test ®. European Annals of Otorhinolaryngology, Head and Neck Diseases, 133(3), 203–206. https://doi.org/10.1016/j.anorl.2015.08.004

Saiki, K., Fukazawa, O., Asaka, H., & Takagi, S. (1994). T&T Olfactometer for Standardized Olfactory Test and Its Uses. Olfaction And Taste XI, 340-340. doi: 10.1007/978-4-431-68355-1_140

Santos, D. V., Reiter, E. R., DiNardo, L. J., & Costanzo, R. M. (2004). Hazardous events associated with impaired olfactory function. Archives of Otolaryngology-Head & Neck Surgery, 130(3), 317. https://doi.org/10.1001/archotol.130.3.317

Scott, K. R., & Barrett, A. M. (2007). Dementia syndromes: Evaluation and treatment. Expert Review of Neurotherapeutics, 7(4), 407–422. https://doi.org/10.1586/14737175.7.4.407

Serrano-Pozo, A., Frosch, M. P., Masliah, E., & Hyman, B. T. (2011). Neuropathological alterations in Alzheimer's disease. Cold Spring Harbor Perspectives in Medicine, 1(1). https://doi.org/10.1101/cshperspect.a006189

Servello, A., Fioretti, A. B., Lambusier, L., Eibenstein, A., Fusetti, M., Ettorre, E., Marigliano, B., Di Biasi, C., Gualdi, G., & Della Volpe, L. (2011). P1‐195: Olfactory deficit and hippocampal volume loss for early diagnosis of Alzheimer's disease. Alzheimer's & Dementia, 7(4S_Part_5). https://doi.org/10.1016/j.jalz.2011.05.475

Sharma, A., Kumar, R., Aier, I., Semwal, R., Tyagi, P., & Varadwaj, P. (2019). Sense of smell: Structural, functional, mechanistic advancements and challenges in human olfactory research. Current Neuropharmacology, 17(9), 891–911. https://doi.org/10.2174/1570159x17666181206095626

Stafford, L. D., & Orgill, K. (2020). The effects of caffeine on olfactory function and mood: An exploratory study. Psychopharmacology, 237(12), 3511–3517. https://doi.org/10.1007/s00213-020-05695-6

Suzuki, H., Teranishi, M., Katayama, N., Nakashima, T., Sugiura, S., & Sone, M. (2021). Relationship between cognitive impairment and olfactory function among older adults with olfactory impairment. Auris Nasus Larynx, 48(3), 420–427. https://doi.org/10.1016/j.anl.2020.11.020

Tarakad, A., & Jankovic, J. (2017). Anosmia and Ageusia in Parkinson's Disease. International Review Of Neurobiology, 541-556. https://doi.org/10.1016/bs.irn.2017.05.028

Taylor, J. E., Lau, H., Seymour, B., Nakae, A., Sumioka, H., Kawato, M., & Koizumi, A. (2020). An evolutionarily threat-relevant odor strengthens human fear memory. Frontiers in Neuroscience, 14. https://doi.org/10.3389/fnins.2020.00255

Tordesillas-Gutierrez, D., Ayesa-Arriola, R., Delgado-Alvarado, M., Robinson, J. L., Lopez-Morinigo, J., Pujol, J., Dominguez-Ballesteros, M. E., David, A. S., & Crespo-Facorro, B. (2018). The right occipital lobe and poor insight in first-episode psychosis. PLOS ONE, 13(6). https://doi.org/10.1371/journal.pone.0197715

Trentin, S., Fraiman de Oliveira, B. S., Ferreira Felloni Borges, Y., & de Mello Rieder, C. R. (2021). Systematic Review and meta-analysis of Sniffin sticks test performance in Parkinson's disease patients in different countries. European Archives of Oto-Rhino-Laryngology. https://doi.org/10.1007/s00405-021-06970-8

Ubeda-Bañon, I., Saiz-Sanchez, D., Flores-Cuadrado, A., Rioja-Corroto, E., Gonzalez-Rodriguez, M., & Villar-Conde, S. et al. (2020). The human olfactory system in two proteinopathies: Alzheimer's and Parkinson's diseases. Translational Neurodegeneration, 9(1). https://doi.org/10.1186/s40035-020-00200-7

Vasavada, M. M., Wang, J., Eslinger, P. J., Gill, D. J., Sun, X., Karunanayaka, P., & Yang, Q. X. (2015). Olfactory cortex degeneration in Alzheimer's disease and mild cognitive impairment. Journal of Alzheimer's Disease, 45(3), 947–958. https://doi.org/10.3233/jad-141947

Velayudhan, L. (2015). Smell identification function and Alzheimer's disease. Current Opinion In Psychiatry, 28(2), 173-179. doi:10.1097/YCO.0000000000000146
Velayudhan, L., Gasper, A., Pritchard, M., Baillon, S., Messer, C., & Proitsi, P. (2015). Pattern of Smell Identification Impairment in Alzheimer's Disease. Journal Of Alzheimer's Disease, 46(2), 381-387. doi:10.3233/jad-142838

Voegels, R., Pinna, F., Imamura, R., Farfel, J., & Godoy, M. (2014). Olfaction in neurologic and Neurodegenerative Diseases: A literature review. International Archives of Otorhinolaryngology, 19(02), 176–179. https://doi.org/10.1055/s-0034-1390136

Wang, J., You, H., Liu, J., Ni, D., Zhang, Z., & Guan, J. (2011). Association of Olfactory Bulb Volume and Olfactory Sulcus Depth with Olfactory Function in Patients with Parkinson Disease. American Journal Of Neuroradiology, 32(4), 677-681. doi: 10.3174/ajnr.a2350

Weller, J., & Budson, A. (2018). Current understanding of Alzheimer's disease diagnosis and treatment. F1000Research, 7, 1161. https://doi.org/10.12688/f1000research.14506.1

Willander, J., Larsson, M. Smell your way back to childhood: Autobiographical odor memory. Psychonomic Bulletin & Review 13, 240–244 (2006). https://doi.org/10.3758/BF03193837

Wilson, D., & Nixon, R. (2010). Should olfactory dysfunction be used as a biomarker of Alzheimer's disease?. Expert Review Of Neurotherapeutics, 10(5), 633-635. doi: 10.1586/ern.10.33

Wilson, R. S., Arnold, S. E., Schneider, J. A., Tang, Y., & Bennett, D. A. (2007). The relationship between cerebral Alzheimer's disease pathology and odour identification in old age. Journal of Neurology, Neurosurgery & Psychiatry, 78(1), 30–35. https://doi.org/10.1136/jnnp.2006.099721

Wolf, A. B., Caselli, R. J., Reiman, E. M., & Valla, J. (2013). APOE and neuroenergetics: An emerging paradigm in Alzheimer's disease. Neurobiology of Aging, 34(4), 1007–1017. https://doi.org/10.1016/j.neurobiolaging.2012.10.011

Yahiaoui-Doktor, M., Luck, T., Riedel-Heller, S. G., Loeffler, M., Wirkner, K., & Engel, C. (2019). Olfactory function is associated with cognitive performance: Results from the population-based life-adult-study. Alzheimer's Research & Therapy, 11(1). https://doi.org/10.1186/s13195-019-0494-z

Yang, J., & Pinto, J. (2016). The Epidemiology of Olfactory Disorders. Current Otorhinolaryngology Reports, 4(2), 130-141. https://doi.org/10.1007/s40136-016-0120-6

Yu, Q., Guo, P., Li, D., Zuo, L., Lian, T., Yu, S., Hu, Y., Liu, L., Jin, Z., Wang, R., Piao, Y., Li, L., Wang, X., & Zhang, W. (2018). Olfactory dysfunction and its relationship with clinical

symptoms of Alzheimer's disease. Ageing and Disease, 9(6), 1084. https://doi.org/10.14336/ad.2018.0819

Word Count: 14,468