ODOR DISCRIMINATION IN YOUNG ADULTS AND OLDER ADULTS

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In Partial Fulfillment
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Master of Arts
in
Psychology

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Andrew Joseph Fiscella
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SAN DIEGO STATE UNIVERSITY

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Odor Discrimination in Young Adults and Older Adults

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8/16/16
Approval Date
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DEDICATION

In loving memory of Sue Ann Pisano.
ABSTRACT OF THE THESIS

Odor Discrimination in Young Adults and Older Adults

by

Andrew Joseph Fiscella

Master of Arts in Psychology

San Diego State University, 2016

Alzheimer’s disease (AD) is a common form of dementia that is marked by the presence of Aβ-plaques, neurofibrillary tangles and cognitive decline. The biggest risk factor for AD is age, as 81% of individuals with AD are 75 years old or older. There is increasing evidence that AD pathology may begin decades before clinical symptoms appear, beginning in the entorhinal cortex. Studies have shown cognitively healthy older adults perform significantly worse on tasks of odor recognition memory, recall and identification than young adults, with this decline more pronounced in those over the age of 65. Interestingly, the latency of brain response to odor identification in older adults is related to one’s body mass index (BMI) and waist circumference, with longer response time in those with higher BMIs and larger waist circumferences. Few studies have investigated the links between odor discrimination, AD and aging, and none have investigated the influence of BMI on odor discrimination. This study examined olfactory event-related potentials (OERPs) in an odor quality discrimination task. Participants were separated into two age groups: young (18-28 years) and older (65+). Odor discrimination were administered a task in which participants were presented with pairs of odors and asked to indicate whether the odors in a pair were the same or different. Participants were also administered an analogous visual task using pairs of colors. Latencies and amplitudes of the OERPs were examined for the N1, P2, N2 and P3 components at the Fz, Cz and Pz electrode sites. A repeated-measures ANOVA with BMI and waist circumference as covariates revealed a significant influence of BMI status on N2 & P3 amplitude when odor pairs were classified as “different.” There were significant effects of waist circumference and BMI on N1 latency. The findings support research suggesting negative effects of a high BMI and waist circumference on ERP recordings during olfactory mediated tasks. As obesity is considered a risk factor for developing AD, deficits in olfactory function as shown by OERPs in conjunction with high BMI could serve as a biomarker for changes in the brain associated with AD.
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ACKNOWLEDGEMENTS

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CHAPTER 1

INTRODUCTION

By the year 2025, Alzheimer’s disease (AD) is expected to affect approximately 7.1 million people ages 65 and older in the United States. That number is estimated to increase to 13.8 million by the year 2050 (Hebert, Weuve, Scherr, & Evans, 2013). While there is currently no cure for Alzheimer’s disease, pharmacological treatments do exist which may slow the progression of the disease and there are continuing efforts to find a cure. However, current diagnostic methods rely on the presence of cognitive symptoms which may not appear until the later stages of AD (Swerdlow, 2007), at which point the drugs that are available and in development may not be as effective as possible. To improve the efficacy of treatment, there is a need for new diagnostic tools allowing for the early detection of AD.

Studies of the olfactory system, which is the first sensory system to be compromised in Alzheimer’s disease (Braak & Braak, 1991, 1996) may show promise in this regard. Not only has it been shown that AD patients have deficits in olfactory perception (Albers et al., 2015; Murphy et al., 2002; Nordin & Murphy, 1996, 1998), but individuals who are considered at-risk for developing AD show deficits as well (Calhoun-Haney & Murphy, 2005; Murphy, Bacon, Bondi, & Salmon, 1998; Oleson & Murphy, 2015; Olofsson et al., 2010; Schiffman, Graham, Sattely-Miller, Zervakis, & Welsh-Bohmer, 2002; Wetter & Murphy, 2001). However, while olfactory deficits in odor identification, threshold and recognition memory have been extensively studied, possible deficits in odor discrimination are in need of further examination.

ALZHEIMER’S DISEASE

Alzheimer’s disease is the most common form of dementia and is marked by the presence of beta-amyloid plaques and neurofibrillary tangles, as well as cognitive decline. While the exact cause of AD is as yet unknown, there are several known risk factors for AD.
including age (Swerdlow, 2011), family history (Farrer et al., 1995) and the ε4 variant of the apolipoprotein e gene (APOE; Corder et al., 1993; Strittmatter et al., 1993). The disease begins in the entorhinal and transentorhinal cortices, which receive olfactory input and serve as a relay point between the hippocampus and neocortical areas (Braak & Braak, 1996).

**Pathology**

The two major biomarkers currently associated with AD are beta-amyloid plaques (Aβ) and neurofibrillary tangles (NFTs). Aβ is produced by the cleavage of the amyloid precursor protein, forming peptide strands of 39-42 amino acids in length (Revett, Baker, Jhamandas, & Kar, 2013). These shortened peptide strands then aggregate to form neuritic plaques. NFTs are formed by tau proteins which have destabilized due to hyperphosphorylation, preventing them from binding to and stabilizing microtubules, disrupting transport pathways within the axon of the neuron. While it is theorized that the weakened affinity of tau to the microtubules leads to an increase of aggregated tau, this has been difficult to confirm in vitro (Mandlekow & Mandlekow, 2012).

While Aβ and NFTs are considered the primary biomarkers of AD, they are only considered to be “necessary but not sufficient” for diagnosis. NFTs are found in multiple brain disease (Goedert, 2004; Nelson et al., 2012) and Aβ levels have been found to increase as part of the normal aging process (Jack et al., 2008; Rodrigue, Kennedy, & Park, 2009). While these protein depositions unquestionably play a role in AD, it remains to be seen whether they are in fact causes of it, or products of another chain of events.

**Diagnosis**

Currently, the only definitive diagnosis of AD is through an autopsy or brain biopsy which shows the presence of plaques and tangles. A diagnosis of probable AD is made through clinical methods which are subjective and based on the individual having met certain criteria for cognitive decline which do not appear until the later stages of the disease (Swerdlow, 2007). In 2011, a collaboration between the U.S. National Institute on Aging and the Alzheimer’s Association created new guidelines for the diagnostic and research criteria for AD (Jack et al., 2011). These new guidelines outlined a progression for AD in three stages: the preclinical phase, the symptomatic pre-dementia, MCI, phase and the
dementia phase. The preclinical phase in particular is characterized by the pathophysiological process (“AD – Pathophysiological” aka. AD – P) as compared to the later phases which also encompass the clinical symptoms (“AD – Clinical” aka. AD – C; Sperling et al., 2011). Currently, the primary biomarker for the preclinical stage is the accumulation of beta-amyloid deposits in the brain, although these depositions are considered to be “necessary but not sufficient” for the later cognitive decline observed in AD (Sperling et al., 2011). However, there is evidence that carriers of the APOE-ε4 allele may show some signs of declining function before the accumulation of Aβ (Filippini et al., 2009; Reiman et al., 2004; Sheline et al., 2010).

**Obesity**

Obesity affects roughly 1 in 3 Americans. Results of the National Health and Nutrition Examination Survey found 69.2% of adults at least 20 years old were considered overweight and 35.9% are obese (Flegal, Carroll, Kit, & Ogden, 2012). Obesity has been linked to multiple diseases including heart disease, hypertension, diabetes and sleep apnea (Malnick & Knobler, 2006).

Both body mass index (BMI) and waist circumference are used as measures of obesity. BMI is calculated as a person’s weight (in kg) over their height (in m²) and scores are grouped into one of four ranges: underweight (≤18.5), normal weight (18.5-24.9), overweight (25.0-29.9) and obese (≥30.0). BMI does suffer from a major drawback in that it does not account for whether a person may be considered overweight due to body fat or muscle mass. Some studies have proposed waist circumference as a better measure because it reflects abdominal obesity (Schneider et al., 2010). Furthermore, several studies have linked abdominal obesity with higher mortality rates (Koster et al., 2008) and an increased risk of developing AD (Whitmer, Gunderson, Barrett-Connor, Quesenberry, & Yaffe, 2005).

**Electroencephalography**

Electroencephalography (EEG) is a method of recording the electrical potential produced by neurons through the use of electrodes placed on the scalp. This potential represents the change in voltage between a reference electrode and the electrode at a site of interest. This was first demonstrated in humans by Hans Berger (1929) and his observations...
were confirmed over the following decade (Gibbs, Davis, & Lennox, 1935; Jasper & Carmichael, 1935). The technique has been refined over time, although the recording methods, as described in the next section, remain quite simple. In addition to its simplicity, EEG is a technique that is not considered invasive and is comparatively less expensive to implement, giving it certain advantages over measures such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI). It should also be noted that EEG enjoys a greater temporal resolution than PET and fMRI, but lacks the spatial resolution of those techniques due to the infinite number of configurations that can produce a given EEG pattern.

**EEG Recording**

To record an EEG, metal electrodes, usually made of tin or coated with silver-chloride are attached to the scalp. Before attaching the electrodes, the impedance of the skin is reduced to 5 kΩ or less by removing dead skin cells, generally using a gentle abrasive (abrasive paste and alcohol pads are the most common). This allows for a cleaner recording. To determine where the electrodes should be placed, most researchers and clinicians use the international 10/20 system (Luck, 2005; Spehlmann, 1985). At minimum, 3 electrodes sites along the midline of the scalp (Fz, Cz and Pz) will be used, although electrode caps containing 64+ electrodes are available.

In its raw form, EEG data is usually used to investigate epilepsy or the different stages of consciousness/sleep. Additionally, a crude topographic distribution of brain waves (across the four major neocortical areas – frontal, temporal, parietal and occipital) can be examined. However, EEG recordings often reflect a larger amount of the brain’s activity than is of interest to the researcher (Gazzaniga, Ivry, & Mangun, 1998; Luck, 2005). In order to focus the recordings on activity in response to a specific task, event-related potentials are used.

**Event-Related Potentials**

When EEG recordings from a series of trials are averaged together, an evoked response or event-related potential (ERP) is recorded. As ERPs are averaged together, beginning at a common time-point, they create a highly accurate visualization of temporal
changes in brain activity. It should be noted that as the ERP is measured using an active electrode and a reference electrode, the “ERP waveform reflects the difference in activity between two sites, not the activity at a single site” (Luck, 2005). In an ERP experiment, the subject is presented with some form of stimuli, usually auditory or visual, olfactory stimuli being employed to a lesser degree. The experimenter then analyzes changes in brain wave activity in response to the stimulus. This can take the form of attempting to localize the group (or groups) of neurons producing the recorded voltage, although this is difficult given the infinite number of neuronal configurations that can produce a given topographical pattern (Handy, 2004). Most ERP research focuses on temporal changes in brain activity after the onset of the presented stimulus.

An ERP waveform is composed of multiple components, which may be defined either functionally (e.g., scalp-recorded neural activity from a given group of neural generators while a specific cognitive function is carried out; Luck, 2005) or by their characteristics within the waveform (Handy, 2004). Components are characterized by their polarity and position within the ERP waveform (e.g., the P3 component has a positive deflection and is the third positive component in the waveform). It should be noted that the component’s position can be defined as its ordinal position or the time it occurs after stimulus onset (e.g., the P3 component is also commonly referred to as P300, for 300ms). Components are not necessarily generalizable, i.e., the N1 component observed during visual tasks is not the same as the N1 observed during olfactory tasks. That being said, depending on the sensory modality, certain components may prove to be of greater interest than others.

Of particular interest in olfactory ERP (OERP) research are the N2 and P3 components. The N2 component seems to reflect activity involved in discriminating and classifying stimuli, with latency determined by how difficult the discrimination is (Donchin, Ritter, & McCallum, 1978; Ritter, Simson, Vaughan, & Friedman, 1979; Ritter, Simson, Vaughn, & Macht, 1982). The exact role of the P3 component is still unclear, but it appears to be affected by the probability of a task-defined stimulus appearing (Duncan-Johnson & Donchin, 1977; Vogel, Luck, & Shapiro, 1998). The amplitude is larger when subjects need to put more effort into a task (Isreal, Chesney, Wickens, & Donchin, 1980). The uncertainty of a stimulus’s status (e.g., target vs. non-target) decreases P3 amplitude and Johnson (1984, 1986) theorized that P3 amplitude = Uncertainty x (Probability + Resource allocation). Due
to the P3 component’s dependence on probability, its latency is affected by how long it takes to categorize a stimulus.

**Olfaction In The Brain**

The human olfactory system is comprised of three major areas: the olfactory epithelium, the olfactory bulb and the olfactory cortex. Odor molecules enter the olfactory epithelium either through sniffing (entry directly through the nose) or through the mouth via retronasal olfaction. The molecules then bind to olfactory receptors lining the epithelium, activating G-protein coupled second-messenger systems (Sela & Sobel, 2010). The olfactory receptors synapse onto glomeruli in the olfactory bulb, which is thought to code for odors based on the pattern of glomeruli activation, although this has yet to be confirmed (Sela & Sobel, 2010). The olfactory bulb projects to the olfactory cortex via the olfactory tract. This direct projection is unique to the olfactory system, as the primary pathways for the other senses are first directed through the thalamus before being routed to the relevant sensory cortices.

There are five major regions within the olfactory cortex: the anterior olfactory nucleus, prepiriform cortex, lateral entorhinal cortex, periamygdaloid cortex and cortical nucleus of amygdala (Sankaran, Khot, & Panigrahi, 2012). Each of these regions performs a unique function. Of particular note is the lateral entorhinal cortex, which is associated with odor memory, emotion and autonomic responses (Coutureau & Di Scala, 2009) and is the first region affected in AD (Braak & Braak, 1991, 1997).

**Age and Olfaction**

While Alzheimer’s may contribute to a decline in olfactory function, deficits can occur due to the normal aging process. Older adults perform significantly worse on tasks of odor recognition memory and recall than young adults while showing greater stability on analogous visual and semantic tasks (Murphy, Nordin, & Acosta, 1997; Murphy, Cain, Gilmore, & Skinner, 1991). Performance on odor identification tasks worsens as part of the normal aging process (Murphy et al., 2002; Nordin et al., 1999; Wehling, Wollschlaeger, Nordin, & Lundervold, 2016). This decline in olfaction is more pronounced in adults over
the age of 65 (Cerf-Ducastel & Murphy, 2009; Green, Cervantez, Graves, Morgan, & Murphy, 2013; Morgan & Murphy, 2010; Royet et al., 2011).

**Olfaction and Alzheimer’s Disease**

Alzheimer’s disease is believed to originate in the entorhinal and transentorhinal regions of the brain, with the initial formation of NFTs beginning in those areas (Braak & Braak, 1991, 1997), which are crucial to olfaction. Deficits in olfactory processing occur to a greater extent in Alzheimer’s patients than deficits due to normal aging (Murphy et al., 2002; Nordin & Murphy, 1998). AD patients have shown deficits in odor identification, threshold and recognition memory. Individuals with questionable AD were shown to have significantly higher odor thresholds than normal controls (Nordin & Murphy, 1996). Additionally, AD patients had significantly more false positives on an odor recognition memory task than normal controls (Gilbert, Barr, & Murphy, 2004; Gilbert & Murphy, 2004).

Individuals at-risk for AD have also shown olfactory deficits. At-risk subjects have higher olfactory thresholds than normal controls (Schiffman et al., 2002). AD patients who are homozygous for APOE-ε4 also score lower, on average, on delayed memory tests than patients who are homozygous for APOE-ε3 (Wetter & Murphy, 2001). APOE-ε4 carriers also have shown deficits in olfactory function, even before the onset of other Alzheimer’s symptoms. Gilbert and Murphy (2004) showed that ε4+ controls had as many false positives as both confirmed and probable AD groups on an odor recognition tasks and all three groups had significantly more false positives than normal controls. APOE4 status has been shown to affect odor identification in healthy, nondemented individuals, with ε4+ individuals having decreased performance compared to ε4- individuals (Bacon, Bondi, Salmon, & Murphy, 1998; Calhoun-Haney & Murphy, 2005; Olofsson et al., 2010). E4+ individuals also demonstrate changes in odor threshold a year prior to AD diagnosis (Murphy et al., 1998; Oleson & Murphy, 2015).

**Olfactory ERPs**

The use of OERPs has provided additional information about the impact of age, AD and APOE4 status on olfactory function beyond behavioral testing. Previous studies have
shown that the P3 wave has increased latency and decreased amplitude in older populations (Corby, Morgan, & Murphy, 2012; Geisler, Morgan, Covington, & Murphy, 1999; Green et al., 2013; Morgan, Geisler, Covington, Polich, & Murphy, 1999; Murphy et al., 2000). AD patients produced significantly longer N1, P2, N2 and P3 latencies compared to age-matched controls (Morgan & Murphy, 2002). Individuals who are ε4+ show greater ERP latencies in an odor identification task than ε4- individuals (Morgan & Murphy, 2012). A 2001 study by Wetter and Murphy using olfactory event-related potentials showed that APOE-ε4+ individuals had greater delays in processing olfactory information than APOE-ε4- individuals. An increased P3 latency was also shown for ε4+ individuals compared to ε4- individuals (Corby et al., 2012). Another OERP study using an odor/visual congruency task found the amplitude of the Pz wave was larger for APOE-ε4- participants than APOE-ε4+ participants (Kowalewski & Murphy, 2012).

EXPANDING ON PAST EXPERIMENTS

To date, only a few studies have investigated the links between odor quality/intensity discrimination and AD and the relationship between the two is still uncertain (Naudin & Atanasova, 2014). In 2007, Luzzi et al. found that AD participants performed significantly worse on an odor discrimination task compared to semantic dementia, frontotemporal dementia, corticobasal degeneration and control participants. Djordjevic, Jones-Gotman, De Sousa, and Chertkow in 2008 found a significant difference in performance on an odor discrimination task between the AD group and control and mild cognitive impairment (MCI) groups when the odor pairs were dissimilar. However, when the odor pairs were similar there was no significant difference between the groups (although it was noted that control and MCI participants performed better than chance while AD participants did not). Royet et al. (2001) showed a significant difference in intensity ratings between AD participants and younger controls, but a multiple regression analysis determined this to be a function of age. No studies to date have examined the relationship between odor discrimination and OERPs.

SUMMARY

Although olfactory function declines as part of the normal aging process, there is an even greater loss of function in patients with Alzheimer’s disease. This loss of function has
also been observed in those considered “at-risk” for developing AD, specifically individuals with the APOE-ε4 allele. This presents a potential avenue for the development of tools for earlier diagnosis of AD. OERPs in particular may be useful, as they have already been used to demonstrate deficits in individuals with AD and those at-risk for AD.

The purpose of this study is to examine the effects of aging on odor discrimination (with visual discrimination serving as a sensory analog). Two hypotheses will be tested.

The first hypothesis is that olfactory N2 and P3 amplitudes will decrease in older adults compared to young adults. Amplitudes on visual ERP components will also be expected to decrease in older participants.

The second hypothesis is that older adults will show longer peak latencies, specifically for the olfactory N2 and P3 latencies than young adults and that this difference will be greater for older males. Older participants will be expected to have longer latencies for visual ERP components.
CHAPTER 2

METHODS

STUDY 1 – STIMULUS BATTERY DEVELOPMENT

Participants

Participants were recruited from the Psychology 101 Participant Pool (SONA) and a research laboratory at San Diego State University (SDSU). Twelve participants (2 male, 10 female) ranging in age from 18-26 years old ($M = 20.83, SD = 2.69$) were recruited for this study. Participants gave informed consent and the study was approved by the institutional review board (IRB) at SDSU.

Materials

ODORS

Odors were selected for pairings based on the presence or absence of a common chemical odorant (referenced using Fenaroli’s Handbook of Flavor Ingredients, 6th Edition). For example, lemon and orange have the odorant citral in common and would be classified as “similar.” Banana and almond do not have any common odorants and would be classified as “dissimilar.” Odors were presented in liquid scintillation vials made of borosilicate glass with metal foil-lined urea screw caps. The vials were wrapped completely in an opaque tape to conceal the odors. The odors used are listed in Table 1.
Table 1. Study 1 Odors

<table>
<thead>
<tr>
<th>Odor</th>
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<tr>
<td>Lemon Extract</td>
<td>OliveNation®</td>
</tr>
<tr>
<td>Orange Extract</td>
<td>OliveNation®</td>
</tr>
<tr>
<td>Cinnamon Extract</td>
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<tr>
<td>Clove Extract</td>
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</tr>
<tr>
<td>Rose Perfume Oil</td>
<td>Wild Rose</td>
</tr>
<tr>
<td>Lavender Extract</td>
<td>OliveNation®</td>
</tr>
<tr>
<td>Spearmint Extract</td>
<td>OliveNation®</td>
</tr>
<tr>
<td>Anise Extract</td>
<td>OliveNation®</td>
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<tr>
<td>Almond Extract</td>
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<td>Pineapple Extract</td>
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<tr>
<td>Peppermint Extract</td>
<td>McCormick®</td>
</tr>
<tr>
<td>Clove Bud Oil</td>
<td>Sigma-Alrich®</td>
</tr>
<tr>
<td>Orange Essential Oil</td>
<td>Echo</td>
</tr>
<tr>
<td>Wintergreen Extract</td>
<td>Old Hickory Brand®</td>
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</tbody>
</table>

Odors used in Study 1. Odors 1-12 were included in the first discrimination task. Odor 16 was included in the second discrimination task. Odors 13-15 were only included in the identification task.

COLORS

Colors representing a range from red to light purple were selected from the Sherwin-Williams® website and recreated on Microsoft Word using the Red/Green/Blue color ratios. The colors used are listed in Table 2. Colors were presented as 2x2” squares with 0.25” white border on all sides.
Table 2. Study 1 Colors

<table>
<thead>
<tr>
<th>Color Name</th>
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<th>Green</th>
<th>Blue</th>
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<td>194</td>
<td>22</td>
</tr>
<tr>
<td>Direct Green</td>
<td>63</td>
<td>138</td>
<td>36</td>
</tr>
<tr>
<td>Nifty Turquoise</td>
<td>1</td>
<td>145</td>
<td>135</td>
</tr>
<tr>
<td>Hyper Blue</td>
<td>1</td>
<td>95</td>
<td>151</td>
</tr>
<tr>
<td>Fully Purple</td>
<td>81</td>
<td>76</td>
<td>126</td>
</tr>
<tr>
<td>Forget-Me-Not</td>
<td>113</td>
<td>105</td>
<td>152</td>
</tr>
<tr>
<td>Dahlia</td>
<td>139</td>
<td>152</td>
<td>196</td>
</tr>
</tbody>
</table>

Procedures

Participants were asked to complete three tasks assessing odor quality discrimination, odor identification and color quality discrimination. The order of the odor and color discrimination tasks was randomized, although the odor identification task was always given immediately after the odor discrimination task.

ODOR DISCRIMINATION

For the odor discrimination task, participants were presented with 24 pairs of odors (6 “different” pairs [see Table 3]) presented twice in A-B/B-A form and 12 “same” pairs (an odor presented against itself) in random order. The participant was asked to close their eyes when each odor was presented and the experimenter held the odor under the participant’s nose for two seconds. There was a 30s interstimulus interval (ISI) between odors and participants were allowed to open their eyes between odors. Participants were instructed to classify the odors in a pair as either exactly the same odor or two different odors and rate how similar the odors were using a modified general labeled magnitude scale (gLMS; Bartoshuk et al., 2004).
After the initial study, three participants were asked to discriminate an additional 14 odor pairs – 8 different pairs and 5 same pairs (see Table 3). Instructions to participants were the same as in round 1.

Table 3. Study 1 Odor Pairs

<table>
<thead>
<tr>
<th>Study 1 – Round 1</th>
<th>Study 1 – Round 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lemon – Orange</td>
<td>Wintergreen – Spearmint</td>
</tr>
<tr>
<td>Cinnamon – Clove</td>
<td>Wintergreen – Peppermint</td>
</tr>
<tr>
<td>Rose – Lavender</td>
<td>Peppermint – Spearmint</td>
</tr>
<tr>
<td>Spearmint – Anise</td>
<td>Banana – Pineapple</td>
</tr>
<tr>
<td>Almond – Banana</td>
<td>Rose – Anise</td>
</tr>
<tr>
<td>Coconut – Pineapple</td>
<td></td>
</tr>
</tbody>
</table>

“Different” odor pairs used in Study 1. In Round 1, the first three odor pairs were considered similar and the second three pairs were considered dissimilar. In Round 2, the first three odor pairs were considered similar and the final two pairs were considered dissimilar.

**ODOR IDENTIFICATION**

For the odor identification task, subjects were presented with 15 odors (see Table 1) in random order. For each odor, subjects were asked to identify what the odor was and rate the odor for pleasantness and intensity using modified versions of the gLMS.

**COLOR DISCRIMINATION**

For the color discrimination task 105 possible “different” pairs and 15 possible “same” pairs were pseudo-randomly split into five sets (sets were designed so that each participant was presented with all 15 base colors at least once). Participants were randomly presented with one of the five sets, consisting of 21 “different” pairs and 3 “same” pairs. Participants were presented with pairs of colors with a 30s ISI between colors. As in the odor discrimination task, participants were instructed to classify the colors in a pair as either exactly the same color or two different colors and rate how similar the colors were using a modified gLMS.

**STUDY 2 – OERPs AND VERPs**

**Participants**

Twenty-six participants were recruited through SONA, social media and the participant pool at the Lifespan Human Senses Laboratory at SDSU. Participants were split
into two age groups: young adult (18-28 years) and older adult (65+ years). In the young adult group, nine participants were women and five were men. In the older adult group, six participants were women and six were men. Participants gave informed consent and the study was approved by the IRB at SDSU.

**Psychophysical and Cognitive Assessment**

Participants were screened for olfactory and cognitive impairment before the ERPs were recorded. Olfactory impairment was tested using a butanol two-alternative, forced choice threshold task (Murphy, Gilmore, Seery, Salmon, & Lasker, 1990). A series of n-butyl alcohol (butanol) concentrations were used, with the highest concentration at 4% v/v in distilled water. Participants were presented with two bottles, one containing butanol (starting at the lowest concentration) and the other distilled water. Participants were asked to smell each solution and identify which bottle had the strongest smell. Solutions were presented to one nostril at a time and the participant was instructed to close the opposite nostril. Solutions were then alternated between each nostril. If a participant chose the distilled water, they were presented with the next highest concentration of butanol. If a participant chose the butanol, they continued at the current concentration until they either chose the distilled water or correctly chose the butanol for five consecutive trials. The threshold was recorded for each nostril and an average odor threshold score of 3 or above served as the cutoff for exclusion from the study. The Mini-Mental State Exam (Folstein, Folstein, & McHugh, 1975) was used to screen for cognitive impairment. A score of ≤ 25 served as the cutoff for exclusion from the study.

**Physical Assessment**

Participants were also asked to fill out a brief health questionnaire and had their height, weight and waist circumference. A participant’s BMI – calculated as their weight (in kg) over their height (in m²) – was then determined from these measurements.

**ERP Recording and Processing**

A continuous EEG was recorded for each participant using a 64-electrode Quik-Cap manufactured by Neuroscan. Neuroscan Quik-Cell® electrolyte solution was used to keep the impedance below 10kΩ. Reference electrodes were applied to the ears (M1 and M2). To
account for extra-ocular noise activity, electrodes were also placed above and below the left eye and directly adjacent to the left and right eyes, beneath the temples. The Ocular Artifact Reduction tool in Scan4.5 was used to exclude extra-ocular activity from the ERP waveforms.

The EEG recordings were processed using a .1 to 9Hz zero phase shift bandpass filter. EEG recordings were split into 24 epochs, sorted by whether the stimulus pair was classified as “same” or “different.” The epochs reflected a time period that included a 500ms pre-stimulus presentation and 1500ms post-stimulus presentation. Epochs were references to the M1 and M2 electrodes and baseline corrected.

**ERP Stimulus Presentation**

Two discrimination tasks were employed during ERP recording: odor and visual. Stimuli for the odor discrimination task were presented using an olfactometer based on the designs of Kobal (1981) and Morgan and Murphy (2002). The STIM2 software program by Neuroscan was used to control the release of odors from the olfactometer. Odors were delivered to the participants using a cannula placed inside a participant’s nostril. Velopharyngeal closure, in which the participant must breathe only through their mouth, was used to ensure a constant odorant flow (Kobal, 1981; Lorig, Elmes, Zald, & Pardo, 1999; Thesen & Murphy, 2001).

Participants were presented with 24 pairs of odors (6 “different” pairs [see Table 4] presented twice in A-B/B-A form and 12 “same” pairs – an odor presented against itself). Participants were randomly assigned to one of four presentation orders, each of which was created using a random number generator. Participants were instructed that they would be presented with pairs of odors, with each odor in a pair presented one at a time. A 3.5 x 5cm grey crosshair was presented on a white background using a 19” Acer® LCD monitor, which was placed 162cm from the participant. The crosshair indicated that an odor would be presented, but the participant was unaware of when during that interval the odors would be released. After both odors in a pair were presented, participants were asked to indicate if the odors were the same or different using a two-button response pad. If the participant did not indicate a response within 10s of the question appearing, it automatically timed out. If the question timed out before a response was indicated, it was not included in an individual’s
averaged waveform. Odors were released for 200ms with a 30s ISI between odors. An example of the timing of the stimulus presentation is given in Figure 1.

Table 4. Different Odor Pairings for ERP Discrimination Task

<table>
<thead>
<tr>
<th></th>
<th>Pairings</th>
<th>M Similarity</th>
<th>SD Similarity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Similar</td>
<td>Lemon – Orange</td>
<td>64.58</td>
<td>30.18</td>
</tr>
<tr>
<td></td>
<td>Cinnamon – Clove</td>
<td>55.96</td>
<td>32.39</td>
</tr>
<tr>
<td></td>
<td>Wintergreen – Peppermint</td>
<td>93.33</td>
<td>7.53</td>
</tr>
<tr>
<td>Dissimilar</td>
<td>Rose – Anise</td>
<td>6.67</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>Almond – Banana</td>
<td>22.92</td>
<td>25.66</td>
</tr>
<tr>
<td></td>
<td>Coconut – Pineapple</td>
<td>44.17</td>
<td>31.71</td>
</tr>
</tbody>
</table>

Different odor pairings used for the ERP Discrimination Task. Similar pairs were rated on average as being closer together (indicated by ratings of 50 or above), while dissimilar pairs were rated as being farther apart (indicated by ratings of 49 or below).

Figure 1. An example of the timing and display for the odor and color discrimination tasks used during ERP recording. The ISI was 30s between stimuli and each stimulus was presented for 200ms. Five seconds after the second stimulus in a pair was presented, a question appeared asking the participant to indicate whether the stimuli presented were the same or two different stimuli. A grey crosshair on a white background was present throughout the tasks, except when a color or question appeared.

The visual discrimination task followed a similar format to the odor task. Participants were presented with 24 pairs of colors (6 “different” pairs [see Table 5] presented twice in A-B/B-A form and 12 “same” pairs – a color presented against itself). Participants were
randomly assigned to one of four presentation orders, each of which was created using a random number generator. Participants were instructed that they would be presented with pairs of colors, with each color in a pair presented one at a time. A 3.5 x 5cm grey crosshair was presented on a white background using a 19” Acer® LCD monitor, which was placed 162cm from the participant. The crosshair indicated that a color would be presented, but the participant was unaware of when during that interval the colors would be shown. Colors were presented as 7 x7cm squares in the center of the screen. After both colors in a pair were presented, participants were asked to indicate if the colors were the same or different using a two-button response pad. If the participant did not indicate a response within 10s of the question appearing, it automatically timed out. If the question timed out before a response was indicated, it was not included in an individual’s averaged waveform. Colors were shown for 200ms with a 30s ISI between colors.

<table>
<thead>
<tr>
<th>Table 5. Different Color Pairings for ERP Discrimination Task</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pairings</strong></td>
</tr>
<tr>
<td>----</td>
</tr>
<tr>
<td><strong>Similar</strong></td>
</tr>
<tr>
<td>Positive Red – Cherries Jubilee</td>
</tr>
<tr>
<td>Fully Purple – Dahlia</td>
</tr>
<tr>
<td>Daisy – Sunny Veranda</td>
</tr>
<tr>
<td><strong>Dissimilar</strong></td>
</tr>
<tr>
<td>Navel – Knockout Orange</td>
</tr>
<tr>
<td>Nifty Turquoise – Forget-Me-Not</td>
</tr>
<tr>
<td>Direct Green – Osage Orange</td>
</tr>
</tbody>
</table>

Different color pairings used for the ERP discrimination task. Similar pairs were rated on average as being closer together (indicated by ratings of 50 or above), while dissimilar pairs were rated as being farther apart (indicated by ratings of 49 or below).
CHAPTER 3

RESULTS

DEMOGRAPHICS

Age and BMI significantly differed between the young and older adults (see Table 6). Odor threshold and MMSE scores did not significantly differ between age groups.

Table 6. ERP Study Demographics

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>BMI</th>
<th>Odor Threshold</th>
<th>MMSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young Adults</td>
<td>20.57 (1.78)</td>
<td>22.95 (3.83)</td>
<td>6.43 (1.47)</td>
<td>28.93 (1.07)</td>
</tr>
<tr>
<td>Older Adults</td>
<td>74.92 (6.57)</td>
<td>26.20 (3.29)</td>
<td>5.83 (1.25)</td>
<td>28.67 (1.30)</td>
</tr>
</tbody>
</table>

The mean (SD) participant demographics for each age group. There was a significant different in age between the young adult and older adult groups F(1,24) = 887.013, p < .001 as well as BMI F(1,23) = 5.120, p < .05.

OLFACTORY ERPs

Repeated-measures ANCOVAs were conducted for each odor pair type (i.e., same and different). Electrode site (Fz, Cz and Pz) was the within-group factor while age group (young or older) was the between-groups factor. Gender, BMI and waist circumference were included as covariates. The dependent variables were the amplitudes and latencies of OERP components N1, P2, N2 and P3. The grand averages comparing older adults and young adults when odors within a pair were different or the same are presented in Figure 2.
Figure 2. Grand OERP averages of different and same odor pairs. Solid lines represent ERP waveforms for young adults. Dashed lines represent ERP waveforms for older adults.

**Amplitudes**

When odors were different there was a significant effect of BMI on the amplitudes of N2 $F(1,12) = 9.218, p < .05, \eta^2 = .434$ and P3 $F(1,12) = 5.626, p < .05, \eta^2 = .319$ such that as BMI increased, the amplitudes of N2 and P3 decreased (see Figures 3 and 4, respectively). There was a significant electrode site x waist circumference interaction $F(2,24) = 3.445, p < .05, \eta^2 = .223$ for P3 amplitude. There were no significant effects of age group, gender, BMI or waist circumference when the odors in a pair were the same.
Figure 3. The relationship between BMI and olfactory N2 amplitude. Results are given for the electrode sites Fz, Cz and Pz.

Figure 4. The relationship between BMI and olfactory P3 amplitude. Results are given for the electrode sites Fz, Cz and Pz.
Latencies

When odors were different, there was a significant effect of BMI $F(1,12) = 6.501, p < .05, \eta^2 = .351$ and waist circumference $F(1,12) = 15.439, p < .05, \eta^2 = .563$ on the latency of N1. As BMI and waist circumference increase, the latency of N1 increases (see Figures 5 and 6, respectively). There were no significant effects of age group, gender, BMI or waist circumference when the odors in a pair were the same.

![Relationship Between BMI and Olfactory N1 Latency](image)

**Figure 5.** The relationship between BMI and olfactory N1 latency. Results are given for the electrode sites Fz, Cz and Pz.
**Figure 6.** The relationship between waist circumference and olfactory N1 latency. Results are given for the electrode sites Fz, Cz and Pz.

**VISUAL ERPs**

Repeated-measures ANOVAs were conducted for each color pair type (i.e., same and different). Electrode site (Fz, Cz and Pz) was the within-group factor while age group (young or older) was the between-groups factor. Gender, BMI and waist circumference were included as covariates. The dependent variables were the amplitudes and latencies of VERP components N1, P2, N2 and P3. The grand averages comparing older adults and young adults when colors within a pair were the same or different are presented in Figure 7.
When colors were different there was a marginally significant effect of age group $F(1,12) = 4.402, p = .058, \eta^2 = .268$ on N1 amplitude with older adults showing smaller amplitudes than young adults. There was a significant electrode site x age group interaction for the N1 $F(1.118,13.410) = 4.626, p < .05, \eta^2 = .278$ and P2 $F(1.09,13.067) = 5.126, p < .05, \eta^2 = .299$ amplitudes. A Greenhouse-Geisser correction was applied when sphericity was violated.

**Amplitudes**

Figure 7. Grand OERP averages of different and same color pairs. Solid lines represent ERP waveforms for young adults. Dashed lines represent ERP waveforms for older adults.
When colors were the same there was a significant effect of BMI $F(1,12) = 8.016, p < .05, \eta^2 = .381$ on N2 amplitude. As BMI increases, N2 amplitude decreases (see Figure 8).

![Relationship Between BMI and Visual N2 Amplitude](image)

**Figure 8.** The relationship between BMI and visual N2 amplitude. Results are given for the electrode sites Fz, Cz and Pz.

### Latencies

When colors were different, there was a significant electrode site x waist circumference interaction $F(2,24) = 3.623, p < .05, \eta^2 = .232$ for N1 latency. There were significant effects of gender $F(1,12) = 10.468, p < .05, \eta^2 = .466$, age group $F(1,12) = 9.067, p < .05, \eta^2 = .430$ and waist circumference $F(1,12) = 5.131, p < .05, \eta^2 = .300$ on N2 latency. Men had longer latencies than women and older adults had longer latencies than young adults. Waist circumference and N2 latency appear to have an inverse relationship as N2 latency decreased as waist circumference increased (see Figure 9). There was a significant effect of waist circumference $F(1,12) = 6.589, p < .05, \eta^2 = .354$ on P3 latency, with the latency decreasing as waist circumference increased (see Figure 10).

There were no significant effects of age group, gender, BMI or waist circumference when colors were the same.
Figure 9. The relationship between waist circumference and visual N2 latency. Results are given for the electrode sites Fz, Cz and Pz.

Figure 10. The relationship between waist circumference and visual P3 latency. Results are given for the electrode sites Fz, Cz and Pz.
CHAPTER 4

DISCUSSION

STUDY 1: DEVELOPING NEW STIMULUS BATTERIES

Although other studies have examined quality discrimination in odor, some (e.g., Mair, Capra, McEntee, & Engen, 1980) failed to account for factors including intensity, odor pleasantness and familiarity which may have provided other cues for discrimination. This study sought to develop a new odor battery which accounted for these factors as well as a color battery to serve as a visual control. Different odor pairs were designed so that the odors within a pair would be considered either similar to one another or dissimilar. Odors that differed significantly in intensity were not paired with each other and no odors within a pair differed significantly in intensity. Additionally, there was no significant correlation between accuracy in identifying the odors and one’s ability to discriminate between them. These results suggest that this is a viable battery for testing odor quality discrimination.

STUDY 2: OLFACTORY AND VISUAL ERPs

Age and Gender

While a number of studies have demonstrated differences between young and older adults in olfactory processing (e.g., Murphy et al., 2002; Nordin et al., 1999; Wehling et al., 2016), this study did not find any significant effect of age on odor discrimination processing.

Additionally, other studies have shown gender differences in olfactory processing. Morgan, Covington, Geisler, Polich and Murphy (1997) demonstrated that older males had significantly worse deficits in olfactory processing than females. Fusari and Ballesteros (2008) found that women between the ages of 60-69 performed better on an odor identification task than men of the same age. These differences may be due to the fact that women have almost twice the number of neurons and glial cells in the olfactory bulb than
men (Oliveira-Pinto et al., 2014). However, the current study did not indicate any significant differences between genders in olfactory processing.

Age and gender effects were observed for the visual N2 component. Older adults had a significantly delayed latency compared to young adults and men had more delayed latencies compared to women. Czigler (1996) demonstrated that the latency of the N2b component was longer for older adults compared to young adults in a color processing task.

Although there is still debate as to whether or not (and to what extent) men and women differ in their perception of color, behavioral evidence does suggest some differences. Women are faster at naming colors (Saucier, Elias, & Nylen, 2002) and appear to be more sensitive to detecting colors along the red-green spectrum (Pardo, Pérez, & Suero, 2007; Rodríguez-Carmona, Sharpe, Harlow, & Barbur, 2008). No research to this point has examined color discrimination and gender using ERPs. This study does suggest that the visual N2 component may be affected by gender as well as age.

### BMI and Waist Circumference

While age and gender did not appear to play a significant role in odor discrimination processing in the current study, the results did suggest a significant effect of BMI and waist circumference. A higher BMI was associated with decreased amplitude of the N2 and P3 components. Additionally, a high BMI and larger waist circumference were associated with an increased latency for the N1 component. This is in line with previous research, which suggested a positive correlation for P3 latency with BMI and waist circumference (Zamora, Bartholow, Green, Morgan, & Murphy, 2011). It is also possible that the effects of increased weight, represented by the measures of BMI and waist circumference, masked the differences due to age. A univariate ANOVA with age group as the dependent variable and BMI and waist circumference as covariates revealed that the older adult group had higher BMI ratings than the young adult group. This difference was marginally significant $F(1,21) = 4.232, p = .052$, $\eta^2 = .168$.

As studies have suggested that differences in olfactory processing, such as delayed ERP latencies, can be detected before the onset of AD (Corby et al., 2012; Morgan & Murphy, 2012; Zamora et al., 2011) it is possible these deficits are exacerbated by abdominal obesity. The additional significant effects of BMI on visual ERP components such as N2
amplitude and waist circumference on the latencies of N2 and P3 suggest that being overweight or obese may impair multiple sensory modalities.

**LIMITATIONS**

The primary limitation of this study was the small sample size, which may have been too small to parse out differences between groups due to age. Additionally, the effects of the apolipoprotein e4 allele, which has been linked to decreased OERP amplitude and increased latency (Corby et al., 2012; Kowalewski & Murphy, 2012; Morgan & Murphy, 2012) were not accounted for in this study.

**CONCLUSIONS**

While the current findings did not support age or gender differences in OERP amplitudes or latencies, potentially because of the small sample size, they do suggest a relationship with VERPs, specifically with the N2 component. The findings support the hypotheses that older adults would have decreased N2 amplitudes and increased N2 latencies compared to young adults. This same relationship also holds when comparing men to women. The findings also support the role of obesity in diminished olfactory functioning and its status as a risk factor for AD.
REFERENCES


