

**Olfaction and Associations with Long-Term Cognitive Transitions and Short-Term
Cognitive Variability**

by

Jamie Knight
BA, University of Victoria, 2015
MSc, University of Victoria, 2017

A Dissertation Submitted in Partial Fulfilment of the
Requirements for the Degree of

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In the Department of Psychology

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We acknowledge and respect the ləkʷəŋən peoples on whose traditional territory the university stands and the Songhees, Esquimalt and W̱SÁNEĆ peoples whose historical relationships with the land continue to this day.

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Abstract

Olfactory function plays an important role in health and well-being. Deficits have been associated with a greater risk of cognitive decline, dementia, and death, indicating that olfactory ability may be an early marker of cognitive impairment and indicator of brain integrity. In the progression of cognitive impairment related to dementia, intraindividual variability in cognition may precede cognitive decline as an early risk factor, indicating that individuals with more variability in their cognitive performance may have an increased risk of cognitive impairment. Despite a significant amount of literature examining the relationship between olfaction and cognitive decline, to the best of our knowledge, no study has yet examined whether olfaction is associated with the earlier marker of cognitive decline, intraindividual variability in cognition.

Project 1. In data drawn from the Rush Memory and Aging Project ($N=1501$), multistate models were used to estimate the association of olfactory identification with transition patterns through cognitive states including non-impaired cognitive functioning, clinically diagnosed mild cognitive impairment and dementia, and death. Additionally, multinomial regression models were fit to estimate life expectancies for overall and cognitively unimpaired years of life, relative to olfactory identification scores. This dissertation aims to contribute to the current body of literature suggesting potential for the use of olfactory identification as a clinically administered marker for the early detection of cognitive decline and risk of dementia.

Project 2. In data collected by our lab ($N=65$), multilevel models were used to examine whether olfactory identification scores were associated with the magnitude and rate of change of intraindividual variability (IIV) in cognitive functioning. This dissertation aims to address whether olfactory identification is associated with IIV in cognition using self-administered mobile cognitive testing in a 14-day micro-longitudinal study.

Preface

A copyedited version of Chapter 2 has been submitted for publication: Knight, J., Yoneda, T., Lewis, N., Muniz-Terrera, G., Bennett, D., Piccinin, A. (under review). Olfaction, Cognitive States, and Mortality: The importance of competing risk factors. *Journals of Gerontology: Medical Sciences*. I am the primary author of this paper with contributions from all co-authors. D. Bennett was responsible for funding and data oversight for the Memory and Aging Project. I identified the project during a Multi-state Modeling workshop with G. Muniz-Terrera and conducted data analysis with support from the workshop team, N. Lewis, T. Yoneda, and G. Muniz-Terrera. Rush University Medical Center Review Board and UVic Research Ethics Board approved this research (approval number: 22-0175).

I am the primary author of Chapter 3. R. Vendittelli and J. Rush developed the study design for reliability testing of mobile cognitive apps. The DASH team consisted of R. Vendittelli, T. Yoneda, N. Lewis, J. Rush, S. Hofer, myself, and several research assistants. We had regular team meetings during this project where I contributed to the design with the inclusion of olfactory identification testing, assisted with training research assistants for the data collection, and contributed to data collection and project management. I designed this specific project with contributions from T. Yoneda and N. Lewis; I conducted the data analysis and wrote the chapter content. Any resulting publication would include all team members. UVic Research Ethics Board approved this study (approval number: 18-1069).

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Dedication

To my mother,

“The most difficult thing is the decision to act, the rest is merely tenacity.”

- Amelia Earhart

Chapter 1: Introduction

As the human population and average life expectancy increases, the world experiences growth in both the size and the proportion of older adults in the population (United Nations, 2020). By 2050, the world population of individuals 60 years and older will double, to 2.1 billion, and 139 million are expected to be living with dementia (United Nations, 2020). While population aging in general will pose a significant burden on health care systems across the globe, the social and medical care costs associated with dementia are expected to reach 2.8 trillion by 2030 (United Nations, 2020). The United Nations has termed 2021-2030 the decade of healthy ageing and is committed to make a concerted global effort to focus research, policy, and the private sectors on topics surrounding healthy ageing. Research focusing on prevention and early indicators of diseases such as dementia are of the utmost importance to ensure that individuals are living healthy lives for as long as possible and that disease is detected as early as possible to ensure time to implement treatment and lifestyle changes. This dissertation will focus on a clinically underutilised and inexpensive potential early indicator of dementia and brain health, olfactory ability. Chapter 1 will begin with an overview of the olfactory system, its relationship to memory, olfactory ability as a potential indicator of brain integrity, then follow with impacts of stress, and conclude with aims.

Olfactory System

Olfactory function plays an important role in health and well-being. It is vital for maintaining appetite, identifying food, avoiding hazards and pathogens, and maintaining intimate social relationships (Albers et al., 2015; Stevenson, 2010). All of the olfactory system's main functions rely on the ability to learn (Stevenson, 2010) making a link between memory and

olfactory functioning vital to these key functions. Unlike other sensory modalities, odour information is relayed directly to the limbic system, the brain region responsible for memory and emotional processes. Thus, memories, mood, attention, hedonic valence, and arousal are all reciprocally impacted by odour (Gottfried, 2010; Lundstrom et al., 2011; Wilson & Rennaker, 2010).

The olfactory pathway consists of the olfactory epithelium in the nasal cavity, cranial nerves (CN I and CN V), the piriform cortex, entorhinal cortex (anterior parahippocampal gyrus), the cortical nucleus of the amygdala in the temporal lobe, periamygdaloid cortex, the olfactory tubercle (in the basal forebrain), and the anterior olfactory nucleus (Freiherr, 2017; Woolsey, Hanaway, & Gado, 2017). From these brain areas, third-order neurons project olfactory information to brain areas responsible for higher cognitive processing including the orbitofrontal cortex, the insula, hippocampus, dorsomedial nucleus of the thalamus, hypothalamus, ventral striatum, cingulate cortex, and the cerebellum (Freiherr, 2017; Wilson & Rennaker, 2010; Shepherd, 2006).

Olfactory functioning is influenced by genes, neurotransmitters (e.g., dopamine), as well as by neuropathology and neurodegeneration. Genes are responsible for individual differences in smell perception (Reed, & Knaapila, 2010) and may also impact olfaction through their involvement in modulating brain plasticity (e.g., presenilin-1). Olfactory dysfunction accompanies disorders with dopaminergic pathology (e.g., attention deficit hyperactivity disorder, autism, Parkinson's disease, and schizophrenia; Schecklmann et al., 2012; Tonacci et al., 2017) as well as neurodegenerative pathology (e.g., Alzheimer's disease). In the brain, dopamine functions as both a neurotransmitter and a neuromodulator. As a neurotransmitter,

dopamine plays a key role in executive function, motor control, motivation, reward, and arousal (Linster & Fontanini, 2014; Hsia, Vincent, & Lledo, 1999). As a neuromodulator, it is responsible for the functional neuromodulation of olfactory processing (Linster & Fontanini, 2014; Hsia, Vincent, & Lledo, 1999). For example, a noxious odour in the environment triggers the release of dopamine, which then bonds to the D2 receptors in the olfactory bulb and suppresses the olfactory responses to that odour (Hsia, Vincent, & Lledo, 1999). In other words, increased dopamine inhibits olfactory transmission in the glomerular layer of the olfactory bulb (Hsia, Vincent, & Lledo, 1999; Koster et al., 1999). In Parkinson's disease, there is a build up of dopamine in the olfactory bulb and a deficit of dopamine in the rest of the body. This pathology-specific dopamine distribution leads to a decrease in olfactory ability and an increase in motor dysfunction (Huisman et al., 2004). Decreased dopamine has a clear involvement in the pathophysiology of cognitive decline, which can be seen in later stages of Parkinson's as well as in Alzheimer's disease (AD; Martorana et al., 2014). Together these studies indicate that the early impact on olfaction stems from different etiologies for different diseases. In Parkinson's, the initial olfactory dysfunction is most likely due to the build up of dopamine in the olfactory bulb whereas in AD the initial olfactory dysfunction is most likely due to the underlying AD neuropathology, which accumulates slowly over decades before cognitive signs of the disease emerge. This provides further evidence that olfaction may be one of the earliest clinically measurable signs of disease, after which, the combination of neurological damage and decreased dopamine compounds to additionally impact cognitive abilities at which point mild cognitive impairment (MCI) may be detectable through clinical cognitive testing (Fullard et al., 2016; Murphy et al., 2019: Figure 6 pictured below).

Abnormalities in olfactory abilities have been linked to mild cognitive impairment (Roalf et al., 2017, Windon et al., 2020; Fullard et al., 2016), increased risk for neurodegenerative diseases (Murphy, 2021; Murphy 2019) and death (Van Regemorter et al., 2020). Olfactory identification is one of the most commonly used olfactory tests, and is the test that is mainly used in dementia research (Murphy, 2021), which is the primary concern of this dissertation. Low olfactory identification scores have been associated with both the development of MCI (Murphy 2019; Roalf et al., 2017) and the conversion from MCI to dementia in elderly community cohorts (Murphy 2019; Devanand et al., 2010). Individuals who are cognitively normal at baseline are more likely to develop cognitive impairment, MCI, or dementia if they show poorer olfactory function at baseline (Murphy 2019; Wheeler & Murphy, 2021). For those with dementia, deficits in olfactory ability are large, easily identifiable (Sun, Raji, MacEachern, & Burke, 2012), and likely denote fundamental neuroanatomic and neurophysiologic pathology specific to the peripheral olfactory system (Royet, Koenig, Paugam-Moisy, Puzenat, & Chasse, 2004) and primary olfactory cortex (Vasavada et al., 2015).

Olfaction and Memory

Research indicates that olfaction has unique properties compared to other memory systems (Wilson & Stevenson, 2003; Herts & Engen, 1996). Although cognitive and perceptual processing systems across senses share a number of commonalities, there are specific characteristics of olfaction that appear to be different due to the neuroanatomical relationships between olfactory processing and the brain structures responsible for emotion, memory, and learning (Herz, 2012). For example, olfactory memory tends to be predicated on associative learning (Engen 1988; Herz, 2012) and olfactory perception is dependent on the integrity of the

memory system in the brain (Wilson & Stevenson, 2003). Not only does olfaction require learning and memory in order to learn and identify new odours (increasing odour discrimination and identification abilities) but an individual's life experiences with odours integrates external cues and memories into the perceptual quality of those odours, impacting hedonics (i.e., whether the odour is pleasant or not; Wilson & Stevenson, 2003). Previous research has also demonstrated that overall cognitive ability has a significant influence on olfactory identification performance (Hedner et al., 2010), with better olfactory performance occurring concurrently on days when cognitive test performance is better than an individual's own average (Knight et al., 2018). These dependencies on other cognitive and memory systems make it somewhat difficult to quantify what exactly olfactory identification tests are measuring. In addition to memory system dependencies, olfactory identification poses specific demands on an individual's semantic knowledge as there are four answer options presented visually during the test. However, results parsing the related memory dimensions are varied in the literature. For example, Hedner and colleagues (2010) found that executive functioning and semantic memory were reliable predictors ($p < .05$) of odour identification, but only accounted for 4.4% of the explanatory variance in odour identification (Hedner et al., 2010; 15% when adjusted for demographic variables). In another study, episodic memory was the only significant predictor of olfactory identification (Wehling et al., 2010). Further, more recent evidence links olfaction and spatial memory (Hamburger & Knauff, 2019; Raithel & Gottfried 2021), supporting the notion that the original function of the olfactory sense may have been to support cognitive mapping and spatial memory (Dahmani et al., 2018; Jacobs, 2012). This is based on evidence that the olfactory and hippocampal brain systems' evolutionary development may have arisen in parallel, as many of the brain structures are shared (Aboitiz & Montiel, 2015; Dahmani et al., 2018). The relationship

between olfaction and spatial memory is further supported by biological research indicating that olfactory receptors are used in localization, such as the olfactory receptors on spermatozoa facilitating chemotaxis, pathfinding, to the fertilisation of human eggs (Spehr et al., 2003). These previous studies substantiate a reliance on certain forms of memory but indicate that olfactory identification may not be measuring the same underlying concepts as other memory tests and that there may be unique components.

Although different types of memory may contribute to overall olfactory functioning, empirical olfactory measurements are capturing something that sets them apart from cognitive tests. Further evidence for this includes new research demonstrating learning transfer between trained and untrained tasks. In a recent study, Olofsson and colleagues (2020) reported that while practice on a visual memory training task did not transfer to (increase performance in) the untrained olfactory memory task, olfactory training not only improved olfactory scores but also transferred to the untrained visual memory task (i.e., olfactory training improved scores on the untrained visual memory task; Olofsson et al., 2020). In other words, olfactory training gains are transferred to visual memory but not vice versa (Olofsson et al., 2020). One potential mechanism for this might be that training could be stimulating neurogenesis and dendritic branching in the olfactory pathway (e.g., hippocampus) and may then improve cognition more broadly due to hippocampal regeneration. Olofsson and colleagues (2020) provide some evidence that olfactory ability includes functional aspects that are not captured by other memory tasks; however, further studies will be required to fully elucidate these nuances. In summary, research on memory and olfaction indicates that an individual's cognitive abilities may influence olfactory identification performance but that olfaction may be a distinct measurement from memory tasks.

Olfaction as an Indicator of Brain Integrity

Olfactory dysfunction is an early clinical symptom of several neurodegenerative diseases and is suggestive of underlying neurodegeneration, making olfactory functioning a potential indicator of brain integrity (Attems, Walker, Jellinger, 2015). The olfactory system is supported by neurogenesis, which continually supplies the olfactory pathway with new neurons, keeping the pathway functional despite damage incurred from cell death and environmental damage (the olfactory nerve is the only cranial nerve directly exposed to the external environment; Brann & Firestein, 2014). Genes that are key players in neurodegenerative diseases (α -synuclein, presenilin-1, tau, huntingtin) are also involved in modulating brain plasticity (Winner et al., 2011), potentially providing another underlying reason for the early impact on the olfactory system, as the plasticity required to maintain olfactory ability may additionally be impacted by systemic changes that decrease neuroplasticity in the brains of individuals with specific genotypes. An overall decrease in neuroplasticity would have a global impact on brain functioning. Further to a decrease in regeneration and plasticity, olfactory and taste cues have been associated with immune-system activation and suppression, such that odours can serve as conditioned cues to either stimulate or suppress immune responses (similar to conditioned taste aversions; Stevenson, 2010) which may explain the olfactory pathway's interactions with the hypothalamic–pituitary–adrenal (HPA) axis.

Impacts of Stress

The HPA axis is a set of activation and suppression interactions between the hypothalamus, the pituitary gland, and the adrenal glands (above the kidneys). The HPA axis controls the body's response to stress and regulates relevant physiological processes such as

digestion, the immune system, emotion, sexuality, and energy storage and expenditure through the release of glucocorticoid hormones, the end products of the activation of the HPA axis (Spencer & Deak, 2017; Sapolsky et al., 2000). Glucocorticoids are the systemic effector hormone of the HPA axis, secreted by the adrenal glands and circulated through the blood. Glucocorticoids are lipid soluble and can cross the blood-brain barrier where they bind to receptor sites in the limbic system and frontal cortex, brain regions involved in memory processing and emotional regulation (Marin et al., 2011; Lupien et al., 2018). The hippocampus, which is integral to the olfactory pathway, is also a key receptor site for glucocorticoids and facilitates regulation of the HPA axis. The integrity of these brain structures (limbic system and frontal cortex) is critical for the optimal functioning of the HPA axis, yet they receive damage from chronic exposure to stress hormones (Marin et al., 2011).

Repeated activation of the HPA axis and exposure to stress hormones over long periods of time can lead to dysregulation of insulin, glucose, and brain neurotransmitters, which in turn impact the cardiac, immune, metabolic, and neurological systems (Lupien et al., 2018; Sapolsky et al., 2000). This multisystemic strain is referred to as allostatic load and is defined as the ‘wear and tear’ on the body and brain under conditions of chronic stress (McEwen, & Seeman, 1999; Lupien et al., 2018). Chronic stress is linked to cellular changes such as telomere shortening (linked to accelerated ageing; Picard et al., 2014), hippocampal neuronal loss, dendritic atrophy and reduced hippocampal volume (Marin et al., 2011). It has also been associated with impaired cognitive performance, particularly on tasks such as spatial memory, which are dependent on hippocampal functioning (Marin et al., 2011; Lupien et al., 2018).

The hippocampus is a key site for adult neurogenesis as it plays a vital role in a multitude of important functions such as spatial navigation, motivation, learning, and memory, and is vulnerable to damage from a variety of stimuli such as glucocorticoids (and the interplay between glucocorticoids, serotonin and excitatory amino acids), neuritic plaques and neurofibrillary tangles (Anand, & Dhikav 2012). Atrophy of the hippocampus additionally affects neuronal connections to a variety of brain locations, including the olfactory tract, limiting the connectivity of the central and peripheral olfactory neurons and potentially leading to impairment of olfactory function (Vaz et al., 2018). Considering these underlying mechanisms, inclusion of stress may provide further insights into short- and long-term olfactory functioning.

Measuring Stress

The Perceived Stress Scale (PSS) was designed to measure the degree to which situations in one's life are appraised as stressful (Cohen, Kamarck, & Mermelstein, 1983). While this type of measure does not necessarily reflect the physiological responses in the body (Shields & Slavich, 2017; Kagan, 2011; Spencer & Deak, 2017) it is a measure of perceived psychological stress in an individual's environment, which can give some indication of an individual's physiological and emotional reaction to stressors. The scale has been widely used, validated, and associated with physical and mental health, brain structure and function, and biological ageing (Cohen et al., 1983; Epel et al., 2004; Gianaros et al., 2007). For example, in adults 65 and older, perceived stress has been associated with lower baseline cognitive scores and a faster rate of cognitive decline (Aggarwal et al., 2014). In women aged 20-50 years old, those with higher perceived stress scores had telomeres, the protective caps on the ends of DNA strands which shorten with each cell division, that demonstrated the equivalent of an additional decade of

ageing compared to women who reported low perceived stress (Epel et al., 2004). Further, higher perceived stress scores were associated with decreased grey matter volume in the right hemispheres of the orbitofrontal cortex and hippocampus (Gianaros et al., 2007), which are key areas in the olfactory pathway.

Measuring Olfaction: Olfactory Identification Tests

Of the different types of assessment, odour identification is one of the most suitable for inclusion in the identification of subclinical dementia disorder, particularly in combination with neuropsychological assessment (Raheyel et al., 2012). There are several measurable domains of olfaction including threshold, differentiation and identification. All of these olfactory domains have empirical, validated tests. However, for the purpose of this dissertation the focus is on olfactory identification. This dissertation includes two different methods of measuring olfaction and a brief background on measurement methods will be provided here to orient the reader with further details on specific tests provided in the methods section of each project.

Richard Doty and colleagues developed the first olfactory identification test in 1984: the University of Pennsylvania Smell Identification Test (UPSIT; Doty, R. L., Shaman, P., & Dann, M, 1984). The test consists of four 10-page booklets with one scent microencapsulated on each page along with a set of four words. Each test booklet can only be used once. Participants pierce the scent capsule and choose one of the four words that best represents the scent on the page (Doty, Shaman, Kimmelman, & Dann, 1984a). It is a 10-minute forced choice test with high test-retest reliability ($r = 0.9$; Doty, Shaman, Kimmelman, & Dann, 1984a). Since its inception, this test has been translated into multiple languages as well as abbreviated into shorter versions such

as the Brief Smell Identification test (BSIT; Doty, Marcus, & Lee, 1996). This shorter BSIT test was used in Project 1 in the Rush Memory and Aging Project.

Another well-established olfactory identification test is the Sniffin' Sticks Olfactory Identification Test (Hummel et al., 1997), which was used in Project 2. It is one part of a three-part battery including threshold and discrimination, and each of these can be used in combination or alone. The identification test consists of sixteen felt-tipped pens administered in 30-second intervals. Similar to the UPSIT, after smelling each pen, participants choose one of four options they feel best represents the scent. One advantage this test has is that it is reusable, and can be used by many participants, providing it is reloaded with scent tubes annually. Reusability, cost efficiency, and ease of administration combined with good test re-test reliability ($r = 0.86$; Haener et al., 2009) has made it a popular choice among researchers.

Timescales in research

Longitudinal studies are critical to measuring intraindividual change and understanding how individuals change over time. By repeatedly measuring the same individuals over a period of years or decades, each individual's trajectory for the measured variables can be obtained over the study time period, allowing for the examination of systematic changes, such as learning or deterioration of health. Longitudinal studies generally feature successive, widely spaced (e.g., annual) assessments and tend to not be designed to examine intraindividual variability, the short-term fluctuations, as a systematic source of individual differences that can also provide predictive value for cognitive and other health-related outcomes (Martin et al., 2004). Microlongitudinal studies, ecological momentary assessments (EMA), and measurement burst designs are ideal for examining short-term fluctuations. These occasion-to-occasion within-

person fluctuations are of interest in understanding the contextual circumstances in which individuals deviate from their typical scores (Rush et al., 2020; Ram & Gerstorf, 2009) and offer the opportunity to examine dynamic fluctuations such as variability vs. stability in scores. The ability to examine short-term fluctuations within an individual's daily life is aided by the use of ambulatory measurement tools such as Fitbits and mobile cognitive assessments, which can capture data in real time within an individual's natural environment. With respect to cognitive performance, ambulatory assessment may play a critical role in understanding intraindividual variability in daily cognitive performance. Ambulatory cognitive measures capture the individual context-specific factors within each person's daily life in order to further elucidate intraindividual differences in short-term fluctuations in cognitive abilities (Hoppmann & Riediger, 2009), providing a more naturalistic snapshot of an individual's performance within their own life's context.

Dissertation Aims

This dissertation consists of two manuscripts, presented in order of completion, that aim to expand existing knowledge of the relationship between olfactory ability, as measured by empirical olfactory identification tests, and cognition. *Project 1* examines long-term changes in cognition and addresses the following research questions: (1) to what extent is olfactory ability associated with transitions between different cognitive states and death?; (2) Do individuals who have high olfactory identification scores at baseline have longer life expectancies (either overall or cognitively unimpaired)? *Project 2* focuses on short-term variability in cognition and addresses the following research questions: (1) is higher olfactory performance associated with lower intraindividual variability (IIV) in cognition?; (2) are individuals who become less variable

in IIV over the course of the study also higher in their olfactory scores?; (3) does perceived stress impact the effect of olfaction on the prediction of IIV in cognition?

Chapter 2: Olfaction, cognitive states, and mortality: The importance of accounting for competing risks

Abstract

Background: Impaired olfaction is associated with an increased risk of cognitive decline. We will determine the extent to which olfaction is associated with transitions between several clinically diagnosed cognitive states and death, as well as the degree to which olfaction relates to life expectancy in the Rush Memory and Aging Project (N=1501; 74% female).

Methods: Multi-state survival models (MSM) will estimate the association of baseline olfaction on transition patterns through cognitive states (unimpaired, mild cognitive impairment [MCI], dementia) and death. Multinomial regression models will be fit using hazard ratios (HRs) from the MSM's to estimate cognitively unimpaired and total life expectancies.

Results: Higher baseline olfactory scores were associated with a lower risk of transitioning from an unimpaired cognitive state to MCI (HR=0.86, 95% confidence interval 0.82-0.88) and from MCI to dementia (HR=0.89, 0.86-0.93). Additionally, higher test scores were associated with a greater likelihood of transitioning backwards from MCI to an unimpaired cognitive state (HR=1.07, 1.02-1.12). Further, MSM suggests that the direct association between olfaction and transition to death was not statistically significant after accounting for transitions through cognitive states. High baseline olfactory scores were associated with up to 6 additional years free of cognitive impairment and up to 5 additional years of lifespan.

Conclusions: Higher olfactory ability is associated with a decreased risk of progressing forward through cognitive states, and associations between olfaction and mortality are likely to occur

primarily through the pathway of neurodegeneration. Together these analyses highlight the differential role of olfaction as a risk factor for changes across cognitive states.

Introduction

Existing research indicates that the link between olfactory ability and cognition is useful for the prediction of future cognitive impairment (Windon et al., 2020), neurodegenerative disease (Devanand, 2016), and mortality (Van Regemorter et al., 2020), however, the extent to which olfaction is associated with cognitively unimpaired lifespan is unclear. Likewise, previous research has not systematically investigated whether olfactory test scores are sensitive enough to predict intraindividual progression through different cognitive states over time. Previous research using Cox regression models to estimate the role of olfactory identification scores in predicting different cognitive outcomes (Van Regemorter et al., 2020; Devanand et al., 2019) has been constrained by the ability to estimate progression to only a single cognitive state (e.g., Mild cognitive impairment [MCI] or dementia), and has not accounted for death or for changes in cognitive states during study follow-up occasions.

Olfactory processing areas, such as the olfactory bulb and the entorhinal cortex, are some of the earliest areas affected by neurodegenerative pathology (Murphy, 2019; Albers et al., 2015). Further, the amount of pathology present in the brain has been shown to be related to the degree of olfactory impairment, suggesting that the underlying mechanism for both cognitive and olfactory decline may be irreparable damage which might be easily identified through declining olfactory scores (Murphy, 2019; Albers et al., 2015). This study extends prior work with the Rush Memory and Aging Project (MAP; Wilson, Schneider et al., 2007; Wilson et al., 2011) to examine the impact of olfaction on transitions between clinically diagnosed cognitive states (unimpaired, MCI, and dementia) and death using multi-state survival modeling (MSM). This approach permits simultaneous estimation of transitions through multiple cognitive states while also accounting for death as a competing risk factor. MSM also supports estimation of both

overall and cognitively unimpaired life expectancies. The following questions were investigated: To what extent is olfactory ability associated with transitions between different cognitive states and death? Do individuals who have high olfactory scores at baseline have longer cognitively unimpaired and total life expectancies? Based on previous research (Windon et al., 2020; Wilson et al., 2011), individuals who have lower scores on olfactory identification tests at baseline may be more likely to transition to impaired cognitive states and death, and may have shorter life expectancies than individuals who have higher olfactory scores at baseline.

Method

Participants

The current analysis will be based on data from 1501 individuals assessed annually from MAP (Bennett et al., 2018) a longitudinal study of older adults with ongoing recruitment from retirement communities in Northeastern Illinois between 1997 and 2019. Olfactory testing first occurred in 2000, while cognitive functioning was assessed annually from study baseline in 1997. Participants met eligibility criteria for this analysis if their data included baseline olfactory assessment and demographic information, as well as cognitive assessment at two or more occasions. Participants had an average of 7.37 years of follow-up ($SD = 3.94$; range = 2-18) with 23% ($n=347$) receiving a diagnosis of dementia at some point during the study; the average age at dementia diagnosis was 87.74 years ($SD = 6.77$; range = 64-106). Baseline characteristics for the sample are presented in Table 1.1.

Table 1.1 *Baseline descriptive statistics for the sample.*

Variable	Mean (SD)	Range
	N (%)	
Olfactory score	8.88 (2.33)	0-12
MMSE	27.71 (2.67)	9-30
MCI (Baseline), n (%)	372 (24.8%)	
Dementia Diagnosis, n (%)	56 (3.7%)	

APOE ε4	311 (20.7%)	
Age	79.65 (7.73)	53-100
Female, n (%)	1117 (74.4%)	
Caucasian, n (%)	1388 (92.5%)	
Chronic Conditions	1.44 (1.06)	0-6
Education (years)	14.72 (3.33)	0-29
Smoking	40 (2.7%)	

Standard protocol approvals, registrations, and patient consents.

The Institutional Review Board of Rush University Medical Center reviewed the study. All participants signed an informed consent and a repository consent that allows their data to be repurposed.

Measures

Olfactory Assessment

Olfaction was assessed using the 12-item Brief Smell Identification Test (B-SIT; Doty et al., 1996). During the test, a microencapsulated patch containing an odorant is scratched with a pencil and placed under the nose of the participant. Response options on the B-SIT are forced-choice: participants choose which out of four presented words best represent the smell.

Consistent with previous research (Wilson et al., 2011), up to 2 missing responses are allowed

(missing items assigned a score of 0.25). If more than 2 items were not answered, the entire test is treated as missing and participants not included in the analysis. Summed scores are computed based on the number of correct responses. Continuous olfactory scores were centered on 11 (score – 11), which represents the minimum score for normal olfactory ability (Doty et al., 1996; Menon et al., 2013). For estimation of life expectancies specific numbers were required and in order to align with previous literature (Doty et al., 1996; Menon et al., 2013, olfactory ability was classified as low (5), moderate (10), and normal (12).

Cognitive Assessment

The cognitive states used in the MSM were based on a 3-step diagnostic protocol, which included a clinical diagnosis of cognitive status made at every assessment based on computer scoring of 19 cognitive tests, clinical judgement by a neuropsychologist, and diagnostic classification by a clinician (neurologist, geriatrician, or nurse practitioner) (Bennett, Schneider Aggarwal et al., 2006). The resulting cognitive assessments were used to operationally define the cognitive states: (i) no clinical diagnosis of cognitive impairment or no cognitive impairment (NCI), which reflects a normal range of cognitive performance without knowledge of an individuals' level of functioning before entering the study, such that an individual may have already declined relative to their own peak, but are still operating within clinically established norms; (ii) the MCI state represents individuals where a neuropsychologist deemed the individual to have cognitive impairment, but they do not meet criteria for dementia; and (iii) a diagnosis of dementia indicates evidence of a meaningful decline in cognitive function relative to a previous level of performance within the study follow-up including impairment in memory and at least one other area of cognition. Assessments were completed annually with up to 15 years of follow-up.

Apolipoprotein E (APOE)

Apolipoprotein E (APOE) allele status was included as a dichotomous variable, in which individuals with one or more ϵ 4 alleles were coded as 1, and individuals without an ϵ 4 allele were coded as 0 (Yu et al., 2017).

Chronic Conditions

To control for the impact of chronic diseases and associated medications on both cognition and olfaction (Doty et al., 2004), a chronic conditions variable was created. The overall burden of chronic diseases was operationalized as a count of the total number of self-reported chronic conditions at baseline: hypertension, diabetes, heart disease, cancer, thyroid disease, head injury with concussion, and stroke.

Education

Education was measured as years of education reported at baseline, and centered at 12 (number of years of education – 12) to represent high school education in the United States.

Smoking

Self-reported smoking status was measured at baseline. Current smokers were coded as 1 and (current) non-smokers were coded as 0.

Statistical analysis

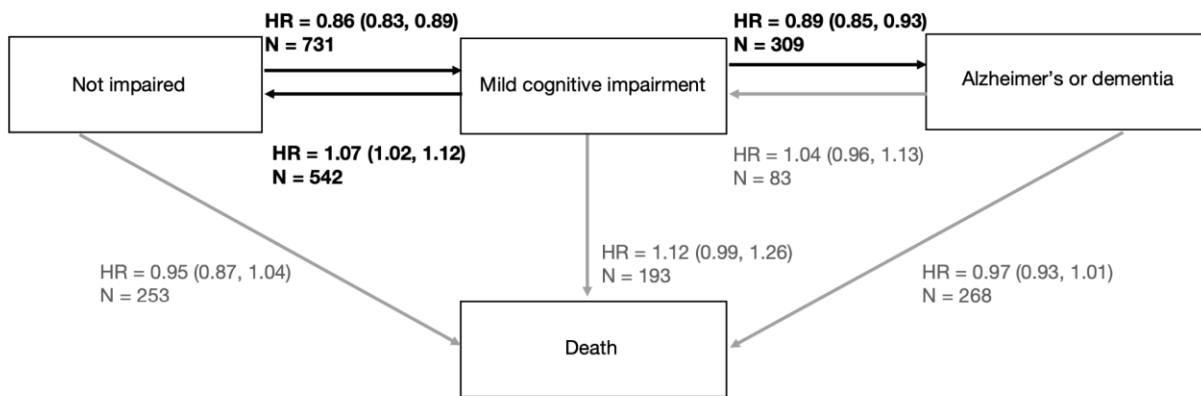
All analyses were conducted in R (Team RC, 2013). The MSM package (Jackson, 2011) was used to estimate the multi-state survival models, while the elect package (Estimating Life Expectancies [LEs] in Continuous Time) (van den Hout et al., 2019) was used to estimate LEs. Multi-state survival modeling (MSM) (van den Hout, 2016) was used to assess individual transitions through different cognitive states (NCI, MCI, dementia), and death as well as backwards transitions from MCI to NCI and dementia to MCI, as shown in Figure 1. While the backwards transition from dementia to MCI is generally not modeled due to theoretical improbability of returning from a true dementia state, we included it in this dissertation as this is clinically diagnosed dementia and there were participants transitioning backwards from AD diagnosis. We further ran a sensitivity analysis, excluding all participants with a transition from dementia to MCI and from dementia to NCI to examine whether individuals with those backwards transitions influenced results. MSM is an extension of traditional survival modelling that allows investigation of the association of olfactory ability with transitions to more than one cognitive state within a single model, while also accounting for death as a competing risk factor (Figure 1). Interval censoring was used in cases where participants had missing data between two states, where state transitions were known to have occurred within this interval, but the exact timing of the transition was unknown (van den Hout et al., 2019). This allows the estimation of transition probabilities even in cases with missing cognitive state data. Further, MSM utilises maximum likelihood estimation, which is robust to data missingness and provides estimates for all participants, even those with missing outcome data. The cognitive states were based on all available longitudinal cognitive assessment data for each participant. Age, sex, education, APOE $\epsilon 4$ allele, baseline olfactory score, smoking status, and chronic conditions were included as

covariates on all transitions. Models including interaction terms between olfactory scores and each of the other key covariates (age, sex, APOE) were additionally fit to determine whether these covariates moderated the association of olfactory scores with the transition probabilities. Further, two sets of follow-up analyses were completed: first, additional MSM models were conducted to assess whether smoking in the past impacted results. Second, a Cox survival analysis estimated the association between baseline olfaction and mortality to improve comparability of the current analysis within the existing literature and to clarify the importance of accounting for cognition when examining olfaction and death. Finally, the elect package fit a multinomial regression model using the hazard ratios (HRs) estimated by the MSM to predict years spent in NCI and impaired states, as well as total years of life expectancy.

Data Availability

MAP data are available via the Rush Alzheimer's Disease Center Research Resource Sharing Hub and can be requested at <https://www.radc.rush.edu>. Qualified investigators can submit requests for de-identified data.

Figure 1.1 Four-state multi-state model illustrating the effect of one additional correct item on the BSIT on transitions between cognitive states including pooled hazard ratios (HR) and 95% confidence intervals.



Results

The total number of individual transitions between cognitive states during the study is reported in Figure 1.1, with significant transitions indicated in bold.

Association with Baseline Olfaction on Transitions between Cognitive States

Higher baseline olfactory ability was associated with a lower risk of transitioning from NCI to MCI (Table 2) and from MCI to dementia. Interpretation of the hazard ratio for clinical utility indicates that for each one-unit increase in olfactory score there was a 14% reduction in risk of transitioning to MCI from NCI (HR = 0.86, 95% confidence interval 0.82-0.88). This indicates that an individual with an olfactory score of 12 (high) would be 65% less likely to transition to MCI from NCI compared to an individual with a score of 5 (low). Higher smell scores were associated with a greater likelihood of backwards transition from MCI to NCI, indicating that an individual with a score of 12 would be 60% more likely to transition back to NCI from MCI compared to an individual scoring 5 on the olfactory test. Baseline olfactory scores were not associated with the transition to death from any of the cognitive states.

Association with Covariates on Transitions between Cognitive States

Age

As expected, older age was associated with a greater risk of transitioning from NCI to MCI and from MCI to dementia. Further, older age was associated with a greater risk of death from NCI, MCI, and dementia, as well as lower likelihood of transitioning backwards from MCI to unimpaired cognitive functioning.

Sex

Male participants had a greater likelihood of transitioning backwards from dementia to MCI and were more likely to transition from dementia to death.

Education

Higher education at baseline was associated with a lower risk of death from NCI, and a greater likelihood of the backwards transition from MCI to NCI.

APOE ϵ 4

Having an ϵ 4 allele was associated with a greater risk of transitioning to MCI from NCI and from MCI to dementia, as well as a lower likelihood of transitioning backwards from MCI to NCI.

Chronic Conditions and Smoking

Having more chronic conditions was associated with a greater risk of transitioning from MCI to dementia, and a greater risk of transitioning from NCI to death. Likewise, more chronic conditions were associated with a greater likelihood of transitioning backward from MCI to NCI, and from dementia to MCI. Smokers had a greater risk of transitioning to MCI from unimpaired cognition and a greater risk of transitioning from NCI to death.

Interaction Terms and Sensitivity Analyses

None of the interaction terms were significant. The sensitivity analysis including previous smoking status suggests that smoking in the past did not impact results. As such, neither the interaction terms nor past smoking were included in the final model. A previous meta-

analysis found that while current smokers have higher risk of olfactory dysfunction former smokers were not significantly different in risk from never smokers (Ajmani et al., 2017).

The sensitivity analysis excluding individuals who transitioned from dementia to MCI and dementia to NCI did not affect olfactory results. Additionally, Cox Survival modelling estimated the risk of all-cause mortality using a method comparable to previous studies (i.e., not accounting for transitions through cognitive states, in contrast to MSM) (Pinto et al., 2014; Ekstrom et al., 2017; Schubert et al., 2017; Devanand et al., 2015; Wilson et al., 2011; Choi et al., 2021; Gopinath et al., 2012; Laudisio et al., 2019; Liu et al., 2019). Results showed that higher olfactory scores significantly reduced risk of death across the full follow up period (HR=0.825; 95% CI: 0.799, 0.851).

Table 1.2 Hazard ratios and 95% confidence intervals for the effect of olfaction and covariates on the transitions through different states of cognitive functioning

MAP (N = 1501)							
Transition	Hazard Ratios (95% CI)						
	Olfaction	Age	Sex	Education	Chronic Conditions	APOE-E4	Smoking
N to MCI	0.86 (0.83,0.89)	1.06 (1.05,1.07)	1.13 (0.95,1.35)	1.00 (0.97,1.02)	1.02 (0.94,1.1)	1.25 (1.04,1.51)	1.82 (1.17, 2.84)
N to Death	0.95 (0.87,1.04)	1.10 (1.07,1.14)	1.37 (0.89,2.11)	0.93 (0.88,0.99)	1.30 (1.09,1.55)	0.96 (0.55,1.65)	2.62 (1.03, 6.63)
MCI to N	1.07 (1.02,1.12)	0.97 (0.96,0.98)	0.98 (0.79,1.22)	1.05 (1.02,1.08)	1.10 (1.01,1.21)	0.66 (0.52,0.84)	1.18 (0.70, 2.00)
MCI to Dem	0.89 (0.85,0.93)	1.06 (1.05,1.08)	0.93 (0.72,1.19)	0.98 (0.94,1.01)	1.12 (1.01,1.25)	1.48 (1.17,1.88)	1.12 (0.52, 2.4)
MCI to Death	1.12 (0.99,1.26)	1.08 (1.02,1.14)	1.67 (0.91,3.06)	1.02 (0.94,1.12)	1.11 (0.81,1.52)	0.57 (0.23,1.45)	1.15 (0.21, 6.38)
Dem to MCI	1.04 (0.96,1.13)	0.98 (0.95,1.01)	1.74 (1.09,2.79)	1.00 (0.94,1.07)	1.26 (1.04,1.53)	0.70 (0.42,1.17)	3.08 (0.79,12.10)
Dem to Death	0.97 (0.93,1.01)	1.07 (1.04,1.09)	1.50 (1.13,1.99)	0.97 (0.93,1.00)	1.07 (0.96,1.20)	0.88 (0.67,1.17)	1.00 (0.39, 2.55)

Note. N = unimpaired cognition; MCI = mild cognitive impairment; Dem = dementia.

Life expectancy

As there are often reported sex differences in life expectancies (Hoogendijk et al., 2019) as well as specifically with dementia (Mosconi et al., 2017), this study reported life expectancies split by sex. Cognitively unimpaired and total life expectancies increased linearly with higher olfactory scores for both female and male participants (Figure 2). For example, an average non-smoking 80 year old female with a high school education, no chronic health conditions, without an *APOE* $\epsilon 4$ allele, and with a low smell score at baseline was estimated to live approximately 4 additional years (to 84) with NCI and 9.5 years overall (Table 2). In comparison, an average female participant with all the above characteristics but with moderate olfactory scores was estimated to have 8 years of life expectancy with NCI and 13 total years of life expectancy, while those with high olfactory scores had 10 years of life expectancy with NCI and 14 years overall. Although female participants consistently had longer estimated life expectancies across all groups compared to male participants, estimated LEs for male participants followed a similar pattern (i.e., NCI and total LE increased with better olfaction). Both male and female participants with one or more *APOE* $\epsilon 4$ alleles had shorter life expectancies compared to individuals without an *APOE* allele across all olfactory levels (Figure 2). Compared to those without an *APOE* $\epsilon 4$ allele, females with one or more *APOE* $\epsilon 4$ allele(s) and with high smell scores would be expected to live an additional 2 years free of cognitive impairment.

Table 1.3 Life expectancies for non-smoking male and female participants at age 80 with a high school education and no chronic conditions for low, medium, and high olfactory scores by *APOE* ϵ 4 status.

	Overall life expectancies in years (95% CIs)	Life expectancies without cognitive impairment in years (95% CIs)
Without <i>APOE</i> ϵ 4		
Female, Olfaction (5)	9.49 (8.48, 10.33)	4.27 (3.65, 4.84)
Female, Olfaction (10)	12.56 (11.55, 13.34)	8.20, (7.36, 8.65)
Female, Olfaction (12)	13.75 (12.32, 14.69)	10.03 (8.93, 10.82)
Male, Olfaction (5)	8.22 (7.08, 9.24)	3.83 (3.27, 4.64)
Male, Olfaction (10)	10.74 (9.38, 12.10)	7.25 (6.48, 8.26)
Male, Olfaction (12)	11.70 (9.99, 13.11)	8.79 (7.59, 10.08)
<i>APOE</i> ϵ 4 carrier		
Female, Olfaction (5)	8.73 (7.74, 9.53)	3.05 (2.48, 3.64)
Female, Olfaction (10)	11.75 (10.46, 12.62)	6.30 (5.44, 7.08)
Female, Olfaction (12)	13.08 (11.43, 14.14)	8.04 (6.87, 9.09)
Male, Olfaction (5)	7.48 (6.58, 8.53)	2.75 (2.18, 3.40)
Male, Olfaction (10)	10.18 (8.84, 11.18)	5.67 (4.73, 6.62)

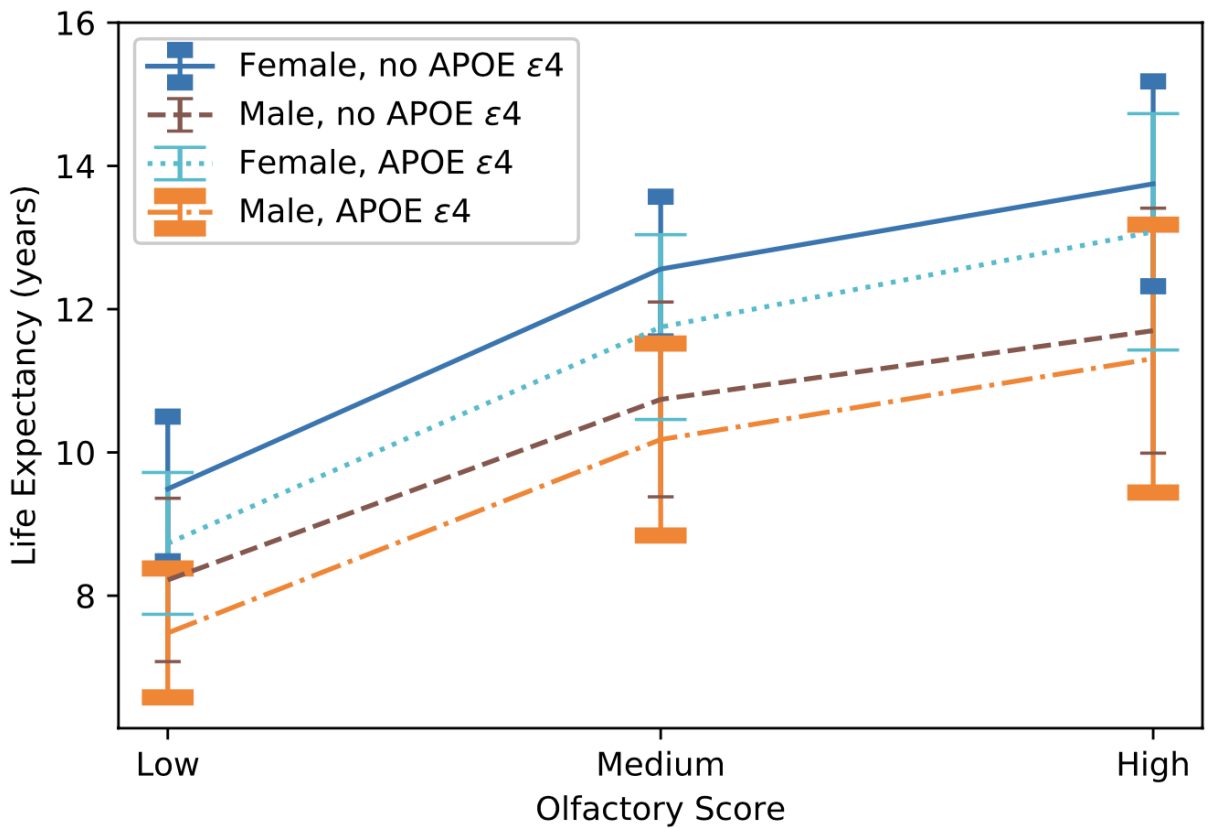
Male, Olfaction (12)

11.31 (9.44, 12.75)

7.21 (5.84, 8.52)

Note. Olfactory scores listed as 5, 10 and 12.

Figure 1.2 Cognitively unimpaired and overall life expectancies for female and male APOE $\epsilon 4$ allele carriers and non-carriers for olfactory scores of 5, 10, and 12.



Note. APOE = apolipoprotein.

Discussion

Olfaction and transitions between cognitive states

Our findings indicate that higher baseline olfactory identification scores are associated with a lower risk of transitioning from NCI to MCI and dementia, adjusting for age, sex, education, smoking, *APOE* ϵ 4 allele status, and chronic conditions (Table 1.2). Higher baseline olfactory scores also had a protective effect, such that those with higher scores on the olfactory identification test were more likely to return to NCI from MCI, as well as have a greater number of years of life without diagnosed cognitive impairment. Healthy individuals with high olfactory scores, on average, lived free of diagnosed cognitive impairment for up to 6 years longer than those who had low olfactory scores (Table 1.3).

Olfaction and mortality, accounting for cognitive states

In this analysis, the multi-state survival model accounts for cognitive impairment across an average of 7.37 years of follow-up (up to 15 years follow-up). Despite existing literature showing that lower olfactory scores are associated with mortality (Pinto et al., 2014; Ekstrom et al., 2017; Schubert et al., 2017; Devanand et al., 2015; Wilson et al., 2011; Choi et al., 2021; Laudisio et al., 2019; Liu et al., 2019), our findings suggest that, once cognitive status is accounted for, olfactory ability is not directly associated with the transition to death from any state. This contrast may help to elucidate potential underlying mechanisms for the link between olfaction and death, which are currently unclear in the literature (Van Regemorter et al., 2020; Gopinath et al., 2012). Specifically, our findings suggest that olfaction may not be associated with mortality above and beyond the competing risk of cognitive decline. Importantly, research suggests that MCI (Bae et al., 2018; Yu, Boyle et al., 2019) and dementia (Smith et al., 2021)

substantially increase risk of death; as such, associations previously reported between olfaction and mortality that do not account for cognition may be partially or largely accounted for by the pathway through cognitive decline. Our findings, that higher olfaction is associated with a substantially decreased risk of transitioning forward through cognitive states (14% per unit increase in olfactory score for NCI to MCI, and 10% per unit increase in olfactory score for MCI to dementia), are consistent with this explanation. Indeed, prior work in MAP applying Cox regression models suggested that low olfactory scores at baseline were associated with increased risk of mortality. That is, in an analysis that did not account for multiple cognitive states, increased risk of mortality was observed in the same sample (i.e., MAP; Wilson et al., 2011). Although low olfactory ability appears to be associated with increased risk of mortality (Wilson et al., 2011) and increased neuropathology in studies using MAP data (Wilson et al., 2007; Vassilaki et al., 2017; Growdon et al., 2015), previous work examining risk of death has not simultaneously accounted for the competing risk of transitions through cognitive states. As a sensitivity analysis, we ran a similar Cox survival model, including additional years of follow up compared to the previous study (Wilson et al., 2011). When the transitions through cognitive states were not accounted for (and instead the models were only adjusted for baseline cognition), we similarly found that olfaction was significantly associated with death. As in the previous findings (Wilson et al., 2011), our Cox analysis also indicated that higher olfactory scores were associated with a 17.5% decrease in mortality risk across the full follow up period (HR=0.825; 95% CI: 0.7998, 0.8512). While our sensitivity analyses modelling the risk of all-cause mortality showed that better olfaction reduced risk of death, the more comprehensive MSM analyses that account for occasion-specific cognition reveal that olfactory impairment was not directly associated with mortality. When the time-varying transitions were accounted for (via multi-state

modeling), our results showed that baseline olfaction alone was not directly associated with death (as suggested by previous research). The MSM approach suggests that the association between olfactory impairment and mortality shares variance with the increased risk of mortality associated with cognitive impairment. That is, the association between olfaction and death is primarily accounted for by the pathway through cognitive decline.

In addition, some research suggests that the association between olfactory ability and mortality may require a substantial amount of time to develop. Previous work using proportional hazards models to examine the association between low olfactory scores and death differentiated between prevalent and incident forms of sensory impairment in an examination of risk of mortality over 10 and 15 years (Schubert et al., 2017). Their results indicated that prevalent low olfactory scores were associated with a higher risk for 15-year mortality (Schubert et al., 2017), consistent with previous studies except one (Gopinath et al., 2012). However, when they examined the risk of mortality in a subsample of individuals without prevalent olfactory deficits (i.e., all participants had high olfactory ability at baseline), but including individuals with incident olfactory deficits (i.e., some participants had decreased olfaction at follow-up occasions), results indicated that low olfactory ability was not associated with mortality in the following 10 years. These results suggest that more than 10 years of olfactory impairment may be required in the prediction of mortality rates. Importantly, these findings suggest that olfaction may be a particularly sensitive marker of neural integrity.

Alternatively, mortality may be partly or fully accounted for by cognitive decline prior to death. That is, rather than causing death, the mechanisms linking olfactory performance to risk of mortality may be more related to the aging central nervous system or underlying pathology build up (Van Regemorter et al., 2020). This postulation is further substantiated by the estimated life

expectancies for individuals with better olfaction (i.e., individuals with higher olfactory ability were estimated to have longer cognitively unimpaired and total years of life expectancy relative to individuals with lower olfactory ability). While this may seem counterintuitive, given that this study did not find a direct association between olfaction and mortality, these findings actually further substantiate our explanation that the association between olfaction and mortality may be accounted for by the pathway through cognitive decline. As higher olfactory ability is associated with longer cognitively unimpaired life expectancies, the olfactory system may be a more sensitive indicator of overall brain health (e.g., brain aging and neuropathology). In other words, individuals with higher olfaction at baseline are less likely to transition to MCI or dementia, which is reflected in their total estimated life expectancy, in addition to their cognitively healthy life expectancy. Together, these results suggest that olfactory testing, although not disease-specific, may be a useful and cost-effective approach for the pre-clinical assessment of brain health. Olfactory tests are readily available for purchase and often already in clinics for testing loss of olfactory functioning (e.g., otolaryngologists).

Covariates

It is well known that age is a risk factor for cognitive decline (Prince et al., 2013). As expected, older age was associated with a greater risk of transitioning forward through cognitive states, as well as death. Male participants with a dementia diagnosis had a greater likelihood of returning to MCI, as well as a higher risk of death. These findings may be due to the small percentage of men in the sample (26%), differences in medication adherence, depression, amount of social or cognitive engagement, hospital stays, or hormonal differences (Mosconi et al., 2017; Nebel et al., 2018). Males may have a higher risk of death due to sex differences in Alzheimer's

disease (Mosconi et al., 2017; Nebel et al., 2018) or differences in lifestyle or life expectancies (Nebel et al., 2018).

Education is often included as a component of socio-economic status (SES), as a proxy for cognitive reserve in late-life cognition (Stern, 2012), and is a reliable predictor of an array of outcomes across the lifespan (Clouston et al., 2012; James et al., 2019). In this study, although more education was associated with a lower risk of death, it was not significantly associated with transitions between cognitive states. This may be due to the high average education in this cohort. Future studies including participants with more variability in education and SES may provide additional insights.

Having more chronic conditions was associated with a greater likelihood of cognitive improvement, indicated by the significant backwards transitions from MCI to NCI and from dementia to MCI. While these results are not intuitive, it is possible that lifestyle changes and medications prescribed in the management of chronic conditions may result in improvements in cognitive performance or mitigate the symptoms of cognitive impairment. For example, better management of chronic conditions could simultaneously lead to better cognitive outcomes. However, interpretation is difficult due to the complexity of interactions between health conditions, medications, and cognition (Fried et al., 2014) and by research suggesting that some medications also affect olfaction (Lotsch et al 2012).

APOE ϵ 4 has been shown to adversely affect both memory (Levy et al., 2004; Anstey et al., 2000) and olfactory functioning (Olofsson et al., 2010; Gilbert & Murphy, 2004). The current analysis suggests that having one or more *APOE* ϵ 4 allele(s) increases the likelihood of transitioning to MCI and dementia, and decreases the likelihood of returning to NCI from MCI, indicating a deleterious effect on cognitive health. Life expectancies were also detrimentally

affected by the presence of one or more $\epsilon 4$ allele(s), with carriers had lower life expectancies across all olfactory ability levels. For example, an average 80 year old non-smoking male participant with a high school education, no chronic conditions, a high olfactory score and no *APOE* $\epsilon 4$ allele had 1.6 years of additional cognitively unimpaired life expectancy and 0.4 years of additional overall life expectancy compared to those with an *APOE* $\epsilon 4$ allele (Table 2). This suggests that the *APOE* allele may not substantially impact total life expectancy, but does impact cognitively unimpaired lifespan. In female participants, there appeared to be a slight upwards trend in cognitively unimpaired life expectancy as smell ability increased in those with an *APOE* $\epsilon 4$ allele. For example, 80 year old females without an *APOE* $\epsilon 4$ allele had 1.3 years (low olfactory score), 1.9 years (moderate), and 2 years (high) of additional cognitively unimpaired life expectancy compared to those with an *APOE* $\epsilon 4$ allele (Table 2). Although the difference is not large, further investigation is warranted to determine the extent of sex differences in the effects of *APOE* $\epsilon 4$ on olfactory ability and life expectancy.

Limitations

These findings are based on a fairly homogenous sample of highly educated, mainly Caucasian, individuals with a mean age of 80 years who agreed to brain donation after death. Cultural and cohort differences could be explored in future studies examining multi-ethnic and mid-life cohorts. While information on cultural impacts would benefit this literature, olfactory test components (i.e., including lavender or anise) change to accommodate cultural knowledge. Considering this, studies also examining changing test items versus training participants on included items could be explored.

As with most olfactory identification tests, the B-SIT is a forced-choice test where scoring may overestimate olfactory ability. For example, imputing results for up to 2 missing olfactory items on the test may potentially skew results higher for individuals who may be skipping questions due to not knowing the answers. Some items on the B-SIT have been found to have low reliability and may not be assessing participant ability as accurately as other items on the test (Menon et al., 2013). Although the B-SIT is a shorter version of the University of Pennsylvania Smell Identification Test (UPSIT), which means that the degrees of olfactory dysfunction may not be as clearly delineated, and errors or missing answers have a greater impact on scores, the B-SIT was found to be comparable to the UPSIT for predicting conversion to dementia (Devanand et al., 2019). In addition, an objective scale for chronic conditions, as opposed to self-report, would provide a better measure of health. Air pollution, while outside of the scope of this project, could also be considered for future studies. Finally, future research conceptually replicating these analyses in additional longitudinal studies of aging would improve our understanding of the importance of accounting for cognition when examining the association between olfactory ability and mortality.

Conclusion

This study provides evidence that olfactory ability indicates neuronal integrity, slower progression through cognitive impairment, and that associations between olfaction and mortality are likely to occur primarily through the pathway of neurodegeneration. Findings are based on data from 1501 participants who were followed annually for up to 15 years using methodology that simultaneously considers olfaction, clinically diagnosed cognitive states, and mortality. Further, olfactory testing may be a useful tool in assessing and monitoring brain health and

implementation of regular olfactory testing as part of general health checkups may improve understanding of cognitive health.

Chapter 3: Olfactory Identification and Intraindividual Cognitive Variability

Abstract

Objective: The objective of this study was to determine whether olfactory scores are associated with short-term intraindividual variability (IIV) in cognition. The following research questions are addressed: (1) is higher olfaction associated with lower IIV in cognition?; (2) do individuals with higher olfactory scores become less variable in IIV over the course of the study (i.e., become more consistent)?; (3) is the predictive value of olfaction for IIV in cognition impacted by perceived stress? (e.g., is the cognitive performance of individuals who have poor olfactory scores more impacted by stress)?

Method: Participants aged 64-78 ($N=65$) completed a demographics questionnaire, a brief survey of well-being, and an olfactory test in-person. Participants took the equipment home with them where they completed daily surveys and cognitive tests on mobile phones four times each day for 14 consecutive days. At the end of the 14 days, participants returned to complete the exit survey and another olfactory test. Multilevel models were used to examine associations between olfactory scores and IIV in cognition across five different cognitive tasks scored for reaction time and accuracy.

Results: Olfactory scores were not consistently associated with IIV across all cognitive tests. However, the interaction of perceived stress and olfaction was significant for the baseline IIV in reaction time for Color Dot and Color Shape tasks.

Conclusion: Although consistent results were not found across all cognitive tasks, perceived stress impacted the effect of olfaction on IIV in 2 of 5 tasks scored for reaction-time, such that for individuals with high stress and high olfaction, IIV reaction-times were more consistent.

Introduction

Adults exhibit considerable intraindividual variability (IIV) in cognitive performance from one occasion to the next (Hultsch et al., 2000). This variability in performance has been linked to both maladaptive and adaptive representations of cognition (Martin et. al., 2004; Allaire & Marsiske, 2005; Macdonald et al., 2009). For example, IIV has been associated with brain dysfunction (Costa et al., 2019), longitudinal decline in basic cognitive abilities (MacDonald et al., 2003). Both inconsistency (the magnitude of IIV) and dispersion (the number of cognitive domains in which variability is present) have been found to predict future cognitive decline (Roalf et al., 2016; Costa et al., 2019; Hultsch et al., 2000). In contrast, early lifespan development, variability is beneficial and is seen as adaptive during tasks such as motor learning and exploration (MacDonald et al., 2006; van Dijk & van Geert, 2014). Research in adults has found that adaptive forms of variability can be observed for tasks amenable to strategy use (MacDonald, Li, & Bäckman, 2009; Li, Aggen, Nesselroade, Baltes, 2001), such as spatial memory tasks (Li, Aggen, Nesselroade, Baltes, 2001). However, continued variability in performance after mastering or obtaining a given level of functioning likely indicates diminished stability in performance (MacDonald, Li, & Bäckman, 2009) and this form of maladaptive variability in adults is consistently associated with cognitive impairment (Dinstein, Heeger, & Behrmann, 2015; Costa et al., 2019) and is interpreted as reflecting brain dysfunction. Neuroimaging data suggest a relationship between IIV and dysfunction of the default mode network, presumably mediated by white matter disintegration in frontal and parietal areas (Costa et al., 2019), which may also impact olfactory functioning.

IIV within a single person across trials in one session, or over multiple sessions, is defined as inconsistency (Costa et al., 2019) and is what will be referred to as IIV. There are

multiple ways to measure IIV and one of the most commonly used approaches is the coefficient of variation (CoV), which divides the individual standard deviation by the corresponding subject's mean reaction time (Costa et al., 2019). CoV shows the extent of variability in relation to the mean, or in other words, the higher the CoV the greater the level of dispersion around the mean. CoV is a ratio, which allows for comparisons across multiple types of tests with different units (e.g., accuracy scores vs reaction timed scored tests). In contrast, when using standard deviation (SD), a measure of how far the average value lies from the mean, SD will typically increase as the units increase, whereas CoV is unitless, allowing comparison across tests. For this study there were five different cognitive tests, each scored for reaction time and accuracy. CoV was chosen in order to make it possible to compare across different methods of scoring (reaction-time vs accuracy scored).

While IIV can be derived from reaction-time or accuracy-based tasks, reaction-time based IIV measures have been found to be better predictors of cognitive impairment (as indexed by overall cognitive and memory performance) than accuracy-based IIV measures, potentially due to the number of trials involved in reaction times testing as well as reaction-time being less sensitive to practice effects (Christ et al., 2018). In contrast, accuracy-based IIV measures may be used as indicators of a specific type of cognitive impairment when there is potential to be linked to a specifically damaged neuroanatomical site or system, such as differentiating AD from controls (Christ et al., 2018).

IIV is believed to be highly sensitive to subtle changes in cognitive function (MacDonald, Nyberg, & Bäckman, 2006) and therefore of special interest in prodromal and early stage neurodegenerative disorders. Several reviews have reported that IIV is associated with cognitive decline and/or conversion to MCI/dementia (Haynes, Bauermeister, & Bunce, 2017; Costa,

Dogan, Schulz, & Reetz, 2019; MacDonald, Li, & Bäckman, 2009; Mumme, Pushpanathan, Donaldson, Weinborn, Rainey-Smith, Maruff, & Bucks, 2021). Similarly, lower olfactory scores have been associated with neurodegeneration and poorer cognitive performance (Murphy 2019, 2020), cognitive decline (Chen et al., 2021; Windon et al., 2019) and conversion to MCI and dementia (Sun et al., 2012; Devanand 2016).

Modifiable lifestyle factors such as physical activity and stress have been shown to impact cognition over both long and short-term time scales. While the association between physical activity and mental (Paluska & Schwenk, 2000) and physical health (Warburton et al., 2006) has been well established, it has also been demonstrated that stress can impede efforts to be physically active (Stults-Kolehmainen & Sinha 2014). Psychological stress is a potentially modifiable risk factor that has been linked to increased rates of MCI (Katz et al., 2016) and AD (Pirainen et al., 2017; Johansson et al., 2013). Further, higher daily stress has been associated with slower reaction times and more variability for cognitive tasks (Sliwinski et al., 2006). Importantly, stress also has a significant deleterious impact on the functioning of the hippocampus (Kim et al., 2015), which may point to a relationship between stress and olfaction (Vaz et al., 2018).

This chapter will examine whether olfactory identification scores are associated with IIV in five cognitive measures. To the best of my knowledge, no study has yet examined the association between olfaction and the short-term dynamics of cognitive variability. Specifically, this study will examine (1) whether olfaction is associated with IIV in cognition in both reaction time and accuracy scored tasks; (2) whether olfactory scores are associated with rates of change in IIV over the course of the study (e.g., are faster rates of decline in IIV associated with better olfactory scores?); (3) investigate whether perceived stress impacts the effect of olfaction on the

prediction of IIV in cognition (i.e., does olfaction matter more for predicting IIV in individuals with more perceived stress?).

Method

Participants

Participants were community-dwelling healthy adults ($N=65$) aged 64-78 ($M=71$; SD 3.57; Table 2.1), primarily identifying as Caucasian (85%), or as East or South East Asian (4%) or South Asian (1%), with the remainder not identifying (10%). Participants were highly educated, with graduate school/Law/Medical degrees (36%), undergraduate degree (24%), some college or university (19%), and the remainder with some highschool or highschool diplomas (9%), or trade school (7%), with 5% missing. Eligibility was determined through a telephone screening questionnaire: participants were required to be able to read and write English, to not have participated in associated studies at UVic (e.g., Cognitive Health Initiative), and to not have any major health concerns (e.g., psychiatric illnesses, cognitive impairment, stroke, serious head injury).

Table 2.1 *Descriptive Statistics ($N=65$) for Covariates, Demographic Variables, and Mean Day Level Cognitive Tests*

	Mean (SD)	%
Age, years	71 (3.57)	
Female		78%
Education		
Low		37%
High		63%

Ethnicity		
Caucasian		85%
Asian		6%

Averaged Olfactory Score	11.72 (2.29)
Perceived Stress Scale (PSS)	20.98 (15.6)
Physical Activity, minutes	48 (52.24)

Cognitive Domains (Day Mean Scores)

Symbol Search RT	2350.63 (499.63)
Dot Memory RT	7531.64 (2521.76)
Colour Dot RT	3387.33 (1296.95)
Colour Shapes RT	2369.46 (525.82)
Stroop RT	1512.31 (300.3)
Symbol Search AC	.97 (0.29)
Dot Memory AC	8.65 (5.29)
Color Dots AC	56.82 (25.6)
Color Shapes AC	.74 (0.16)
Stroop AC	.92 (0.15)

Note. RT = Reaction-time scored; AC = Accuracy Scored

Procedure

This study used an intensive measurement design in which participants completed initial intake surveys in-person where a demographics questionnaire, a brief survey of well-being, and an olfactory test were administered. Participants took a measurement kit home with them which included a Fitbit, a blood pressure monitor (not used for this current study), and an Android phone. They were asked to wear the Fitbit continuously for the duration of the study and they completed 7-10 minute daily surveys and cognitive tests on the provided phone four times each day for 14 consecutive days as well as measuring their blood pressure twice daily. At the end of the 14 days, they returned to complete the exit survey and another olfactory test. These ambulatory assessments permit measurement of behaviours, physiology and psychological states in naturalistic settings in real-time, which can be designed to distribute assessments randomly throughout the day, and across a number of days, in order to obtain a representative sampling of moments for each person (Hoppmann & Riediger, 2009).

Demand on participants was relatively high for this study. Correspondingly, 71 participants agreed to participate and 6 dropped out before completion (two due to the beginning of COVID restrictions), leaving a sample of 65 participants. Participants were provided with a \$75 honorarium (\$25 at intake and \$50 at debrief) to acknowledge the time spent participating in the study. The project was approved by the University Of Victoria (UVic) Human Research Ethics Board in the spring of 2019.

Measures

This project was not designed as a follow-up from the first project but as a design to explore the utility of mobile cognitive assessments. As such, it does not include some of the covariates included in Project 1, such as smoking (only 3 people smoked between 3-6 cigarettes per day), due to small numbers or limitations around what our funding could cover (e.g., genetic testing).

Olfactory Test

Sniffin' Sticks Olfactory Identification Test (Burghardt, Wedel, Germany; Hummel et al., 1997) were used to assess olfactory identification performance at intake and debrief. The test consisted of 16 felt-tipped scented pens. Participants sat in front of a computer screen with blindfold goggles to reduce visual stimulation. The test administrator presented each pen in order from 1 to 16 with 30 seconds of rest in between each scent to prevent olfactory desensitisation. For each pen, the administrator removed the pen cap and held the tip of the pen approximately 2 cm in front of the participant's nose for 3 seconds. After smelling each pen, participants lifted the blindfold on the goggles and were asked to identify which odour they had just smelled from a list of four options presented on the screen. Participants took the olfactory test at the beginning of the study and again at the end. The two occasions were highly correlated ($r = 0.78$) and a paired-sample t-test revealed that there was not a significant difference ($t(66) = -0.144$; $p = 0.886$) between the pre- ($M = 11.7$; $SD = 2.63$) and post- ($M = 11.73$; $SD = 2.42$) olfactory identification tests, indicating that there were no substantial practice or learning effects. Previous literature has shown that olfactory performance can be impacted by the total number of tests taken with the strongest effect between the first and second testing (Martinec Nováková, &

Havlíček, 2020). In order to reduce the impact of poor performance on a single test, improve measurement precision, and provide a reliable estimate of each individual's olfactory identification, the average of both tests was used in all analyses ($M = 11.72$, $SD = 2.29$; Skewness towards higher scores = -1.06 , Table 2.1). Olfactory identification scores were centred on the mean score of 12 (i.e., olfactory score - 12).

Education

Participants in this sample were highly educated. Education levels were dichotomized into individuals with some high school, highschool degree, trade school, and some college = 0 (37%); and those with an undergraduate degree or graduate school, law or medical school = 1 (63%).

Ethnicity

Participants identified as Caucasian (84%; 0) and South East, East or South Asian (5%; 1) with 10% not selecting an ethnicity.

Cognitive Tests

Cognitive tests were presented as “brain games” and delivered to participants via an app (Hofer & Rush, 2020) on the provided phones. Participants completed the set of cognitive tests and survey components once in the morning, twice randomly during the day, and once in the evening (see Appendix A.4 for screenshots). Each morning and evening session included five mobile cognitive tests, and the two randomised daytime sessions had three cognitive tests each. Each session included 2 -12 trials of each cognitive test. All cognitive tests were scored for both

reaction time and accuracy (see Table 2.1 for descriptives) and the intraindividual variability of each test for each day was calculated as the coefficient of variation (CoV): the standard deviation divided by the mean score and multiplied by 100. This provided a CoV for each person for each day for each of the 5 cognitive tests (see table 2.2). CoV is a ratio of the standard deviation to the mean providing a measure of variability for each day for each individual in relation to each individual's own day mean (intraindividual mean). The univariate distributions for the CoV reaction time measures were all normally distributed and therefore used as outcomes in the models. However, three of the cognitive tests are typically scored as accuracy based tests (Sliwinski et al., 2018; Brewster et al., 2021). In order to offer a comparison that would align with previous literature the accuracy scored version of the coefficient of variation for each test was also provided.

Symbol Search Test. Instructions for the task were presented in text on the mobile phone screen asking participants to select the symbol pair on the bottom of the screen that matched the pair on the top of the screen as quickly as possible. The phone then displayed a row of three symbol pairs at the top of the screen and two symbol pairs at the bottom of the screen. This task had 12 trials in each session and is generally regarded as a reaction-time test. This test has been validated for use on mobile devices (Sliwinski et al., 2018; Brewster et al., 2021). Reaction time scoring was in seconds, with lower values representing higher cognitive performance ($M = 2350.64$; $SD = 499.63$; Skewness towards faster scores = 0.35; Table 2.1). Accuracy scoring was dichotomous with 0 representing incorrect and 1 representing correct. The resulting reaction time and accuracy scores were used to compute separate reaction time and accuracy IIV scores, with

lower values on the IIV representing more consistency and higher values representing more variability.

Dot Memory Test. After instructions were presented, the app briefly displayed a 5 by 5 grid with three red dots randomly placed in the grid. Following that, participants were shown a distractor task (locating F's in a screen full of E's). Then, the (empty) grid re-appears, and the participant is asked to touch the screen where the original three dots had been located. This task is correlated with working memory (Sliwinski et al., 2018) and spatial memory tests (Ezzati et al., 2016), and has been previously validated for use on mobile devices (Sliwinski et al., 2018). A score of zero was given if a participant correctly recalled the location of the dots. If the dots were incorrectly placed, the Euclidean distance discordance between the original dot location and the selected dot location was calculated to provide a continuous score (in grid units) with lower values indicate higher cognitive performance. Each session had two trials and the mean accuracy of both trials was computed to represent the participants' score at each occasion. Reaction time scores were in milliseconds with lower values representing faster times. Reaction time and accuracy scores were then used to compute their respective IIVs.

Colour Dot Test. After instructions were presented, three different coloured dots were presented on the screen followed by a non-coloured dot in the same location as one of the original three dots. Participants were instructed to select the original colour of the dot from a set of colours in a bar at the bottom of the screen. Next, participants were asked where another coloured dot was originally presented (e.g., “where was the blue dot?”) and were asked to touch the screen where the dot had been originally located. There were two trials in each session. This

test is a variation of a delayed reproduction task (Liang et al., 2016) and was scored continuously (in grid units) by calculating the Euclidean distance discordance between the original dot location and where the participant touched the screen (selected dot location), with lower values indicating higher cognitive performance for accuracy. Two trials were presented at every session, providing an indication of spatial localization error in memory and relational binding. . . . Reaction time scores were in milliseconds with lower values representing faster times. Reaction time and accuracy scores were then used to compute their respective IIVs.

Colour-Shape Test. After the instructions, three objects of various shapes and colours were briefly presented on screen. Participants were instructed to remember the shape and colour of the objects. Then, a new screen depicting the same three objects was shown but the location of the objects differed by placement and/or rotation and participants were asked to identify if the colour-shape combinations of the three objects were the same or different from the original objects. This test assessed visual short-term memory in binding and impairment on this task is characterised by a loss of the ability to retain complex objects as a whole (e.g., colour and shape; Parra et al., 2010). Participants completed six trials in each session. Accuracy was scored dichotomously (correct/incorrect), with lower values representing higher cognitive scores. Reaction time scores were in milliseconds with lower values representing faster times. IIV was calculated from these, with higher scores representing more variability and lower scores representing more consistency.

Stroop (Cognitive Interference). After the instruction screen, discordant word-colour pairs were presented on the screen. The mismatch in stimuli (e.g., the word red, in green font),

allows assessment an individual's ability to inhibit the cognitive interference that occurs when processing contradictory stimuli. Participants were instructed to select whether the word-colour pairs were consistent or inconsistent as quickly as possible. The test is typically considered a test of executive functioning and cognitive control, has been previously validated for use on mobile devices (Bouvard et al., 2018), and has been correlated with medial and lateral prefrontal cortical activation (Egner & Hirsh, 2005). Participants completed 12 trials for each session. Reaction time was scored in milliseconds with lower values representing higher cognitive performance. Accuracy scores were based on the number of correctly identified stimuli. IIV was calculated from these for each day with higher scores representing more variability and lower scores indicating more consistency.

Perceived Stress

The perceived stress scale (PSS) is a widely used index of psychological stress that has been associated with biological outcomes hypothesised to be influenced by chronic stress, such as immune (Maes et al., 1999) and endocrine functioning (Pruessner et al., 1999), and telomere length (Epel et al., 2004). In this study, participants responded nightly regarding the frequency, on a scale of 0 (never) to 4 (very often), to a modified five-item version of the PSS (Cohen et al., 1983). The questions included: Over the course of the day, how often have you (1) been upset because something happened unexpectedly? (2) felt nervous or stressed? (3) felt confident about your ability to handle your personal problems? (4) felt like you could not cope with all the things you have to do? (5) been angered because of things that were outside of your control?

Scores were summed to obtain a relative score of perceived stress ($M = 20.98$, $SD = 15.6$), with higher scores representing higher perceived stress. This variable was then split into

two variables to separately account for within and between person components. The between-person portion was each individual's person-mean centred score (each individual's own mean score for the duration of the study; PSS_PM) included as a time-invariant level 2 predictor and centred on the sample mean of 20. Further to the time invariant score, a time-varying within-person PSS score (PSS_WP) was calculated by subtracting each person's own personal mean from the PSS score.

Statistical Analysis

Statistical analyses were performed using the R statistical package, R Studio (R Core Team, 2018), and the multilevel modeling package lme4 (Bates, Mächler, Bolker & Walker, 2015). In order to examine the associations between olfactory identification scores and IIV, multilevel models for the IIV of each of the five cognitive tests were estimated for both reaction time scored and accuracy scored versions of the tests, resulting in ten models. Models were built up from unconditional models, adding olfaction then demographic predictors of intercept and slope (e.g., age, sex, education) and finally covariates (e.g., stress and physical activity) and an interaction term between olfaction and stress. Models for all of the reaction time and accuracy scored CoV outcomes were estimated, as 3 of the 5 measures (Dot Memory, Color Dot, and Color shapes) have previously established scoring using accuracy in prior studies (Sliwinski et al., 2018; Brewster et al., 2021). Having both methods of scoring the measures will provide comparisons to previous literature and allow for the examination of whether individuals were becoming more consistent in their reaction time as well as their accuracy.

Model Selection

From the unconditional model, models were assessed using AIC after each new predictor was added. As each cognitive test was slightly different in the parameters that contributed to the best fitting model, deciding on inclusion criteria in order to run the same model across all tests meant that some of the models were not the best fitting for some of the tests. Ethnicity and education did not contribute to many models and were excluded. Age, sex and stress were removed from slope but included on the intercept. Further, while including physical activity did improve the models in the majority of the cognitive tests, its inclusion led to over-parameterization (as indicated by slope-intercept correlation of 1, rho) of many of the models, so it was excluded (see supplementary section A2 for results with PA). The equation for the final model is presented here.

Final Model

Level 1:

$$\text{IIVCognition}_{ti} = \beta_{0i} + \beta_{1i} (\text{Time.day}_{ti}) + \beta_{2i} (\text{Stress}_{ti} - \text{StressPM}_{i}) + e_{ti}$$

Level 2:

$$\begin{aligned} \beta_{0i} = & \gamma_{00} + \gamma_{01} (\text{Olfaction}_{i-12}) + \gamma_{02} (\text{Age}_{i-71}) + \gamma_{03} (\text{Male}) + \gamma_{04} (\text{Stress}_{i-20}) \\ & + \gamma_{05} (\text{Stress}_{i-20})(\text{Olfaction}_{i-12}) + U_{0i} \end{aligned}$$

$$\beta_{1i} = \gamma_{10} + \gamma_{11} (\text{Olfaction}_{i-12}) + U_{10i}$$

$$\beta_{2i} = \gamma_{20} + U_{20i}$$

The Level 1 equation depicts change in cognitive performance relative to baseline on a given day (t), for a given individual (i), and specifies an intercept (β_{0i}), change over time (day) (β_{1i}), within-person main effects of stress (β_{2i}), and the within-person residual (e_{ti}).

Level 2 specifies fixed effects for the common intercept (γ_{00}), olfaction (γ_{01}), fixed effect slope for time (γ_{10}) and the interaction between olfaction and between-person perceived stress (γ_{05}). Person-specific deviations (random effects) from the fixed intercept (U_{0i}) and fixed linear effect of time (U_{10i}) are also included. Age (centered at the mean) and biological sex (female as reference) were included as covariates in the final model.

Results

Descriptive Statistics

The olfactory identification test was scored out of 16 and ranged from 4 to 15.5 ($M = 11.7$; $SD = 2.3$; Table 2.1). Descriptives for olfaction and demographics can be found in Table 2.1 and the cognitive test CoVs can be found in Table 2.2.

Table 2.2 *Baseline (Day 0) Descriptive Information for Cognitive Test Coefficients of Variation (CoV)*

	Reaction Time	Accuracy
Cognitive Domains, CoV	$M (SD)$	$M (SD)$
Symbol Search	31.23 (5.65)	9.20 (9.11)
Dot Memory	32.72 (11.82)	71.70 (33.16)
Colour Dots	23.81 (14.22)	63.15 (32.75)
Colour Shapes	31.11 (9.08)	74.15 (35.94)
Stroop	23.75 (5.11)	29.80 (33.80)

In addition, the study level CoV for all the cognitive tests were calculated in order to examine the correlation between variability at the day and study level (see supplementary table S2 in Appendix). There were significant positive correlations between day and study level CoV of all tasks, indicating that individuals who were more variable at the day level were also more variable over the course of the study.

Model Results

In the following section, significant results are described in the same pattern for the final models for reaction time and accuracy scored CoV for each cognitive test. Unconditional and final model parameter estimates of the reaction time CoVs as well as final accuracy CoV models are provided in tables.

Symbol Search Test, Coefficient of Variation (CoV)

Symbol Search reaction times became more variable over the course of the study ($b = 0.17$, $SE = 0.054$, $p = 0.002$; Table 2.3).

Dot Memory Test, Coefficient of Variation (CoV)

Both reaction time ($b = 0.63$, $SE = 0.422$, $p < 0.001$) and accuracy ($b = 2.02$, $SE = 0.422$, $p < 0.001$, Table 2.4) versions became more variable over the course of the study.

Colour Dot Test, Coefficient of Variation (CoV).

Reaction times became more consistent over the course of the study ($b = -0.23$, $SE = -0.11$, $p = 0.046$, Table 2.5). The interaction between olfaction and perceived stress (PSS) was also significant ($b = -0.08$, $SE = 0.027$, $p = 0.002$), such that for every additional unit of PSS the association between olfaction and CoV ($b = -0.27$) becomes more negative, stronger, by the interaction effect of -0.08 (e.g., $-0.27 - 0.08 = -0.35$). This indicates that olfaction matters more for predicting cognitive variability in people with more perceived stress.

For the accuracy scored test, within-person perceived stress was associated with CoV ($b = 0.21$, $SE = 0.422$, $p = 0.01$), such that higher than usual stress (relative to the individual's own mean) is associated with more variability in accuracy for that specific day.

Colour Shape Test, Coefficient of Variation (CoV)

Reaction time scores became consistent more rapidly for those with higher olfactory scores ($b = -0.10$, $SE = 0.037$, $p = 0.013$; Table 2.6).

The significant interaction between olfaction and PSS ($b = -0.05$, $SE = 0.023$, $p = 0.014$) in predicting reaction time CoV indicates that, for every additional unit of PSS, the association between olfaction and CoV ($b = 0.48$) is reduced (weaker) by the interaction effect of -0.05 such that the association between olfaction and Colour Shape CoV is smaller for people who perceive more stress. Interpreted the other way, how the effect of PSS depends on smell score, the between-person effect of PSS (PSS_PM; $b = -0.03$) becomes more negative by -0.05 . This indicates that the interaction strengthens the between-person effect of PSS (i.e., the impact of PSS is stronger in individuals with higher olfactory scores), and that PSS matters more for predicting CoV in individuals who have higher smell scores.

Consistency in accuracy scores increased over the course of the study ($b = -1.71$, $SE = 0.35$, $p < 0.01$).

Stroop (Cognitive Interference), Coefficient of Variation (CoV)

Consistency in accuracy increased over the course of the study ($b = -0.77$, $SE = -0.22$, $p = 0.001$; Table 2.7).

Table 2.3 *Multilevel Model Results for Symbol Search Task Coefficient of Variation (CoV)*

	Symbol Search RT CoV			Symbol Search RT CoV			Symbol Search AC CoV		
	<i>B</i>	<i>CI</i>	<i>p</i>	<i>B</i>	<i>CI</i>	<i>p</i>	<i>B</i>	<i>CI</i>	<i>p</i>
Fixed Effects									
(Intercept)	32.21	31.13 – 33.29	<.001	32.47	31.31 – 33.63	<.001	9.89	7.96 – 11.83	<.001
Day	0.17	0.07 – 0.26	.001	0.17	0.07 – 0.27	.002	-0.16	-0.33 – 0.01	.077
Olfaction				0.14	-0.34 – 0.61	.568	0.18	-0.62 – 0.99	.656
Age				-0.03	-0.27 – 0.22	.816	0.34	0.00 – 0.69	.053
Male				-1.03	-3.07 – 1.02	.330	-0.87	-3.74 – 2.00	.556
Perceived Stress (BP)				-0.00	-0.07 – 0.07	.982	0.01	-0.09 – 0.10	.858
Perceived Stress (WP)				0.02	-0.01 – 0.06	.140	-0.00	-0.06 – 0.05	.957
Olfaction:Day				0.00	-0.04 – 0.04	.924	-0.07	-0.14 – 0.00	.069
Olfaction:Perceived Stress (BP)				0.02	-0.01 – 0.05	.170	0.04	-0.01 – 0.08	.092
Random Effects									
σ^2		17.379			17.300			54.908	
$\tau_{00, id}$		13.293			12.258			34.633	
ρ_{01}		-0.474			-0.458			-0.757	
N_{id}		61			61			61	
ICC_{id}		0.433			0.415			0.387	

Observations	745	745	745
R^2 / Ω^2	.471 / .460	.474 / .463	.398 / .384
AIC	4409.168	4417.282	5245.692

Note. RT = reaction time; AC = accuracy; BP = between-person; WP= within-person. Marginal R-squared (R^2) considers only the variance of the fixed effects, while conditional R-squared (Ω^2) takes both fixed and random effects into account. σ^2 is the residual variance after adjusting for predictors (within-person variance). τ_{00} is the between-person variance. ρ_{01} is the random slope-intercept correlation. Perceived Stress BP is the person-mean perceived stress, centred at 20; Within-person is the (time varying) component of perceived stress.

Table 2.4 *Multilevel Model Results for Dot Memory Task Coefficient of Variation*

	Dot Memory RT CoV			Dot Memory RT CoV			Dot Memory AC CoV		
	<i>B</i>	<i>CI</i>	<i>p</i>	<i>B</i>	<i>CI</i>	<i>p</i>	<i>B</i>	<i>CI</i>	<i>p</i>
Fixed Effects									
(Intercept)	30.94	28.76 – 33.12	<.001	31.61	29.23 – 33.99	<.001	65.26	57.88 – 72.63	<.001
Day	0.65	0.37 – 0.93	<.001	0.63	0.34 – 0.91	<.001	2.02	1.21 – 2.84	<.001
Olfaction				0.34	-0.63 – 1.31	.495	-1.07	-4.03 – 1.89	.481
Age				0.14	-0.36 – 0.65	.587	-0.72	-2.44 – 1.00	.417
Male				-2.18	-6.46 – 2.11	.322	8.07	-6.40 – 22.54	.279
Perceived Stress (BP)				-0.00	-0.15 – 0.14	.955	-0.19	-0.67 – 0.28	.430
Perceived Stress (WP)				0.01	-0.10 – 0.13	.798	-0.07	-0.35 – 0.21	.631
Olfaction:Day				-0.07	-0.19 – 0.06	.297	0.09	-0.26 – 0.43	.622
Olfaction:Perceived Stress (BP)				0.03	-0.03 – 0.10	.338	0.14	-0.08 – 0.35	.218
Random Effects									
σ^2	216.924			216.102			1330.553		
$\tau_{00, id}$	13.200			11.225			270.518		
ρ_{01}	1.000			1.000			0.434		

N _{id}	61	61	61
ICC _{id}	0.057	0.049	0.169
Observations	740	740	710
R ² / Ω ²	.237 / .222	.238 / .224	.385 / .374
AIC	6160.464	6170.511	7260.244

Note. RT = reaction time; AC = accuracy; BP = between-person; WP= within-person. Marginal R-squared (R²) considers only the variance of the fixed effects, while conditional R-squared (Ω²) takes both fixed and random effects into account. σ² is the residual variance after adjusting for predictors (within-person variance). τ₀₀ is the between-person variance. ρ₀₁ is the random slope-intercept correlation. Perceived Stress BP is the person-mean perceived stress, centred at 20; Within-person is the (time varying) component of perceived stress.

Table 2.5 *Multilevel Model Results for Colour Dots Task Coefficient of Variation*

	Colour Dots RT CoV			Colour Dots RT CoV			Colour Dots AC CoV		
	<i>B</i>	<i>CI</i>	<i>p</i>	<i>B</i>	<i>CI</i>	<i>p</i>	<i>B</i>	<i>CI</i>	<i>p</i>
Fixed Effects									
(Intercept)	23.13	21.04 – 25.23	<.001	23.39	21.40 – 25.38	<.001	53.70	50.39 – 57.01	<.001
Day	-0.23	-0.44 – -0.02	.038	-0.23	-0.45 – -0.01	.046	-0.38	-0.80 – 0.05	.089
Olfaction				-0.27	-1.10 – 0.55	.519	-0.96	-2.36 – 0.45	.188
Age				0.21	-0.18 – 0.60	.290	0.15	-0.38 – 0.69	.584
Male				-1.55	-4.86 – 1.77	.363	0.63	-3.93 – 5.20	.787
Perceived Stress (BP)				0.01	-0.10 – 0.12	.806	0.04	-0.11 – 0.19	.571
Perceived Stress (WP)				0.04	-0.05 – 0.13	.411	0.21	0.05 – 0.37	.010
Olfaction:Day				0.01	-0.09 – 0.10	.868	0.07	-0.12 – 0.25	.470
Olfaction:Perceived Stress (BP)				-0.08	-0.13 – -0.03	.002	-0.06	-0.12 – 0.01	.112
Random Effects									
σ^2	138.840			138.685			449.472		

$\tau_{00, id}$	28.680	12.318	22.863
ρ_{01}	-0.716	0.507	-0.599
N_{id}	61	61	61
ICC_{id}	0.171	0.082	0.048
Observations	738	738	738
R^2 / Ω^2	.216 / .194	.208 / .191	.144 / .112
AIC	5813.391	5817.095	6662.206

Note. RT = reaction time; AC = accuracy; BP = between-person; WP= within-person. Marginal R-squared (R^2) considers only the variance of the fixed effects, while conditional R-squared (Ω^2) takes both fixed and random effects into account. σ^2 is the residual variance after adjusting for predictors (within-person variance). τ_{00} is the between-person variance. ρ_{01} is the random slope-intercept correlation. Perceived Stress BP is the person-mean perceived stress, centred at 20; Within-person is the (time varying) component of perceived stress.

Table 2.6 *Multilevel Model Results for Colour Shapes Task Coefficient of Variation*

	Colour Shapes RT CoV			Colour Shapes RT CoV			Colour Shapes AC CoV		
	<i>B</i>	<i>CI</i>	<i>p</i>	<i>B</i>	<i>CI</i>	<i>p</i>	<i>B</i>	<i>CI</i>	<i>p</i>
Fixed Effects									
(Intercept)	30.24	28.62 – 31.86	<.001	30.58	28.87 – 32.29	<.001	70.77	63.60 – 77.95	<.001
Day	0.13	-0.06 – 0.32	.193	0.09	-0.10 – 0.27	.362	-1.74	-2.37 – -1.11	<.001
Olfaction				0.48	-0.22 – 1.19	.186	-1.81	-4.71 – 1.10	.228
Age				0.02	-0.31 – 0.36	.890	0.31	-1.29 – 1.90	.707
Male				-0.70	-3.53 – 2.13	.631	-3.74	-17.04 – 9.55	.583
Perceived Stress (BP)				-0.03	-0.12 – 0.07	.578	0.18	-0.26 – 0.62	.423
Perceived Stress (WP)				0.01	-0.06 – 0.08	.823	-0.02	-0.21 – 0.17	.832
Olfaction:Day				-0.10	-0.18 – -0.02	.013	-0.01	-0.28 – 0.26	.932
Olfaction:Perceived Stress (BP)				-0.05	-0.10 – -0.01	.014	-0.14	-0.34 – 0.05	.159
Random Effects									
σ^2	80.483			80.345			585.615		
$\tau_{00, id}$	17.934			15.236			466.772		
ρ_{01}	-0.368			-0.312			-0.331		

N _{id}	61	61	61
ICC _{id}	0.182	0.159	0.444
Observations	740	740	740
R ² / Ω ²	.287 / .258	.275 / .252	.562 / .555
AIC	5751.341	5452.815	7018.660

Note. RT = reaction time; AC = accuracy; BP = between-person; WP= within-person. Marginal R-squared (R²) considers only the variance of the fixed effects, while conditional R-squared (Ω²) takes both fixed and random effects into account. σ² is the residual variance after adjusting for predictors (within-person variance). τ₀₀ is the between-person variance. ρ₀₁ is the random slope-intercept correlation. Percieved Stress BP is the person-mean perceived stress, centred at 20; Within-person is the (time varying) component of perceived stress.

Table 2.7 *Multilevel Model Results for Stroop Task Coefficient of Variation*

	Stroop RT CoV			Stroop RT CoV			Stroop AC CoV		
	<i>B</i>	<i>CI</i>	<i>p</i>	<i>B</i>	<i>CI</i>	<i>p</i>	<i>B</i>	<i>CI</i>	<i>p</i>
Fixed Effects									
(Intercept)	22.77	21.86 – 23.69	<.001	22.87	21.89 – 23.86	<.001	23.97	15.18 – 32.76	<.001
Day	0.07	-0.05 – 0.19	.217	0.07	-0.05 – 0.19	.273	-0.77	-1.21 – -0.33	.001
Olfaction				0.15	-0.24 – 0.55	.448	-0.42	-3.93 – 3.08	.815
Age				0.18	-0.04 – 0.41	.112	0.94	-1.13 – 3.01	.376
Male				0.21	-1.70 – 2.11	.833	-3.41	-20.47 – 13.66	.697
Perceived Stress (BP)				0.06	-0.00 – 0.12	.060	0.46	-0.11 – 1.02	.118
Perceived Stress (WP)				-0.02	-0.07 – 0.02	.348	-0.06	-0.15 – 0.03	.194
Olfaction:Day				-0.02	-0.07 – 0.03	.443	-0.11	-0.30 – 0.08	.254
Olfaction:Perceived Stress (BP)				0.02	-0.00 – 0.05	.096	0.02	-0.23 – 0.27	.860
Random Effects									
σ^2	34.416			34.119			128.709		
$\tau_{00, id}$	3.364			2.359			899.082		
ρ_{01}	1.000			1.000			-0.361		

N _{id}	61	61	61
ICC _{id}	0.089	0.065	0.875
Observations	742	742	742
R ² / Ω ₀ ²	.296 / .284	.301 / .290	.899 / .899
AIC	4933.342	4838.215	6081.935

Note. RT = reaction time; AC = accuracy; BP = between-person; WP= within-person. Marginal R-squared (R²) considers only the variance of the fixed effects, while conditional R-squared (Ω²) takes both fixed and random effects into account. σ² is the residual variance after adjusting for predictors (within-person variance). τ₀₀ is the between-person variance. ρ₀₁ is the random slope-intercept correlation. Perceived Stress BP is the person-mean perceived stress, centred at 20; Within-person is the (time varying) component of perceived stress.

Discussion

The primary goal of this study was to examine the relationship between olfaction and IIV in cognition, two early indicators of cognitive decline. While our results did not demonstrate a consistent association between olfactory identification scores and IIV over all five cognitive tests, I found that individuals with higher olfactory scores became more consistent in their reaction time scores more rapidly in the Colour Shapes task. The second goal was to explore how perceived stress may influence the association of olfaction on IIV in cognition. This study showed that the interaction between olfaction and stress was significantly associated with IIV for the reaction time scored Colour Shapes and Color Dots task. Together, these findings provide preliminary evidence that olfaction may be associated with IIV in certain types of cognitive tasks over small time scales, as well as support for the inclusion of stress measurements in future olfactory research.

IIV and Cognition

Lower IIV indicates that individuals are more consistent in their cognitive scores. In a healthy sample, a decrease in IIV over the course of the study potentially implies an improvement or an increase in skill, whereas an increase in IIV indicates more variability in an individual's responses. Lower IIV over the short-term may imply that the brain areas responsible for those tasks are healthy whereas more variability may indicate neurodegeneration (Costa et al., 2019). Assuming that practice or learning effects over the course of the study are represented by increased consistency, those that become more consistent faster may be more cognitively adept, have more neuroplasticity or hippocampal functioning (Anand, & Dhikav 2012).

Considering that both IIV and olfactory deficits are potential early indicators of cognitive dysfunction, I expected to find an association between them. Firstly, I expected that individuals would become more consistent in their cognitive scores (IIV) over the course of the study. While this finding was not consistent across all cognitive tests, I did find that accuracy became more consistent for Color Shape and Stroop (two tests where there was relatively high accuracy) and less consistent for Dot Memory over the course of the study. Reaction times became more consistent for the Colour Dot task and more variable over the course of the study for Dot Memory and Symbol Search. Since findings were not consistent across all measures, replication with a larger sample with a broader spectrum of ages, education, and ethnicity is warranted.

Olfaction and Interactions with Stress

Although there were no significant main effects for olfaction, these results provide some evidence that associations are detectable at the day-level for short-term variability. Previous work has found that day-to-day variability is influenced by different factors compared to within session variability, as some predictors, such as stress, change over days but likely not within a session (Macdonald et al., 2009; Costa et al., 2019). In the current study, I expected that perceived stress within a day would increase IIV. Specifically, increased stress would be associated with greater IIV. In the Colour Dots accuracy-scored test, higher than usual PSS (within-person PSS) was associated with increased variability on the same day. Further, there was a significant interaction effect between olfaction and between-person stress (in reaction time for Color Dots and Color shapes), which will be detailed below.

The second goal of this study was to explore how stress and physical activity may impact the effect of olfaction on intraindividual variability in cognition. Due to sample size limitations, I removed physical activity from the models during the model selection process, results can be seen in supplementary section A2. This study showed that there was a significant interaction between olfaction and stress. The results indicated that, in individuals with higher olfactory scores, daily perceived stress was an important factor in predicting the consistency of reaction time in Colour Shapes and Color Dot tasks. This may indicate that in individuals who do not have a substantial build up of neuropathology (i.e., healthy brains), that stress is more impactful on variability in cognitive performance as it may be impacting the brain through HPA-axis activation. However, I would postulate that once there is some damage to the underlying structures (as potentially identified by low olfactory scores), perceived stress (a transient short-term impact on cognition) is a less important indicator compared to the underlying neurological damage (long-term impact on functioning). Further work in this area is warranted and could validate the associations between specific tests and olfactory performance. Previous studies have reported activation in the middle frontal gyri for spatial tasks with high working memory (such as memory for previously presented shape; McCarthy et al., 1996) as well as substantial activation in the hippocampus for visuospatial tasks (Mandal et al. 2012). Future studies may be able to assess activation for these specific tasks to determine whether there are differences between and within individuals with differing olfactory abilities and stress conditions, and link that to magnitude of activation in specific brain areas, potentially elucidating early hippocampal damage.

The Color Shapes task may be of specific interest for future olfactory studies as it is a visuospatial task that requires recognition and adoption of a strategy for both high accuracy and speed of completion. Once participants discovered that when one shape was the same or different they were all the same or different, they performed at a high accuracy level (often 100% accuracy, see supplemental plots in A3), cutting down on the cognitive memory load from remembering three shapes, to remembering one. In this case, reaction time would capture differences in this task for those who have already learned the strategy and were receiving high accuracy scores while also capturing the longer reaction times of those who have not learned the strategy for the task, making reaction time scoring for this test potentially more appropriate for determination of variability between individuals and especially for those with high accuracy. The correlation between CoV in Colour Shapes (reaction-time) and mean scores for Colour Shapes (reaction time) was weak but significant and positive ($r = 0.2$; $p < .001$) indicating that more variability in RT scores is correlated with higher mean RT scores (slower RT): those who were more variable were slower. Further, the correlation between CoV for the day and over the full protocol was significant and positive ($r = 0.30$, $p = 0.02$), indicating that more variability within a day is correlated with more variability over the course of the study. This finding is consistent with previous literature indicating that individuals who are more variable on smaller time scales (e.g., day) are also more variable on mid-term time scales (e.g., weeks; Stawski, MacDonald....Halliday et al., 2017). However, any correlations for this study should be considered exploratory, as a sample of 250 is generally recommended for accurate correlations (Schonbrodt & Perugini, 2013).

Although these preliminary results are exploratory in nature, there is a demonstrable impact of perceived stress for the prediction of IIV for individuals who are obtaining higher

scores on the olfactory test. Of note, the majority of our findings were between-person, a significant association between within-person perceived stress was only found for the accuracy scored Color Dot test. Fewer within-person results may be due to measuring daily PSS, which did not represent cumulative stress, or potentially the effect was not strong enough to be detected at the day level. Follow-up studies could examine trial-level variability in order to explore a smaller time scale, which may provide more sensitivity to detect associations as the day level requires averaging the trials within a day, and therefore some information is lost.

Limitations and Future Directions

Our sample consisted of highly educated, mainly Caucasian, physically active, older adults who were willing to undertake a highly demanding study. Considering this, results may not be representative of the general public, and replication in a larger, more diverse sample would benefit the literature.

Funding and time constraints for the current study did not permit a larger sample and this was a limitation for interpreting the between-person effects and correlations. While I would have expected associations between olfaction and all tasks with high spatial processing (Aboitiz & Montinel, 2015; Raithel, & Gottfried, 2021) and inhibitory control (Elliott, & Deakin, 2005) these associations may require a larger sample size. Correlations generally require sample sizes of around 250 to ensure accuracy (Schonbrodt & Perugini, 2013) and due to our small sample, the correlations should be interpreted with caution. Further, the between-person effects in the MLM also had a small number of individuals which limited our ability to include all the predictors I thought may be impactful, as well as limited estimation (e.g., between person

estimates were based on 61 individuals). However, the majority of our findings were between person and not within person (in colour dots PSS_WP was associated with CoV: higher than usual stress is associated with more variability in accuracy for colour dots test), which could potentially be attributed to Type I error as ten models were estimated. Models should be considered exploratory and not confirmatory. While these preliminary exploratory analyses did not reveal any consistent findings across the different cognitive tests this study may aid in hypothesis generation and cognitive test selection for future work. Further studies are warranted to examine replicability of these findings as well as the impacts of stress on olfaction.

While there is substantial research indicating a significant association between low education and olfactory dysfunction, there are still a number of studies reporting conflicting results (James et al., 2021). Participants in Study 2 were highly educated, so a lack of variability in education, combined with a small sample size, may have played a part in why education was not a significant contributor to the models (and was not included in the final models), this was a limitation of our particular sample.

In this study, olfactory ability was not measured on a daily basis. However, future studies examining IIV in cognition may consider including repeated measures of olfaction to examine whether variability in olfaction is associated with variability in cognition. Considering the easily reached ceiling of the shorter tests, olfactory tests with more items should be considered, such as a 40-item test (Doty et al., 1984). Future directions might include examining speed in learning and olfactory ability and the interaction of olfaction and stress.

Conclusions

This study examined the relationship between olfaction and day level cognitive variability, calculated as CoV. This study found that higher olfactory scores were associated with faster consistency of reaction-time scores in the Colour Shapes task and that the interaction between olfaction and stress was significant across three different cognitive tasks IIVs. This study provides preliminary evidence for the utility of olfaction in the prediction of cognitive variability and that perceived stress plays a role in this relationship.

Concluding Discussion

Project 1

Substantial literature exists on the associations between olfaction, cognitive impairment, and dementia (Murphy, 2019; Devanand, 2016). There is general consensus that olfactory deficits occur early and predict the progression of dementia along the disease trajectory (see review articles: Bathini et al., 2019; Murphy, 2019; Devanand, 2016; Sun et al., 2012). Further, research has reported that there may be a coupled relationship between within-person fluctuations in olfactory identification and memory performance (Knight et al., 2018). For example, when an individual is performing worse than their own average on olfactory identification tests, they are likely to also be performing worse than their own average on their episodic memory task at the same occasion, and this effect is stronger for those with more AD pathology (Knight et al., 2018). Previous research has found that increased density of tau tangles in the entorhinal cortex, hippocampus, and inferior temporal cortex is associated with lower olfactory identification scores (Wilson et al., 2007) and that higher pathology at death is associated with lower olfactory scores and faster declines (Knight et al., 2018). Taken together, this research suggests that cognition and olfaction fluctuate together and are concurrently impacted by the buildup of pathology in the brain. Although indicated by declining cognition and olfaction, the buildup of pathology is likely what leads to dementia, which then increases risk of mortality due to cascading effects from those neurological changes that build up over time (James et al., 2014). This risk of mortality should then also be detectable via olfactory (Van Regermorter et al., 2020) and cognitive changes (Sliwinski et al., 2006). However, while the risk of mortality is detectable through declines in olfaction (Van Regermorter et al., 2020), the study described in Project 1 of this dissertation shows that olfaction itself is not substantially

contributing to a risk of mortality. Extrapolating, this research suggests that olfaction could be utilized as an indicator of brain health. As such, olfactory testing can indicate that the brain areas in the olfactory pathway are not functioning well and because these brain regions (e.g., the hippocampus) are crucial to a substantial number of cognitive tasks, this could lead to early interventions to potentially slow pending cognitive impairment.

This dissertation adds nuance to previous studies indicating that there is an increased risk of mortality associated with decreased olfactory ability (see review Van Regermorter et al., 2020). Specifically, further refining the hypothesis to specify that declines in olfaction can predict mortality through the association with cognition and that the risk of mortality is likely caused by the underlying neuropathology. By controlling for cognition and death concurrently in one comprehensive multi-state model, I demonstrate that olfaction is not associated with mortality above and beyond cognitive declines, thus indicating that the likely route is through neurodegeneration which impacts both cognition and olfaction. This work further substantiates the idea that olfactory changes are paralleling cognitive decline but are more readily detectable, and earlier, in the disease progression. Consistent with previous literature, our findings also indicate that higher olfactory ability decreases the risk of transitioning to MCI and from MCI to dementia. For those already clinically diagnosed with MCI, higher olfactory scores increased the chances of returning to a cognitively unimpaired state. These results provide additional support for the notion that olfaction is able to predict the development of clinically diagnosed MCI and dementia. Results from this study clarify previous research that, while olfaction can predict mortality, it is correlated with underlying pathology rather than causal. This provides support for the clinical value of olfactory testing, as a low olfactory score indicates an increased risk of mortality (Pinto et al., 2014; Ekstrom et al., 2017; Seubert et al., 2017; Devanand et al.,

2015; Wilson et al., 2011; Choi et al., 2021; Laudisio et al., 2019; Liu et al., 2019), and this current study suggests that this is likely due to the degeneration of brain areas that support both cognition and olfaction. Lifestyle changes such as increased physical activity (Yoneda et al., 2021) and added vitamin D (Navale et al., 2022) could be implemented at an earlier stage if olfactory testing became widely used for the early detection of cognitive decline.

In addition, this study provided estimates of both overall and unimpaired life expectancies. By examining the number of years of life expectancy that individuals have without cognitive impairment, we can see the overall impact on years of life for those with low, medium, and high olfactory scores. Results indicate that an average non-smoking 80-year-old female with no chronic health conditions and high olfactory identification scores had 10 years of unimpaired life expectancy while those with moderate olfactory ability had 8 years, and those with low olfactory ability had 4 years of unimpaired life expectancy. While the number of unimpaired years were similar for males (9, 7, and 4 years, respectively), life expectancies were consistently lower for males than for females. These unimpaired life expectancies indicate a demonstrable increase in healthy life span for individuals with higher olfactory scores, and we would postulate that this is due to a healthy brain.

Project 2

Project 1 clarified that olfactory ability is associated with transitions between cognitive states over long term time scales and annual assessments. However, the question of how early a link between cognitive dysfunction and olfaction be clinically useful remained unanswered. One of the earliest signs of possible cognitive decline is variability in cognitive test responses, intraindividual variability (IIV; Costa et al., 2019; Hultsch et al., 2000). The underlying disease

process of dementia occurs over years and decades (Jack et al., 2013), and earlier detection of degeneration in the brain leads to better chances of ameliorated outcomes. For example, considering the numerous cascading and complex components to a healthy brain (e.g., eating habits, physical activity, stress; Mosconi, & McHugh, 2015; Nebel et al., 2018), earlier detection would allow for lifestyle changes and potential enrollment into research or intervention studies (Santos et al., 2017).

Clinically diagnosed cognitive decline occurs relatively late in the dementia disease process (Jack et. al., 2013) and current theories postulate that olfactory dysfunction occurs at the earliest stages, closely following tau-mediated neuropathology (Murphy, 2019). To the best of our knowledge, no one has yet examined associations between IIV and olfaction, and this project provides novel contributions to the literature regarding interactions between stress, olfaction, and cognitive test selection.

Stress and Olfaction

Stress is a basic biological mechanism with complex underlying interactions in the body and brain, and its impacts on cognition vary depending on intensity and length of the stress (Sandi, 2013). In general, theories suggest that, in the presence of stress, cognitive deficits are typically observed for tasks dependent on hippocampal and prefrontal cortex functioning, while implicit memory tasks may show improved performance (Sandi, 2013). Both olfactory identification and spatial tasks are highly dependent on these areas, therefore it would be expected that an individual's level of stress would impact both their olfactory ability and the variability in their cognitive scores for tasks that require spatial ability (e.g., Colour Dots and Colour Shapes tasks). This study measured daily perceived stress and found that higher than

usual stress levels (within-person PSS) were associated with more variability in accuracy in the Colour Dots task. Further, the olfaction by stress interaction was significantly associated with IIV in reaction time scored Color Dot and Color Shapes tasks. These findings suggest that daily perceived stress is an important factor that impacts the effect of olfaction for predicting variability in cognition.

Specifically, these findings indicate that variability in cognitive functioning may be disproportionately affected by perceived stress for individuals who have high olfactory scores. I postulate that this may be due to the fact that a higher olfactory score indicates that those individuals do not have a substantial build up of neuropathology or neural damage and therefore stress is the more salient disruptor of cognition on a daily level. However, for those with lower olfactory scores, who possibly have experienced more chronic stress and/or sustained some damage to relevant brain areas, olfaction may be more important than stress as a predictor of cognitive variability. In general, theories suggest that chronic or sustained exposure to stress induces physiologically harmful effects (McEwen 1998) and negatively impacts olfaction and the olfactory pathways supporting brain structures (Vaz et al., 2018). Future research in this area should consider including measures of momentary stress as well as cumulative stress to better capture how chronic or long-term stress is related to variability and olfactory ability.

Research incorporating cognition, olfaction, and stress is scarce in the current literature and would benefit from further investigation regarding adaptive and maladaptive effects of stress and olfaction. For example, previous studies have shown that both perceived and physiological stress can be alleviated by olfactory cues (e.g., the scent of a partner; Hofer et al. 2018; Jousain

et al., 2014). Questions as to whether olfactory cues can also improve cognitive performance could also be examined as well as whether these effects are also impactful with long-term chronic stress.

Cognitive Test Selection

In this study, the olfaction by stress interaction was significant for two (Color Dots RT and Colour Shapes RT) out of ten cognitive tests. Both of these were highly spatial in nature, with Colour Shapes being the most complex as well as visuospatially demanding task. In the Color Dot test, participants were required to remember where one out of three displayed dots had been displayed on the screen, requiring a memory for the colour and placement of each dot. In the Colour Shapes task, participants were required to remember the colour and shape of three objects but were also required to mentally rotate the objects as the placement and or the rotation would change. More complex tasks tend to provide more sensitive IIV estimates (Burton, Strauss, Hultsch, Moll, & Hunter, 2006; Murtha, Cismaru, Waechter, & Chertkow, 2002) and the Colour Shapes task is the most spatially complex task in the set provided to participants in this study. In the Color Shapes task, individuals with higher olfactory scores became more consistent in their reaction times faster than those with lower scores. Although this was not a consistent finding across multiple cognitive tests, it is consistent with olfaction having evolved as a navigational tool (Aboitiz & Montinel, 2015; Raithel & Gottfried, 2021). Since it is the most spatially demanding task, we postulate that it may be more sensitive to an association with olfaction over a short period of time. In other words, it is possible that the brain areas required for proficiency on the Colour Shapes task maps onto similar brain areas needed for olfaction (i.e., they may share neural substrates). However, further research is required to substantiate this

claim. Ideally, the first steps would include a follow-up study with a larger number of participants to validate whether these results are replicable.

Intraindividual Variability (IIV) in Cognition and Olfaction

IIV can be detected in individuals without measurable cognitive impairment. Further, IIV shows a positive association with severity of cognitive impairment (Burton et al., 2006; Reckess, Varvaris, Gordon, & Schretlen, 2014), with patients who have more severe cognitive deficits showing an increased magnitude of IIV. In addition, IIV has been shown to be a significant predictor of incident Alzheimer's disease (AD; Anderson et al., 2016). To the best of our knowledge, this study is the first to examine associations between IIV and olfaction, two very early indicators of cognitive decline, which may both be caused by underlying neural damage. For example, previous research has demonstrated that loss of white matter integrity is associated with higher IIV (Costa et al., 2019). Specifically, using diffusion tensor imaging, Fjell and colleagues found that disconnectivity in white matter pathways was associated with increases in IIV variability (Fjell et al., 2011). Further, in an MRI study, Bunce and associates showed that three different IIV measures (raw standard deviation, CoV, and intraindividual standard deviation) reliably predicted white matter hyperintensities (a risk factor for cognitive decline; Bunce et al., 2013). Similarly, olfactory decline is associated with loss of functional connectivity, decreased hippocampal volume and decreased grey and white matter volume (Han et al., 2019; Yi et al., 2022, Bitter et al., 2010). These previous studies point towards potential in using olfaction and IIV in tandem for future studies examining the prodromal stages of dementia.

Future Directions

It is my hope that this work will fuel further research on IIV and olfaction. As previously discussed, we have demonstrated that research on IIV and olfaction is possible and may yield interesting insights into the prodromal stage of dementia. Future research could explore whether cognition becomes variable before, after, or concurrently with decreases in olfaction. Further, is IIV the first detectable cognitive measure to show declines?

Some research has been done with subjective cognitive decline and olfaction. Current findings suggest that olfactory dysfunction is present in subjective cognitive decline (Jobin et al., 2021) and cross sectional research has demonstrated that olfactory dysfunction increases in severity through stages of cognitive decline (e.g., subjective and MCI) and dementia (Wang et al., 2021). Individuals reporting subjective cognitive decline also display reduced hippocampal activation and increased frontal brain activation indicating increased compensatory neuronal effort (Erk et al., 2011). This suggests that once the hippocampus sustains injury, subjective cognitive decline and olfactory deficits become apparent. Is cognitive performance variable at this point as well? As subjective and objective measures of cognition are not correlated in most studies (Collins et al., 2018), future studies using IIV could add subjective cognitive decline measures to further examine differences in objective and subjective measures for both cognition and olfaction.

Further research establishing which behavioural tests are most sensitive to hippocampal dysfunction/deterioration are needed. Specifically, working towards establishing how to track hippocampal plasticity and health through clinical tests (e.g., olfactory tests) would benefit the literature.

Conclusion

These two projects contributed several novel findings to the literature. In the first project, higher olfactory identification ability was associated with an increased likelihood of returning to an unimpaired cognitive state from a clinically diagnosed state of mild cognitive impairment. Conversely, lower olfactory identification scores were associated with an increased likelihood of transitioning from unimpaired to MCI and from MCI to dementia but not significantly associated with an increased likelihood of transitioning to death from any state. In the second project, we examined olfaction and cognition over the short-term and found a significant interaction effect of olfaction by stress for predicting variability in cognitive scores in the Colour Shapes and Colour Dots tasks. Indicating that for individuals with high olfactory ability, higher perceived stress was associated with reaction times that are more consistent.

While further work is needed, we propose that olfactory testing may be a promising tool for routine clinical practice as a potential early indicator of dementia and brain health. It may be particularly sensitive to hippocampal dysfunction and AD pathology, and as such, an excellent indicator of compromised neurological functioning.

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Appendices

Appendix A - Supplemental Information for Chapter 3

A.1 Correlations

Table S1

Table of Correlations between Day and Study level CoV

Day Level CoV	Study Level CoV
Symbol Search RT	0.60 (p < 0.001)
Symbol Search AC	0.52 (p < 0.001)
Dot Memory RT	0.40 (p = 0.001)
Dot Memory AC	0.50 (p < 0.001)
Color Dot RT	0.42 (p = 0.001)
Color Dot AC	0.46 (p < 0.001)
Color Shape RT	0.29 (p = 0.022)
Color Shape AC	0.60 (p < 0.001)
Stroop RT	0.49 (p < 0.001)
Stroop AC	0.86 (p < 0.001)

Table S2*Supplementary Table of Correlations between Cognitive Tests CoVs and Means, Scored**According to Accuracy Versus Reaction Time*

Cognitive Test	Scoring	
	Reaction Time $r(p)$	Accuracy $r(p)$
Symbol Search	-0.39 ($p=0.002$)	-0.99 ($p < 0.001$)
Dot Memory	0.17 ($p=0.19$)	-0.80 ($p < 0.001$)
Colour Dot	0.51 ($p < 0.001$)	0.34 ($p = 0.008$)
Colour Shape	0.02 ($p < 0.001$)	-0.99 ($p < 0.001$)
Stroop	0.29 ($p=0.03$)	-0.99 ($p < 0.001$)

Table S3*Table of ICCs*

	Intraclass Correlation Coefficients	
	% Variance Between Person	
	Reaction Time	Accuracy
Symbol Search CoV	42%	37%
Dot Memory CoV	5.4%	21%
Color Dots CoV	17.2%	7.4%
Color Shape CoV	18%	47%
Stroop CoV	9.4%	88%
<hr/>		
PSS_WP (Time Varying)	3%	
PA_WP (Time Varying)	8.4%	
PA	36%	
PSS	54%	

Note. PSS_WP = within-person perceived stress.

Table S4*Table of Demographic Correlations with Olfactory Identification*

	Correlation with Olfactory Identification
	<i>r</i> (<i>p</i>)
PA_PM	0.084 (p=0.2)
PSS	-0.4 (p=0.27)
Education	0.09 (p=0.14)
Age	-0.17 (p<0.001)
Sex (Male)	-0.15 (p<0.01)

Note. Significant correlations are bolded.

Table S5*Table of Cognitive Coefficient of Variation (CoV) Correlations with Olfactory Identification*

	Correlation with Olfactory Identification	
	Scoring	
	Reaction Time <i>r</i> (<i>p</i>)	Accuracy <i>r</i> (<i>p</i>)
Symbol Search CoV	ns	-0.14 (p<0.001)
Dot Memory CoV	ns	ns
Color Dots CoV	ns	ns
Colour Shapes CoV	ns	-0.14 (p<0.001)
Stroop CoV	ns	-0.16 (p<0.001)

Note. Ns = not significant.

A.2 MLM including Physical Activity

For the 14 days of the study, each participant wore a Fitbit Charge 2 (Fitbit Inc. San Francisco, CA), which uses a proprietary algorithm (John, & Freedson, 2012) to estimate activity levels, heart rate, and energy expenditure each minute. They were instructed to charge the Fitbit as needed while they were inactive (e.g., watching TV). The Fitbit provided the number of minutes of lightly active, fairly active, and very active activity for each day. The number of moderately active and very active minutes were added together to compute a score of physical

activity for the day ($M = 48.06$, $SD = 52.24$). Higher scores represent more minutes of physical activity. This variable was also split into between - and within-person components. We computed each individual's personal mean score for the duration of the study to be included as a time-invariant predictor and centred it on the grand mean of 48 (PA_PM). In addition, a time-varying physical activity variable where each individual's personal mean across the study was subtracted from their raw scores (PA_WP) was calculated.

The following tables include the full set of variables that were considered for inclusion. There were no significant associations on the day level with physical activity in most of the cognitive tests. In the Dot memory Reaction time (between-person) higher overall PA was associated with more variability in reaction time at baseline. For the Stroop task, higher (between-person) PA was associated with taking longer to become more consistent in their accuracy scores. These results are not what we were expecting and may be due to chance findings (e.g., Type 1 error). Many of the models have a correlation of 1 for the intercept-slope (ρ), which is an indication of too many parameters in the model.

Table S6

Reaction Time Scored Models Including Physical Activity

	Sym_RT_CoV			DM_RT_CoV			CD_L_RT_CoV			CS_RT_CoV			ST_RT_CoV		
	B	CI	p	B	CI	p	B	CI	p	B	CI	p	B	CI	p
Fixed Parts															
(Intercept)	30.98	29.36 – 32.60	<.001	29.50	26.27 – 32.72	<.001	22.62	19.80 – 25.45	<.001	30.86	28.46 – 33.25	<.001	22.34	20.77 – 23.91	<.001
day0	0.16	0.05 – 0.27	.005	0.62	0.31 – 0.93	<.001	-0.21	-0.44 – 0.02	.085	0.06	-0.12 – 0.24	.513	0.08	-0.05 – 0.21	.229
smelltotal_avgM	0.04	-0.42 – 0.50	.852	0.23	-0.72 – 1.17	.638	-0.27	-1.11 – 0.57	.530	0.61	-0.07 – 1.30	.082	0.10	-0.32 – 0.52	.630
age_71	-0.14	-0.39 – 0.10	.266	0.19	-0.29 – 0.68	.432	0.23	-0.20 – 0.65	.295	0.07	-0.29 – 0.44	.697	0.18	-0.07 – 0.43	.157
Male	-1.23	-3.22 – 0.77	.233	-4.56	-8.54 – -0.58	.028	-2.27	-5.75 – 1.21	.206	-0.98	-3.96 – 2.00	.522	0.04	-2.00 – 2.08	.969
educ2	2.37	0.53 – 4.21	.014	4.19	0.59 – 7.78	.026	1.02	-2.14 – 4.18	.530	-0.30	-3.02 – 2.42	.831	0.70	-1.17 – 2.57	.468
ethn2	-0.72	-4.06 – 2.62	.675	3.57	-3.19 – 10.33	.304	5.31	-0.59 – 11.20	.082	4.37	-0.67 – 9.42	.094	-0.43	-3.90 – 3.05	.811
PSS_PM20	0.01	-0.08 – 0.09	.878	0.08	-0.09 – 0.26	.354	0.08	-0.08 – 0.23	.329	-0.22	-0.35 – -0.09	.001	0.06	-0.02 – 0.14	.121
PSS_WP	0.02	-0.01 – 0.06	.170	0.02	-0.10 – 0.14	.739	0.05	-0.04 – 0.14	.305	0.01	-0.06 – 0.08	.833	-0.01	-0.06 – 0.03	.586
fitB_PM48	-0.02	-0.05 – 0.02	.310	0.07	0.00 – 0.14	.048	-0.02	-0.08 – 0.04	.523	-0.05	-0.10 – 0.00	.078	0.00	-0.03 – 0.04	.798
fitB_WP	-0.00	-0.01 – 0.01	.601	-0.01	-0.03 – 0.02	.592	-0.00	-0.02 – 0.02	.794	0.00	-0.02 – 0.02	.923	0.01	-0.00 – 0.02	.156
day0:smelltotal_avgM	0.00	-0.04 – 0.05	.965	-0.06	-0.19 – 0.07	.343	0.01	-0.09 – 0.11	.819	-0.10	-0.18 – -0.03	.005	-0.02	-0.07 – 0.04	.569
day0:PSS_PM20	0.00	-0.01 – 0.01	.777	-0.00	-0.03 – 0.02	.813	-0.01	-0.03 – 0.01	.223	0.03	0.01 – 0.04	<.001	0.00	-0.01 – 0.01	.642
smelltotal_avgM:PSS_PM20	0.01	-0.02 – 0.04	.363	0.05	-0.01 – 0.11	.131	-0.09	-0.14 – -0.03	.002	-0.06	-0.10 – -0.01	.017	0.02	-0.01 – 0.05	.150
day0:fitB_PM48	-0.00	-0.00 – 0.00	.558	0.00	-0.01 – 0.01	.603	-0.00	-0.01 – 0.01	.968	0.00	-0.00 – 0.01	.175	-0.00	-0.01 – 0.00	.509
Random Parts															
σ^2		17.009			220.380			139.874			83.463			34.675	
τ_{00_id}		10.529			2.872			10.159			10.325			2.614	
ρ_{01}		-0.486			1.000			0.640			1.000			1.000	
N_{id}		58			58			58			58			58	
ICC _{id}		0.382			0.013			0.068			0.110			0.070	
Observations		685			680			678			680			682	
R^2 / Ω_0^2		.482 / .471			.233 / .223			.214 / .199			.260 / .249			.305 / .294	

Note. Marginal R-squared considers only the variance of the fixed effects, while conditional R-squared takes both fixed and random effects into account. Sigma2 is the residual variance after adjusting for predictors (within-person variance). Tau00 is the between-person variance. Rho01 is the random slope-intercept correlation. PSS_PM20 = the Person-mean perceived stress, centred at 20; PSS_WP is the within-person component (time varying) of perceived stress; fitB_PM48 is the person-mean minutes of physical activity centred at 48; fitB-WP is the within-person component (time varying) of physical activity.

Table S7

Accuracy scored models including Physical Activity

	Sym_AC_CoV			DM_AC_CoV			CD_AC_CoV			CS_AC_CoV			ST_AC_CoV		
	B	CI	p	B	CI	p	B	CI	p	B	CI	p	B	CI	p
Fixed Parts															
(Intercept)	10.91	8.35 – 13.47	<.001	56.55	45.12 – 67.97	<.001	54.16	49.91 – 58.41	<.001	70.04	58.94 – 81.15	<.001	25.49	12.70 – 38.28	<.001
day0	-0.13	-0.30 – 0.04	.132	2.21	1.38 – 3.04	<.001	-0.38	-0.82 – 0.06	.096	-1.72	-2.40 – -1.03	<.001	-0.69	-1.08 – -0.30	.001
smelltotal_avgM	0.34	-0.46 – 1.15	.406	-2.16	-5.18 – 0.85	.166	-1.25	-2.63 – 0.12	.080	-1.59	-4.60 – 1.42	.305	-0.26	-3.54 – 3.02	.877
age_71	0.46	0.11 – 0.81	.013	-1.10	-2.93 – 0.74	.247	-0.04	-0.62 – 0.55	.904	0.36	-1.39 – 2.11	.689	0.69	-1.38 – 2.75	.517
Male	-0.19	-3.08 – 2.69	.896	3.85	-10.97 – 18.67	.613	-0.12	-4.98 – 4.74	.962	-1.56	-15.60 – 12.49	.829	-2.13	-18.52 – 14.27	.800
educ2	-1.37	-4.01 – 1.27	.314	14.88	1.18 – 28.58	.038	-0.36	-4.72 – 4.01	.873	-0.60	-13.64 – 12.44	.928	-8.53	-23.95 – 6.89	.283
ethn2	0.42	-4.38 – 5.22	.864	-14.86	-39.93 – 10.20	.250	-2.12	-10.35 – 6.10	.615	10.36	-13.18 – 33.89	.392	19.97	-7.38 – 47.32	.158
PSS_PM20	0.07	-0.08 – 0.22	.368	-0.03	-0.60 – 0.53	.915	-0.07	-0.32 – 0.19	.615	0.12	-0.44 – 0.69	.677	-0.09	-0.71 – 0.53	.783
PSS_WP	-0.00	-0.06 – 0.06	.935	-0.04	-0.34 – 0.26	.814	0.15	-0.02 – 0.31	.080	-0.03	-0.23 – 0.16	.745	-0.07	-0.16 – 0.02	.109
fitb_PM48	0.00	-0.06 – 0.06	.895	0.06	-0.16 – 0.28	.607	0.06	-0.04 – 0.16	.228	-0.13	-0.35 – 0.09	.254	-0.24	-0.48 – 0.01	.060
fitB_WP	-0.01	-0.02 – 0.01	.462	0.00	-0.07 – 0.07	.990	-0.02	-0.05 – 0.02	.402	-0.03	-0.08 – 0.01	.175	0.00	-0.02 – 0.02	.776
day0:smelltotal_avgM	-0.07	-0.14 – 0.00	.069	0.18	-0.16 – 0.52	.315	0.09	-0.10 – 0.27	.348	-0.01	-0.29 – 0.28	.949	-0.14	-0.30 – 0.02	.098
day0:PSS_PM20	-0.01	-0.02 – 0.01	.393	-0.01	-0.07 – 0.05	.738	0.01	-0.03 – 0.04	.669	-0.02	-0.07 – 0.03	.456	0.01	-0.02 – 0.04	.361
smelltotal_avgM:PSS_PM20	0.05	0.00 – 0.09	.036	0.09	-0.13 – 0.32	.417	-0.07	-0.14 – 0.00	.070	-0.18	-0.39 – 0.04	.110	-0.03	-0.27 – 0.22	.818
day0:fitb_PM48	-0.00	-0.01 – 0.00	.645	-0.01	-0.04 – 0.02	.439	-0.01	-0.02 – 0.00	.188	0.00	-0.02 – 0.02	.875	0.01	0.00 – 0.02	.045
Random Parts															
σ^2		57.248			1393.669			445.817			597.895			122.486	
$\tau_{00, id}$		32.304			237.687			10.992			476.150			738.107	
ρ_{01}		-0.837			0.636			-0.419			-0.344			-0.318	
N_{id}		58			58			58			58			58	
ICC _{id}		0.361			0.146			0.024			0.443			0.858	
Observations		685			650			678			680			682	
R^2 / Ω_0^2		.373 / .361			.378 / .368			.134 / .109			.572 / .565			.896 / .895	

Note. Marginal R-squared considers only the variance of the fixed effects, while conditional R-squared takes both fixed and random effects into account. Sigma2 is the residual variance after adjusting for predictors (within-person variance). Tau00 is the between-person variance. Rho01 is the random slope-intercept correlation. PSS_PM20 = the Person-mean perceived stress, centred at 20; PSS_WP is the within-person component (time varying) of perceived stress; fitB_PM48 is the person-mean minutes of physical activity centred at 48; fitB-WP is the within-person component (time varying) of physical activity.

Table S7

Colour Shapes Models including Physical Activity

	CS_RT_CoV			CS_RT_CoV			CS_RT_CoV		
	<i>B</i>	<i>CI</i>	<i>p</i>	<i>B</i>	<i>CI</i>	<i>p</i>	<i>B</i>	<i>CI</i>	<i>p</i>
Fixed Parts									
(Intercept)	30.18	28.61 – 31.75	<.001	31.18	28.74 – 33.63	<.001	30.88	28.49 – 33.27	<.001
day0	0.12	-0.06 – 0.30	.191	0.07	-0.10 – 0.24	.408	0.05	-0.12 – 0.23	.543
smelltotal_avgM				0.79	0.11 – 1.48	.027	0.59	-0.09 – 1.28	.093
PSS_PM20				-0.18	-0.31 – -0.05	.008	-0.22	-0.35 – -0.09	.001
fitb_PM48				-0.03	-0.08 – 0.02	.206	-0.05	-0.10 – 0.00	.077
age_71				0.07	-0.31 – 0.45	.721	0.07	-0.29 – 0.44	.695
Male				-0.44	-3.42 – 2.54	.773	-0.96	-3.94 – 2.02	.530
educ2				-0.95	-3.69 – 1.78	.498	-0.30	-3.02 – 2.42	.830
ethn2				5.15	-0.04 – 10.33	.056	4.35	-0.69 – 9.39	.096
day0:smelltotal_avgM				-0.10	-0.17 – -0.03	.006	-0.10	-0.17 – -0.03	.006
day0:PSS_PM20				0.03	0.02 – 0.04	<.001	0.03	0.01 – 0.04	<.001
day0:fitb_PM48				0.00	-0.00 – 0.01	.222	0.00	-0.00 – 0.01	.174
PSS_WP							0.00	-0.07 – 0.08	.892
fitB_WP							0.00	-0.02 – 0.02	.972
smelltotal_avgM:PSS_PM20							-0.06	-0.10 – -0.01	.016
smelltotal_avgM:fitB_WP							0.00	-0.00 – 0.01	.329
Random Parts									
σ^2		80.711			82.958			83.350	
$\tau_{00, id}$		17.321			12.837			10.267	
ρ_{01}		-0.278			1.000			1.000	
N_{id}		65			58			58	
ICC_{id}		0.177			0.134			0.110	
Observations		772			692			680	
R^2 / Ω_0^2		.286 / .258			.259 / .247			.261 / .250	

Note. Marginal R-squared considers only the variance of the fixed effects, while conditional R-squared takes both fixed and random effects into account. Sigma2 is the residual variance after adjusting for predictors (within-person variance). Tau00 is the between-person variance. Rho01 is the random slope-intercept correlation. PSS_PM20 = the Person-mean perceived stress, centred at 20; PSS_WP is the within-person component (time varying) of perceived stress; fitB_PM48 is the person-mean minutes of physical activity centred at 48; fitB-WP is the within-person component (time varying) of physical activity.

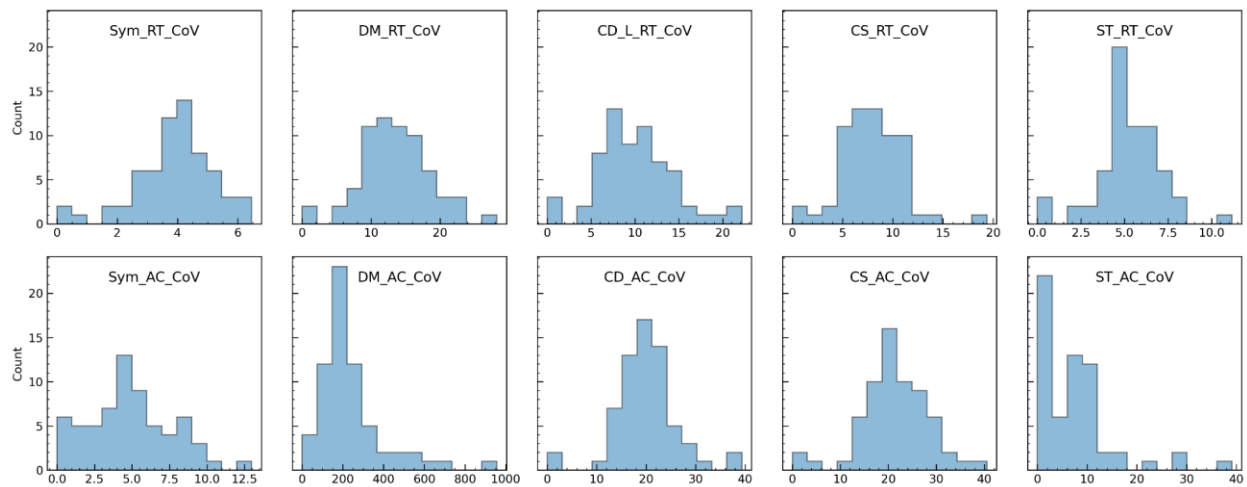
A.3 Plots for the data distribution

Plots of the Standard Deviations (SD) of the CoV Variables used in Analyses.

The following plots show the count of individuals on the y-axis who have variability in their CoV scores. For example, in the reaction-time Symbol Search Task (Sym_RT_CoV), there are two individuals who have no variation in their scores (e.g., SD of 0) and 15 individuals who have an SD of 4. These plots show the spread of variability in CoV scores for all of the participants and were created by grouping by ID, then taking the SD for the values for a given ID then plotting them all as histograms.

Figure S1

Plot of Standard Deviations of the Coefficient of Variation (CoV) for both Reaction and Accuracy Scored Cognitive Tests

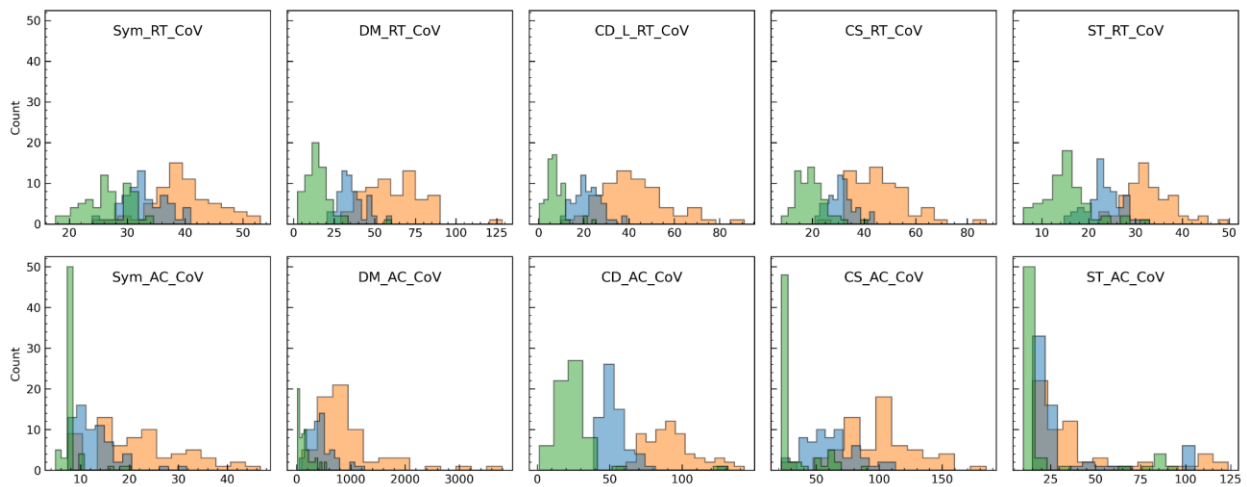


Plots of the Minimum, Maximum, and Mean scores of the CoV Variables used in Analyses.

The following plots show the count of individuals on the y-axis for the minimum (green), maximum (orange) and mean (blue) CoV scores. For example, in accuracy scored Symbol Search Task (Sym_AC_CoV), 50 people had a minimum score of 8, and around 10 people had maximum scores of 15 and 20. These plots were created by grouping by ID, then taking the std, min, mean, and max for the values for a given ID then plotting them all as histograms.

Figure S2

Plot of Minimum, Maximum and Mean scores of the Coefficient of Variation (CoV) for both Reaction and Accuracy Scored Cognitive Tests



Plots for Day Mean Scores.

In the blue plots, we can see there is very little variation in accuracy in Stroop score and in the color plot down below we can see this is because most people are getting perfect scores.

Figure S3

Plot of Standard Deviations of the Day Mean for both Reaction and Accuracy Scored Cognitive Tests

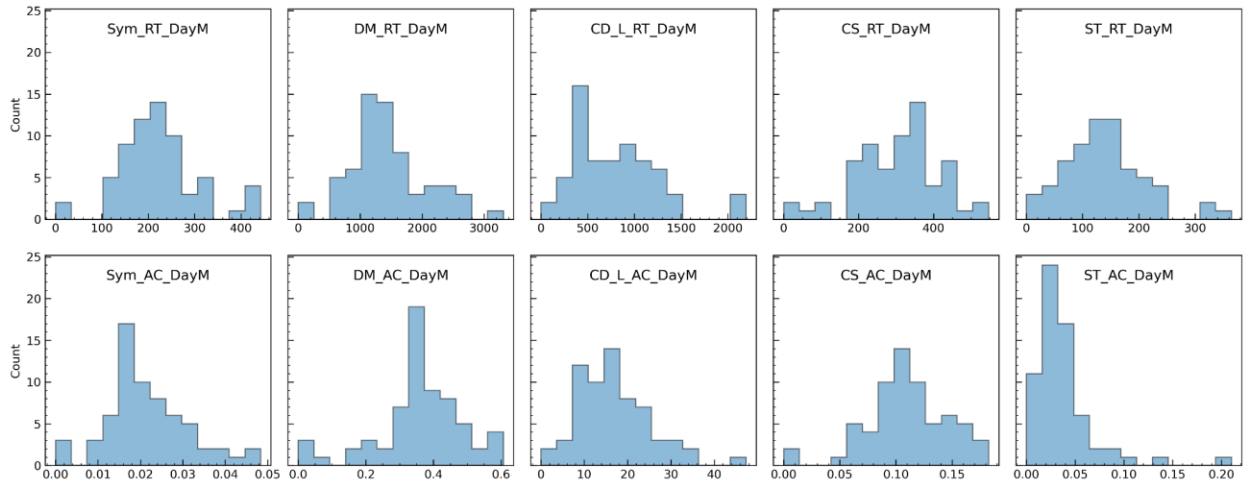
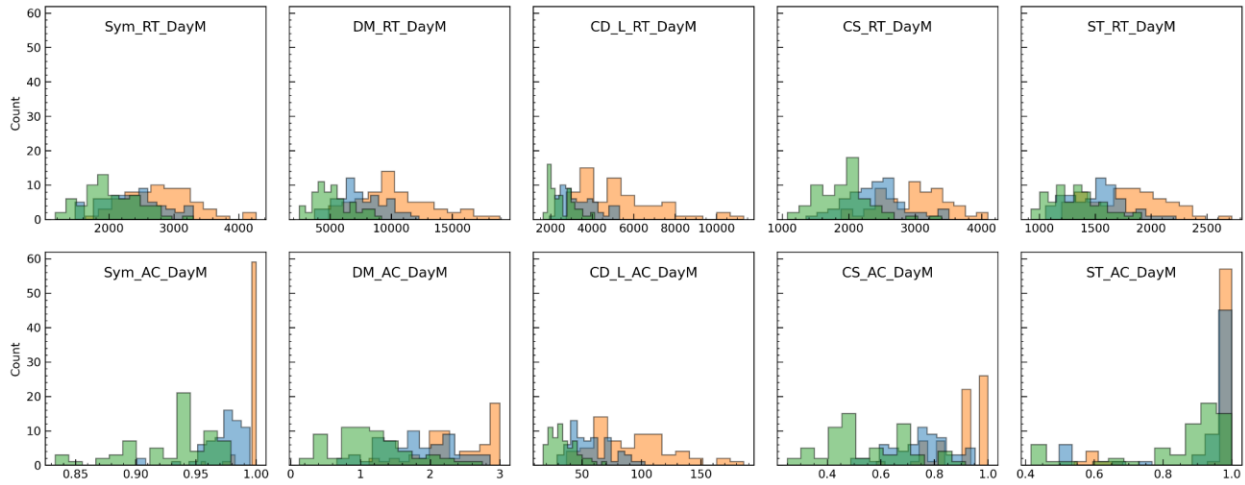


Figure S4

Plot of Minimum, Maximum and Mean scores of the Day Mean for both Reaction and Accuracy Scored Cognitive Tests



A.4 Screen Shots for Cognitive Tests

Symbol Search

Instructions

--You will see 3 pairs of symbols on the top of the screen and 2 pairs of symbols on the bottom of the screen.

--As quickly and as accurately as you can, please touch the pair on the bottom that exactly matches one of the pairs on top.

PREVIOUS

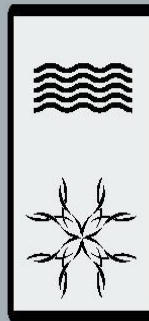
START



Which of these matches
a pair above?



or



Dot Memory

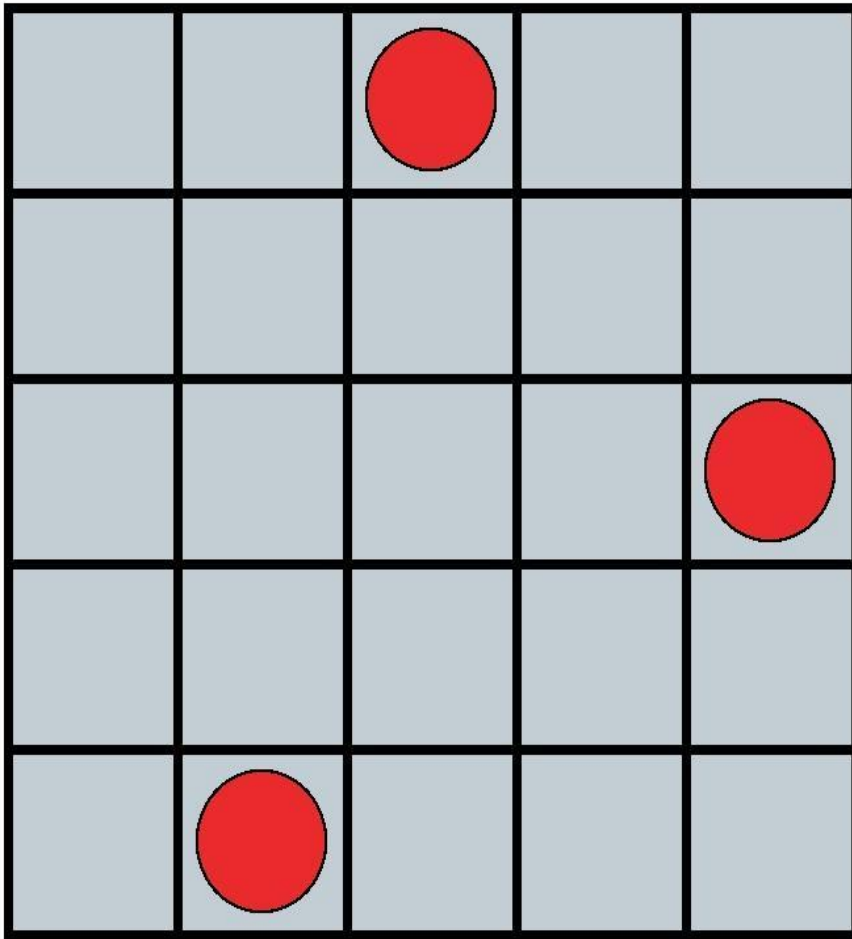
Instructions

- You will see 3 dots appear briefly on a grid.
- Try to remember the location of these dots, because they will soon disappear.
- Next you will see a screen full of E's and F's. Please tap all the F's that you see.
- When you see the empty grid, tap the locations where you recall having seen the dots.

PREVIOUS

START

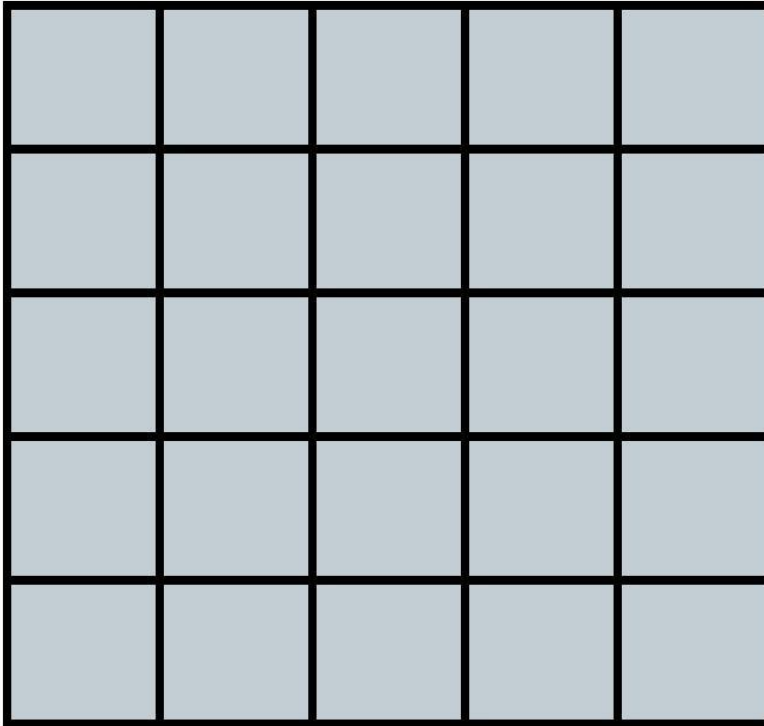
Remember the dot
locations!



Touch the F's!

E	E	E	E	E
E	E	E	F	E
E	E	F	E	E
E	F	E	E	E
E	E	F	E	E
E	F	E	E	E
E	E	E	F	E
E	E	E	E	E

Where were the dots?



DONE

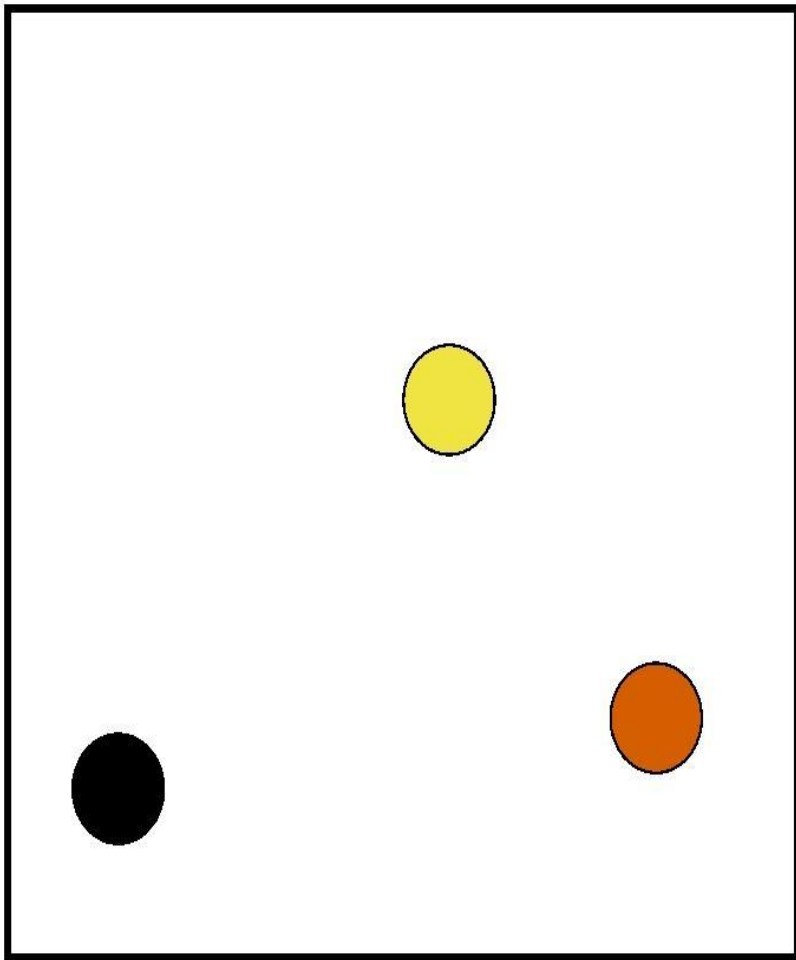
Color Dots

Instructions

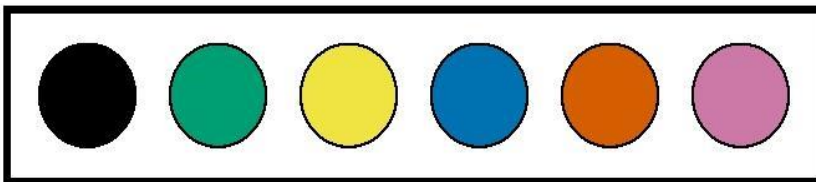
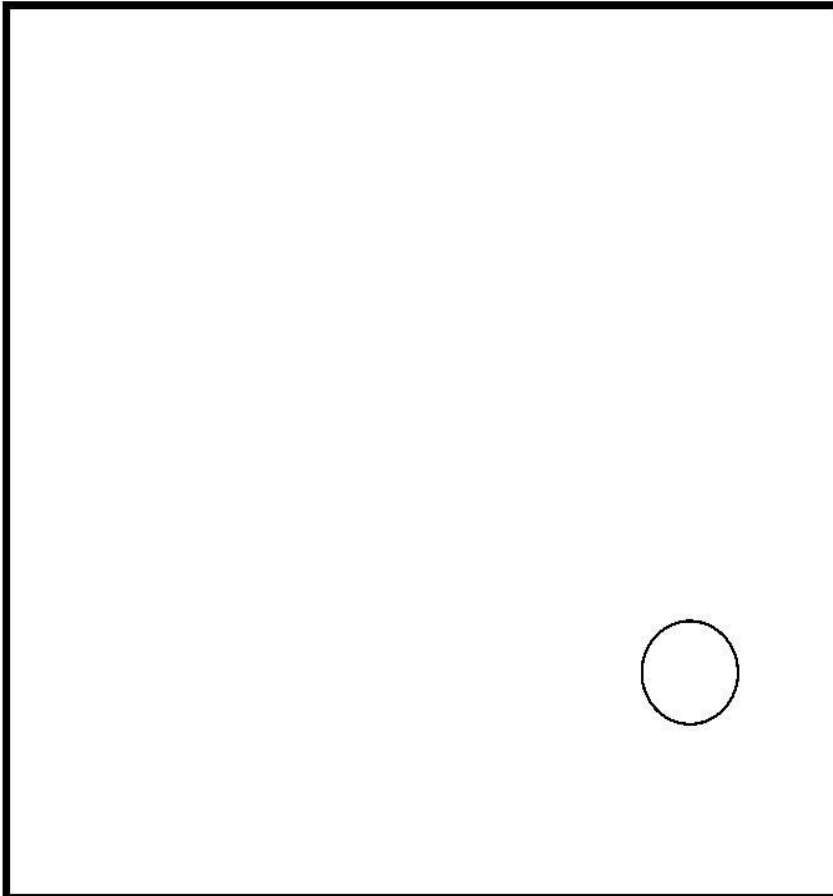
- You will see 3 colored dots appear briefly on the screen.
- Try to remember the location of these colored dots, because they will soon disappear.
- Next, you will be asked to recall the location of these colored dots on the screen.

PREVIOUS

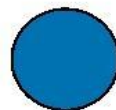
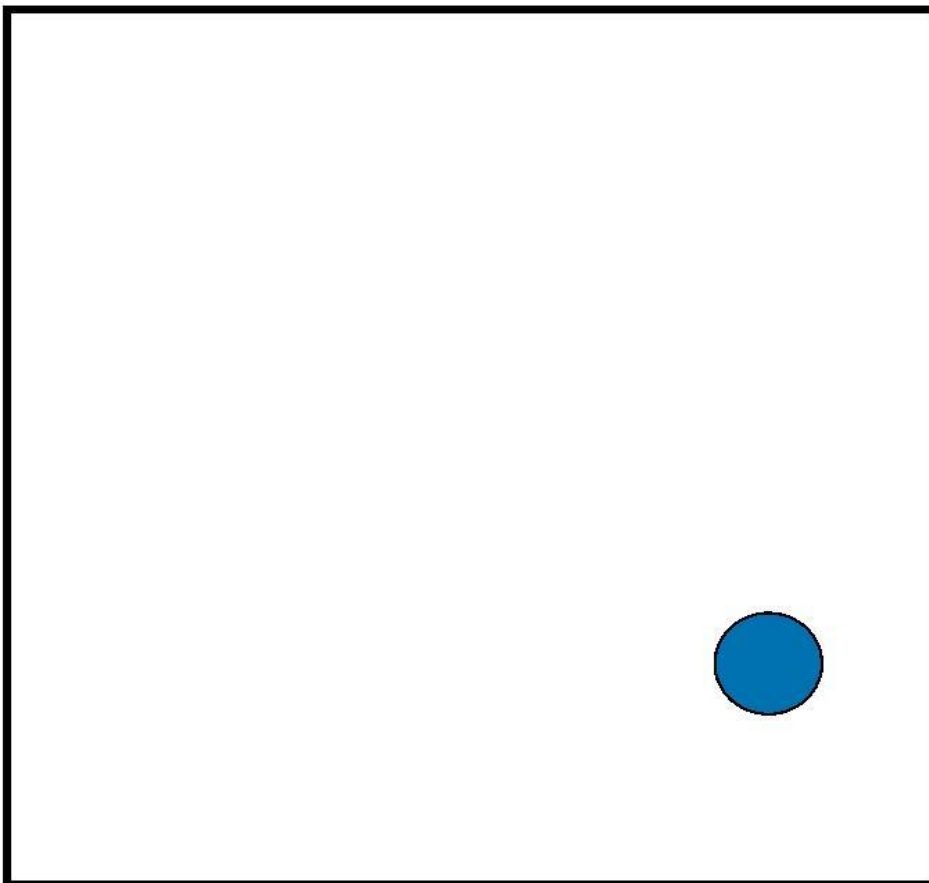
START



What color was this dot?



Where was this dot?



Touch screen to move the dot.

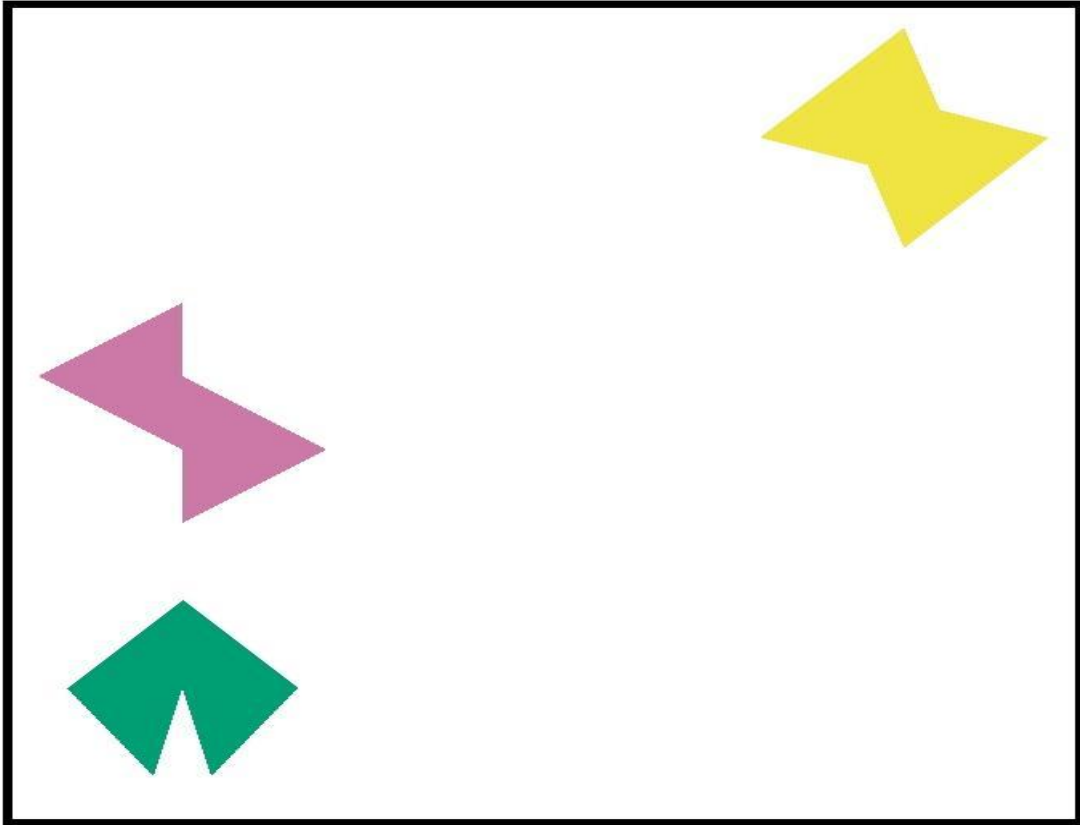
Color Disp

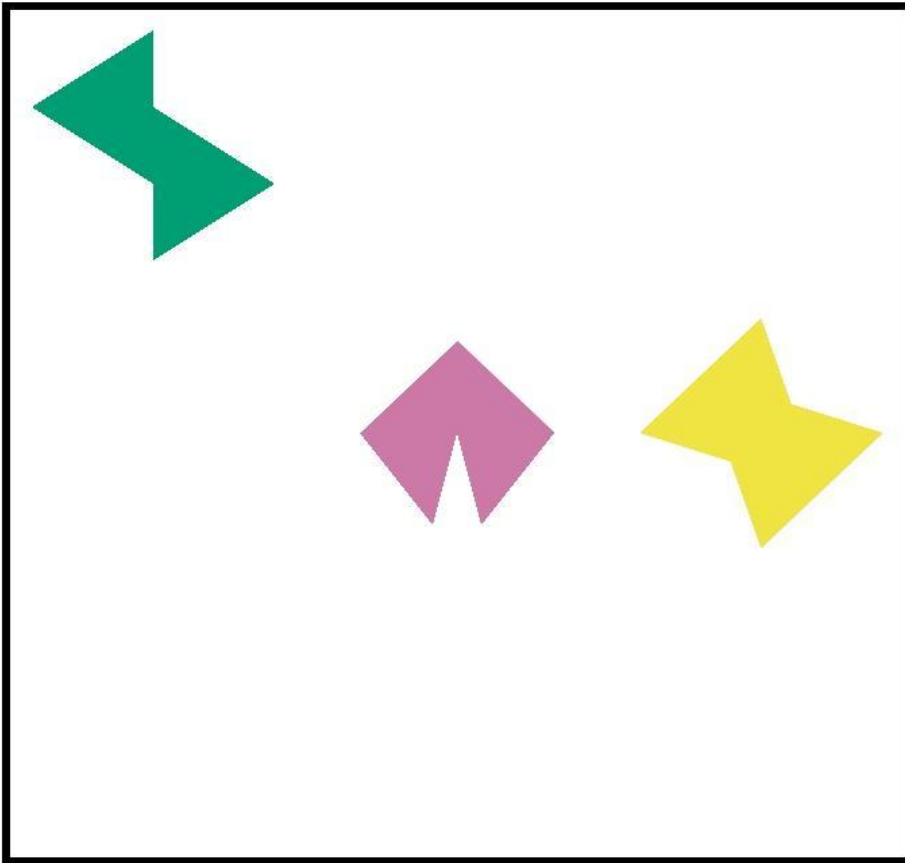
Instructions

- Colored shapes will appear briefly on the screen.
- Try to remember the shapes and their colors, because they will soon disappear.
- Next, you will see the same shapes reappear.
- Please answer whether the shapes have the **SAME** or **DIFFERENT** colors as they had before.

PREVIOUS

START





SAME

DIFFERENT



Color Naming Task

Instructions

--You will see COLOR WORDS presented in the center of the screen.

--For each COLOR WORD displayed, touch the word at the bottom that matches the color of the FONT the COLOR WORD is displayed in.

--Please respond as quickly and accurately as possible.

PREVIOUS

START

What color is the font?

ORANGE

YELLOW

ORANGE

What color is the font?

BLUE

RED

BLUE