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ASSESSMENT OF THE INFLUENCE OF COGNITION AND COGNITIVE PROCESSING SPEED ON THREE TESTS OF OLFACTION

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ASSESSMENT OF THE INFLUENCE OF COGNITION AND COGNITIVE PROCESSING SPEED ON THREE TESTS OF OLFACTION

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Abstract

Diminished test performance on standard olfactory tasks is known to be related to the level of cognitive impairment in individuals with diverse neurologic and psychiatric disorders. It is unclear, however, to what extent olfactory losses reflect sensory dysfunction in the early stages of olfactory processing, pathology related to higher-order processing of odors, non-olfactory cognitive deficits that emulate or exacerbate the appearance of olfactory losses, or some combination of all of these factors. Ambiguity currently exists because the most widely used measures of olfaction do not adequately differentiate higher-order from early processing stage impairments. A novel, valid and reliable approach to the evaluation of olfaction, the Sniff Magnitude Test (SMT), was recently developed and may minimize the influence of non-olfactory cognitive information processes in the evaluation of olfactory functioning. Recently, the SMT was found to be a valid indicator of olfactory ability in children and individuals with limited English-language abilities, which provided preliminary support for the claim that the test is only minimally influenced by variations in attentional and memory capacities, as well as language and odor familiarity. The present study used analysis of covariance structure procedures to determine the extent to which measures of retrieval of semantic and episodic verbal information, working memory, and cognitive processing speed relate to 3 measures of olfaction believed to have differing degrees of cognitive complexity. One hundred thirty-eight adults (ages 56-93 years) completed a battery of neuropsychological tests and the SMT, the phenyl ethyl alcohol threshold test (PEAT), and the University of Pennsylvania Smell Identification Test (UPSIT). Results indicated that the retrieval of verbal information significantly affects the UPSIT, working memory significantly affects the UPSIT and to a lesser extent the PEAT, and cognitive processing speed significantly affects the UPSIT and to a lesser extent the PEAT. As predicted, verbal retrieval, working memory and cognitive processing speed did not influence performance on the SMT. It was confirmed that measures of olfaction dependent on the ability to recognize

odors or detect odor intensities may overestimate olfactory loss when cognition and cognitive processing speed weaknesses are not taken into account. The minimal dependence of the SMT on these cognitive and processing speed processes may prove useful to efforts aimed at understanding the role of the olfactory system in a number of neurodegenerative disorders.

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CHAPTER I

Introduction

Olfactory abilities are commonly diminished in individuals with neurologic and psychiatric conditions, as well as in nondemented older adults. Research indicates that odor detection, discrimination, identification and recognition memory deficits exist in individuals diagnosed with a variety of disorders. For example, olfactory deficits have been reported across an array of disorders such as alcohol dependence (Rupp, Kurz, Kemmler, Mair et al. , 2003), adults with attention deficit/hyperactivity disorder (Gansler, Fucetola, Krengel, Stetson, Zimering, & Makary, 1998), anorexia and bulimia nervosa (Fedoroff, Stoner, Andersen, Doty, & Rolls, 1995), Down's syndrome (Murphy & Jinich, 1996), human immunodeficiency virus (Razani, Murphy, Davidson, Grant, & McCutchan, 1996), Alzheimer's disease (Murphy, 1999), Parkinson's disease (Hawkes, 2003), and seasonal affective disorder (Postolache, Doty, Wehr, Jimma et al., 1999), to name a few. The diverse range of disorders associated with olfactory loss raises questions about the specificity of olfactory dysfunction. In addition, it is unclear to what extent olfactory losses reflect sensory dysfunction in the early stages of olfactory processing, pathology related to the higher-order processing of odors, non-olfactory cognitive deficits that emulate or exacerbate the appearance of olfactory losses, or some combination of all of these factors (Martzke, Kopala, & Good, 1997).

The early stages of olfactory information processing begin when odor molecules enter the nasal cavity and dissolve in the mucus of the olfactory epithelium located at the roof of the nasal cavity (Lewis & Dahl, 1995; see Buck, 2000 for a review). Figure 1 depicts the major efferent peripheral and central pathways of the olfactory system. From the olfactory epithelium, information travels to synapses in the glomeruli at the olfactory bulb where initial lower-order olfactory processing begins. The neurons of the olfactory bulb then relay information to temporal lobe structures that serve as primary olfactory cortex (Shipley & Ennis, 1996). Structures in the primary olfactory cortex include the anterior olfactory nucleus, piriform cortex,

olfactory tubercle, entorhinal cortex, and anterior dorsomedial nucleus of the amygdala (Carmichael, Clugnet, & Price, 1994). These areas have been identified in PET and fMRI studies as being important to the initial emotional, identification and memory processing of olfactory information (Dade, Zatorre, & Jones-Gotman, 2002; Kareken, Doty, Moberg, Mosnik et al., 2001; Royet, Zald, Versace, Costes et al., 2000). From here, information is sent to the mediodorsal nucleus of the thalamus, hippocampus, insular cortex and orbitofrontal cortex. The hippocampus is a structure

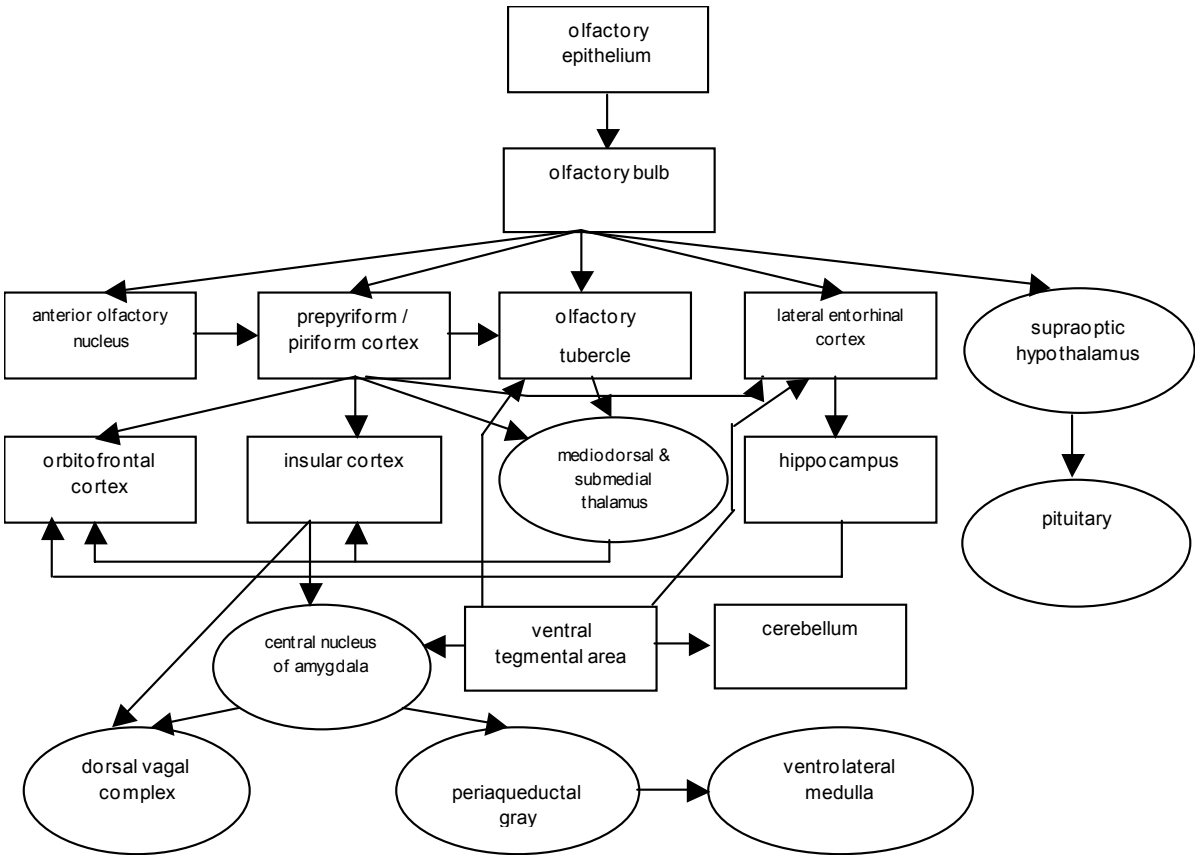

Figure 1. Major peripheral and central pathways of the olfactory system. Circles represent subcortical regions and squares represent cortical regions. Adapted from McLean & Shipley (1992), Dalton (2002); Carmichael, Clugnet, & Price (1994), Cavada et al. (2000), and Sobel et al. (1998b).

that may be involved in the encoding or consolidation of olfactory information (e.g., Murphy, Jernigan, & Fennema-Notestine, 2003; see Eichenbaum, Schoenbaum, Young, & Bunsey, 1996 for a review). PET and fMRI studies implicate the orbitofrontal cortex in the manipulation of

olfactory information in a working memory store, retrieval of odor labels, as well as in the processing of hedonic, familiarity and edibility judgments (Dade, Jones-Gotman, Zatorre, & Evans, 1998; Dade, Zatorre, Evans, & Jones-Gotman, 2001, Royet, Hudry, Zald, & Godinot et al., 2001). Using fMRI, others have recently hypothesized that the cerebellum, through indirect and direct ventral tegmental area connections, is involved in the processing of olfactory information; hypothesized to reflect the motoric monitoring of sensory information in the nasal cavity and epithelium when sniffing odors (e.g., Ferdon & Murphy, 2003; Sobel, Prabhakaran, Desmond, Glover et al., 1998a, 1998b).

Loss of the sense of smell in non-demented older adults and in various patient populations is hypothesized to result from structural/physiologic deficits in different CNS regions. For example, in non-demented older adults, declines have been attributed to atrophy in the olfactory epithelium (Naessen, 1971), degeneration in the olfactory bulb (Meisami, Mikhail, Baim & Bhatnagar, 1998), and neurofibrillary tangles in the anterior olfactory nucleus, parahippocampal gyrus, and hippocampal field CA1 (Price, Davis, Morris, & White, 1991). In patients with Alzheimer's disease, odor sensitivity deficits may reflect the disease process associated with the presence of neuritic plaques and neurofibrillary tangles found in the olfactory bulb and odor identification deficits in limbic system structures (Braak & Braak, 1995; Ohm & Braak, 1987). Similarly, neuronal degeneration due to plaques and tangles in the entorhinal cortex and hippocampus may lead to olfactory dysfunction in adults with Down's syndrome (Hyman, 1992). In multiple sclerosis, odor identification deficits are hypothesized to result from plaques within inferior frontal and temporal lobe regions (Doty, Li, Mannon, & Yousem, 1998, 1999). In Huntington's disease, olfactory deficits may be related to neuronal degeneration in the entorhinal cortex that may disrupt the transmission of olfactory information to the prefrontal cortex (Braak & Braak, 1992; Hamilton et al., 1999).

The main problem with understanding what poor performance on olfactory tests actually represents is that, in addition to adequate olfactory sensitivity, normal performance on these

tasks typically requires attention, working memory, verbal comprehension, and the retrieval of verbal information (Larsson, 2002). Consequently, olfactory loss due to a breakdown in the early stages of information processing may be overestimated if the impact of non-olfactory cognitive limitations is not taken into account. Further, higher-order olfactory losses may be overestimated if early stage olfactory losses cannot be adequately determined or if cognitive limitations inflate the appearance of poor sensory test performance. This is a significant issue because several olfactory tasks are currently being used in clinical and research test batteries to help predict, diagnose and better understand neurophysiological, neuroanatomical and behavioral problems associated with neurologic and psychiatric disorders (Doty, 2001; Kobal, Klimek, Wolfensberger, Gudziol, et al., 2000; Mann, 2002; Liberini, Parola, Spano, & Antonini, 2000).

There are several reports of significant relationships between poor olfactory functioning and reduced general cognitive ability. For example, general cognitive impairment is associated with poor olfactory test performance in patients with Alzheimer's disease (AD; Larsson, Semb, Winblad, Amberla, Wahlund, & Bäckman, 1999; Morgan et al., 1995; Murphy, Gilmore, Seery, Salmon, & Lasker, 1990; Murphy, Nordin, & Jinich, 1999; Nordin, Almkvist, Berglund, & Wahlund, 1997; Serby, Larson, & Kalkstein, 1991), Down's syndrome (Murphy & Jinich, 1996), human immunodeficiency virus (Razani et al., 1996), Parkinson's disease (Tissingh et al., 2001), schizophrenia (Stedman & Claire, 1998), and vascular dementia (Gray et al., 2001). In the longitudinal evaluation of olfactory functioning, a more rapid rate of progression of a disease (e.g., AD) is related to a faster rate of deterioration of loss of olfactory sensitivity (Murphy et al., 1999). Further, progressive loss of odor identification ability predicts poorer overall level of cognitive functioning (Graves, Bowen, Rajaram, McCormick, et al., 1999). There are also reports that both individuals with mild cognitive impairment[1] and non-demented individuals at

[1] a stage between nondemented and a diagnosis of probable AD; Petersen, Doody, Kurz, Mohs, et al., 2001.

risk for AD have significantly poorer odor threshold and odor identification deficits compared to nondemented older adults and adults not at risk for AD (Devanand, Michaels-Marston, Lui, Pelton, et al., 2000; Murphy, Bacon, Bondi, & Salmon, 1998; Murphy et al., 1999; Nordin & Murphy, 1996; Peters, Hummel, Kratzsch, Lotsch, Skarke, & Frolich, 2003; Serby, Mohan, Aryan, Williams, Mohs, & Davis, 1996). The relationship between general cognitive decline and olfactory impairment may reflect global CNS deterioration that affects both peripheral and central olfactory processes. This is not the case for peripheral visual and auditory sensory systems since acuity associated with these sensory systems are often spared in individuals with global cognitive impairment. Thus, some researchers have suggested that olfactory tasks may be more sensitive to disease progression in the CNS compared to tests administered in the visual or auditory modalities given that both sensory and cognitive aspects of olfactory functioning are associated with disease progression (e.g., Nordin & Murphy, 2002).

Other studies indicate that measures of olfaction and specific non-olfactory cognitive domains are also related in non-demented adults. For example, poorer odor threshold and poor identification abilities are related to poor performance on measures of cognitive processing speed (Dulay & Murphy, 2002; Larsson, Nilsson, Olofsson, & Nordin, 2004), attention and working memory (Danthiir, Roberts, Pallier, & Stankov, 2001; Hulshoff Pol, Hijman, Baare, van Eekelen, & van Ree, 2000), vocabulary level (Larsson et al., 2004), reasoning ability (Danthiir et al., 2001; Dulay & Murphy, 2002) confrontation naming (Stevens, Cruz, Marks, & Lakatos, 1998), verbal memory (Brewer, Edwards, Anderson, Robinson, & Pantelis, 1996; Danthiir et al., 2001; Dulay & Murphy, 2002; Finkel, Pedersen, & Larsson, 2001; Larsson, Finkel, & Pedersen, 2000; Oberg, Larsson, & Backman, 2002; Royall, Chiodo, Polk, & Jaramillo, 2002; Stevens et al., 1998; Swan & Carmelli, 2002) and general cognitive impairment (Morgan et al., 1995). On the basis of these results, investigators have hypothesized that performances on all sensory and cognitive tests are related because they are both impacted by age- and disease-related physiological changes in the central nervous system (Baltes, & Lindenberger, 1997;

Lindenberger & Baltes, 1994). If this is the case, olfactory test performance may be an early indicator of the presence of certain disease processes such as mild cognitive impairment, which could be important when effective treatments are identified to slow or prevent these disorders (Jones, 2003).

Alternatively, non-olfactory cognitive deficits may influence performance on olfactory tests, thereby emulating or exacerbating the appearance of olfactory losses (Martzke et al., 1997). These 'secondary factors' might include general cognitive impairment, incomprehension, or specific cognitive domain deficits such as attention or memory impairment, and/or slow cognitive processing speed. As an individual's general level of cognitive functioning deteriorates, performance on olfactory tasks may be impaired despite relatively intact olfactory functioning. For example, a significant relationship between general level of cognitive functioning and level of olfactory functioning may reflect the ability/inability of participants to perform the olfactory tasks because performance on all ability tests is impaired. General cognitive impairment might also cause a participant to misunderstand instructions, which in turn could affect test performance (e.g., Padovani, Di Piero, Bragoni, Iacoboni et al., 1995). Indeed, complex tests are often simplified for patients with moderate to severe comprehension deficits to improve the validity of testing (e.g., Bickel, Pantel, Eysenbach, & Schroder, 2000; Nordin et al., 1997). These verbal comprehension deficits can occur even in patients with mild to moderate forms of a dementing illness (Grossman, McKanin, Onishi, & Hughes, 1996). Furthermore, it is well known that working memory deficits lead to reduced performance on tests of visual and verbal memory in some nondemented older adults (e.g., Brebion, 2003). It may also be that factors similar to those that reduce cognitive ability create the appearance of olfactory deficits. For example, slow cognitive processing speed could impact tasks that require working memory because the information is lost due to the temporal limitations of the working memory store (Salthouse, 1991a). Importantly, olfactory tests are difficult to perform compared to tests that primarily require vision and audition. For example, healthy people have great

difficulty identifying odors without a prompt (see Richardson & Zucco, 1989 for a review). Because olfactory tasks are difficult, they may pose a disproportionate challenge to individuals who are elderly or who have neuropsychiatric illness.

In summary, the main problem with interpreting diminished olfactory test performance is that it may be difficult to differentiate early peripheral from later more central olfactory losses, and/or from the secondary influences of non-olfactory cognitive demands (e.g., general cognitive impairment, general memory impairment, cognitive processing speed). These confounds make it difficult to conclude that olfactory losses as measured by typical clinical tests are associated with underlying neurochemical and neuroanatomical dysfunction associated with a disorder or normal aging.

A novel approach to the evaluation of olfaction has recently been developed that may minimize the influence of non-olfactory cognitive information processes (Frank, Dulay, & Gesteland, 2003; Frank, Dulay, Niergarth, & Gesteland, 2004). The recent creation of the Sniff Magnitude Test (SMT) provides an opportunity to test the hypothesis that different measures of olfactory function possess varying degrees of cognitive complexity. Magnitude and latency characteristics of a sniff in response to pleasant and unpleasant odors of different concentrations have received some attention in the past (Laing, 1983; Raudenbush, Schroth, Reilly, & Frank, 1998; Sobel et al., 1998b; Teghtsoonian, Teghtsoonian, Berglund, & Berglund, 1978). However, only recently has sniffing behavior been used as a clinical measure of olfactory function (Frank et al., 2003, 2004). Previous research has demonstrated that sniff magnitude and latency decrease in the presence of a malodor for people with a typical sense of smell, but that people with an impaired sense of smell do not reduce their sniffs when malodors are presented (Frank et al., 2003). In a sample of 100 younger and older adults, performance on the SMT was significantly correlated with scores from a two-alternative forced choice butanol threshold test (-0.66) (Doty, Reyes, & Gregor, 1987), the University of Pennsylvania Smell Identification Test (-0.61) (Doty, 1995), and the Alcohol Sniff Test (-0.64) (Davidson & Murphy,

1997) providing support for the convergent validity of the SMT as a measure of olfactory function. In addition, Frank et al. (2003) documented moderate to high test-retest reliability for the SMT (r=0.80). Recently, the SMT was found to be a valid indicator of olfactory ability in children and individuals with limited English-language abilities (Frank et al., 2004), which provided preliminary support for the claim that the test is minimally influenced by variations in attentional and memory capacities, as well as language and odor familiarity.

Sniffing behavior is quantified by measuring the reflexive-like reduction in airflow through the nostrils in response to an odor (Frank et al., 2003; 2004; Sobel, Prabhakaran, Desmond, Glover, Sullivan, & Gabrieli, 1997; Walker, Kendal-Reed, Hall, Morgan, Polyakov, & Lutz, 2001). Although both good and bad odors reduce sniffs compared with sniffs to no odor, more suppression occurs to a malodor, and the level of the suppression to a malodor is more uniform in comparison to other odors (Raudenbush et al., 1998). This uniformity reduces individual differences in sniff response to an odor, and thus is an important psychometric feature of a task that may improve efforts to correctly classify those who can smell (Stevens, Cain, & Burke, 1988; Walker, Hall, Walker, Kendal-Reed, Hood, & Niu, 2003; see Dalton, 2002 for a review). Sniff inhibition in response to an odor may be reflexive because it is a behavior closely tied to survival, for example, people may instinctively stop sniffing a malodor to reduce the likelihood of exposure to dangerous chemicals (Jacob, Fraser, Wang, Walker, & O'Conner, 2003). Recent research suggests that the assessment of sniffing behavior may rely on a subcortical feedback loop, and that sniffing behavior could be used in better understanding sensory-motor impairments associated with diseases that affect motoric functioning (Johnson, Mainland, & Sobel, 2003; Sobel et al., 1998a; Sobel, Thomason, Stappen, Tanner et al., 2001). There is also evidence to suggest that malodors are difficult to describe verbally compared with neutral and pleasant odors (Alaoui-Ismaili, Robin, Rada, Dittman, Vernet-Maury, 1997). SMT procedures require that an individual be vigilant when the command "ready" is given, inhale through the nose when the "sniff" command is given, and then respond by breathing through the nose.

Because air pressure changes associated with sniffing are used to quantify olfactory function, there is no need to explicitly rate, categorize or remember anything about an odor stimulus, and no verbal response is required.

The over-arching goal of the present study was to determine the extent to which the SMT is influenced by variations in cognition and cognitive processing speed, as compared to widely used clinical tests of olfaction. The present study included three olfactory tasks that are presumed to have differing levels of cognitive complexity. Cognitive complexity refers to "the hypothesized number of *cognitive* processing operations required to perform a task (Salthouse, 1991b, page 309; italicized word added)." It is assumed that an olfactory task has lower cognitive demand when test performance is associated with a fewer number of cognitive processes. To operationalize the idea of lower cognitive complexity, the present study draws upon Atkinson & Schiffrin's (1968) information processing (IP) model, which originally posited

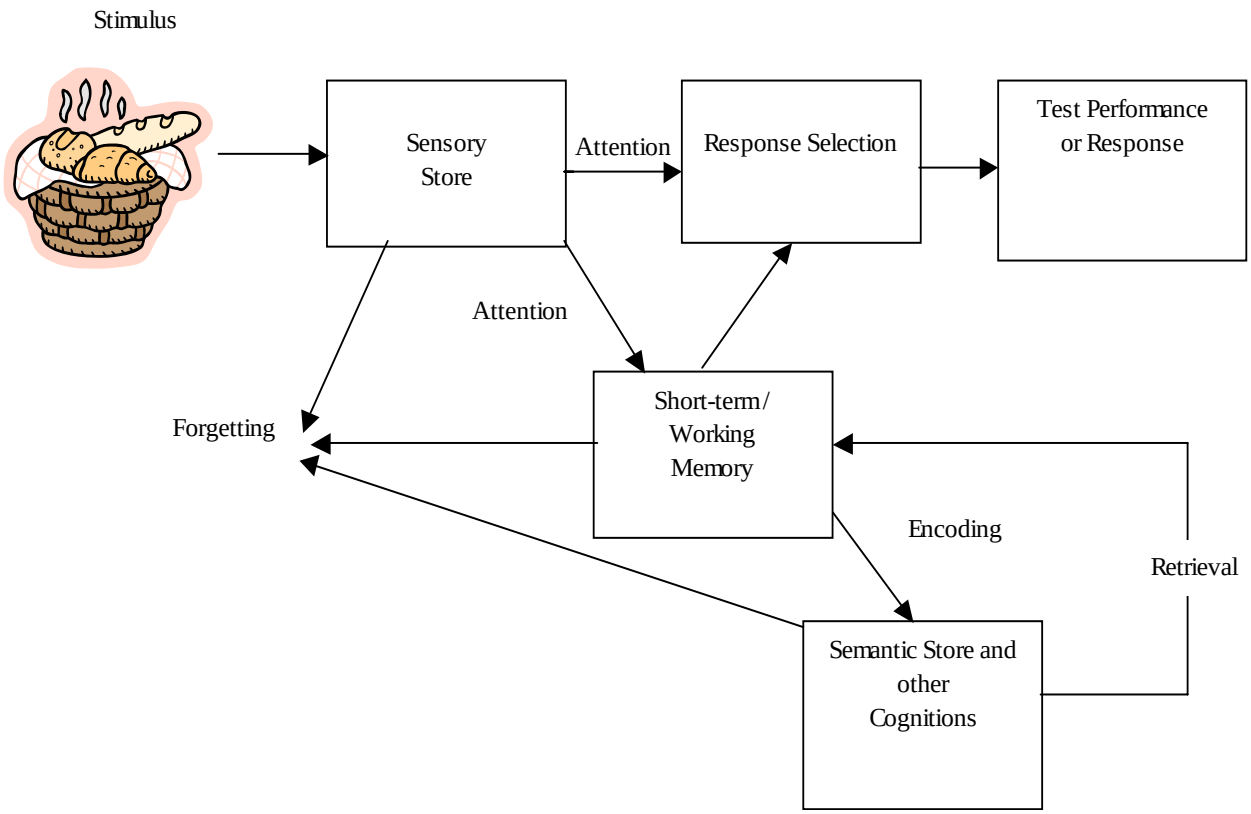

Figure 2. Depiction of the possible stages involved in the processing of olfactory information.

that memory processing occurs in stages. The IP model (see Figure 2) suggests that different stimuli are processed in hierarchical and recursive stages; for example, information can be attended to, then encoded, stored and retrieved (Atkinson & Schiffrin, 1968; Royet et al., 1999). The more stages required to perform a given task, the more likely it is that a breakdown at any level will result in poor test performance[2]. The concept of working memory is also used in the present study to represent the manipulation of information in a short-term store (Baddeley, 1981). The IP model is useful in the present study because it assumes an integral relationship between sensory and cognitive processing (Schneider & Pichora-Fuller, 2000). In terms of olfaction, the model would predict that later-stage olfactory functions (e.g., odor identification and recognition memory) rely upon early-stage olfactory functions (e.g., detection and simple discrimination tasks) for the competent completion of a task. In addition, even simple lower order olfactory functions can rely on some level of cognitive processing if the information must be manipulated mentally (Dade et al., 2001; Larsson, 2002; Stevenson & Boakes, 2003). For example, research suggests that an olfactory short-term memory store exists that is independent of the verbal encoding system and that is employed when performing an odor discrimination task (White, Hornung, Kurtz, Treisman, & Sheehe, 1998).

As noted above, the SMT is based on the assessment of the reflexive-like reduction in sniffing in response to a bad odor. The University of Pennsylvania Smell Identification Test (UPSIT), the most widely used measure of the ability to identify odors, requires several cognitive and linguistic skills (Doty, 1995; Larsson, 2002). The task requires matching an odor percept with one of four verbal labels. Referring back to the IP stages in Figure 2, possible olfactory and non-olfactory abilities involved in performing the UPSIT include adequate sensory transduction/registration, sustained attention to each of 40 items, encoding of the odor percept,

[2] Though not represented in Figure 2, it is important to note that the parallel processing of olfactory information also occurs at different levels (Savic, Gulyas, Larsson, & Roland, 2000).

holding a percept and verbal label in short-term or working memory, accessing semantic memory, retrieving the verbal label into short-term/working memory, selecting a response, and then making the written or oral response (Dade et al., 2001; Larsson et al., 2000; White et al., 1998). Any component weakness caused by aging or disease that impacts one or more processes (stages) involved in identifying odors may create the appearance of poor odor identification test performance. However, this deficient score may reflect not only olfactory impairment, but also impaired non-olfactory functions.

The olfactory sensory acuity task most commonly used in previous studies is a two-alternative forced-choice threshold task (Cain, Gent, Catalanotto, Goodspeed, 1983; Doty, Reyes, & Gregor, 1987). Although it has been suggested that this task does not depend on cognitive abilities (see Martzke et al., 1997 for a review), it does place some demand on working memory, attention and decision-making. The task requires sustained attention as an individual holds a percept in short-term/working memory and then discriminates between a peri-threshold stimulus and a non-odorized blank. The task also requires that a participant provide a verbal response after determining which of two samples has a stronger odor. This task requirement essentially makes the process equivalent to a discrimination task. People also must set criteria for making responses in the face of an ephemeral and uncertain peri-threshold stimulus.

The primary aim of this study was to test the hypothesis that the SMT demands a significantly lower degree of cognitive complexity than the UPSIT and the two-alternative forced choice phenyl ethyl alcohol threshold test (two measures that are commonly used in the clinical assessment of olfactory ability). Using analysis of covariance structures, this study assessed the direct effects of semantic/episodic verbal retrieval, attention/working memory, and cognitive processing speed on these three measures of olfaction. Cognitive domains were chosen based on the hypothesis that poor performance in these particular areas would influence performance on the olfactory tests. Chronological age was also included in the analyses as a covariate given

the nature of the sample (adults between the ages of 56 and 93) and based on the findings of age-related reductions in processing speed (Salthouse, 1996), attention (Plude, Schwartz, & Murphy, 1996), working memory (Babcock & Salthouse, 1990), confrontation naming (Albert, Heller, & Milberg, 1988), verbal memory (Zelinski, Gilewski, & Schaie, 1993) and olfaction (Hummel, Heilmann, & Murphy, 2002). It was hypothesized that (a) retrieval of semantic and episodic verbal information (from this point on referred to as verbal retrieval) would have a direct effect on the UPSIT, (b) attention/working memory would have direct effects on the UPSIT and the PEAT, (c) cognitive processing speed would have direct effects on the UPSIT and the PEAT, (d) chronological age would significantly effect performance on the 3 latent constructs and the 3 olfactory tasks and, (e) there would be no significant direct effects of the 3 cognitive domains on the Sniff Magnitude Test.

CHAPTER II

Methods

Participants

Cross-sectional data were obtained from 142 older adults. The University of Cincinnati Institutional Review Board approved the project, and all participants provided written informed consent. Participants were recruited from five non-assisted living and assisted-living retirement communities in Cincinnati, Ohio. Potential participants were required to (a) understand English so that they could comprehend the test instructions and to (b) have adequate visual and motor skills to complete the tasks in the battery. No other exclusionary criteria were applied to increase the sampling distribution of individuals that would be included in the study to avoid limiting the variability in performance on the olfactory tests and cognitive measures. This was important given that a main objective of the study was to determine the between test relationships. One individual was excluded from testing because he had suffered a left hemisphere stroke that left him with an expressive aphasia. Three participants were excluded because of visual acuity deficits (e.g., as a result of macular degeneration), which made it difficult to perform the visual-based cognitive tasks. Thus, 138 individuals completed the study.

Demographic and medical history data for the sample are presented in Table 1. These data are drawn from a self-report questionnaire that asked about history of nasal sinus disease, allergies, current medication regimen, current taste and smell complaints, lifetime and current history of neurological conditions, current psychiatric diagnoses, current smoking status (i.e., smoker or non-smoker), and number of medications (range from 0 to 16 meds), as well as demographic variables such as age (range from 56 to 93 years), education (range from 0 to 19 years), and race/ethnicity. Average duration of current smoking habit was 37 years at an average of one pack per day. Previous research suggests that cigarette smoking has a detrimental impact on level of olfactory ability (Frye, Schwartz, Doty, 1990; Murphy, Schubert, Cruickshanks, Klein, Klein, & Nondahl, 2002). Three individuals reported having a diagnosis of

Parkinson's disease, 2 a diagnosis of epileptic seizures, and 3 had a history of a cerebral vascular accident. Twenty-one participants indicated that they were currently being treated for a mood or anxiety disorder and one person was receiving treatment for schizophrenia. A current psychiatric diagnosis was based on self-report of current treatment from a psychiatrist, psychologist, or primary care physician. No individual reported the presence of a learning disorder.

Table 1. Sample demographic and medical history information (N=138)

	mean	SD	
Age (in years)	77.08	8.50	
Education (in years)	13.02	3.13	
	%	%	%
Sex (%)	80.4 (Female)	19.6 (Male)	
Race/Ethnicity (%)	77.5 (Caucasian)	22.5 (African American)	
Handedness (%)	93.0 (Right)	6.0 (Left)	1.0 (Ambidextrous)
# of Medications	3.93 (mean)	3.33 (SD)	
Inflamed Allergies (%)	15.9 (Yes)	44.9 (No)	39.1 (No Allergies)
Smoking Status (%)	9.4 (Currently)	49.3 (Never)	41.3 (Formerly)
Smell Complaints (%)	20.3 (Yes)	79.7 (No)	
Taste Complaints (%)	8.7 (Yes)	91.3 (No)	
Psychiatric Condition (%)	15.9 (Yes)	84.1 (No)	
Neurologic Condition (%)	6.5 (Yes)	93.5 (No)	

SD = standard deviation. Inflamed Allergies = whether or not an individual's allergies were acting up on the day of testing.

Apparatus and Procedures

Tests were administered in 2 one-hour sessions on 2 different days, separated by no more than 3 weeks. Testing was conducted in quiet rooms at the different retirement communities. The average time between testing sessions was 10 days. Participants received $20.00 per session in compensation for their time. Before testing began, informed consent was obtained and the goals of the experiment were explained. Test administration was structured so

that olfactory and non-olfactory neuropsychological tests were never given in the same order as the previous two participants. However, test administration was not systematically counterbalanced. Olfactory and non-olfactory tasks organized by their representative cognitive domains are presented in Table 2. A measure of verbal intelligence, general cognitive functioning, and the ability to understand simple one- and two-step commands were also included to relate olfactory test performance to these abilities. Administration of all tests followed standard procedures.

Table 2. Tests and representative domains

Domain	Tests
Olfaction	Sniff Magnitude Test (SMT) The University of Pennsylvania Smell Identification Test (UPSIT) Phenyl Ethyl Alcohol Threshold Test (PEAT)
Verbal Retrieval	Boston Naming Test (BNT)- Short Form California Verbal Learning Test-II (CVLT-II) - Short Form Category Fluency (CF) - Animals, Fruits, Vegetables
Attention/Short-term/Working Memory	Attention subscale of DRS-2 (DRS-A) Letter-Number Sequencing (LNS)
Cognitive Processing Speed	Digit Symbol-Coding (DS-C) Symbol Search (SSRCH) Trail Making Test (TMT) - Part A
Premorbid Estimate of Intelligence	American National Adult Reading Test (AMNART)
General Cognitive Impairment	Dementia Rating Scale-2 (DRS-2)
Verbal Comprehension	Token Test - Short Version

Olfactory Measures

Sniff Magnitude Test (SMT; Frank et al., 2003, 2004). The SMT dependent variable was quantified by measuring air pressure changes associated with airflow through the nose. Air pressure changes were measured with a nasal cannula connected to a piezoelectric

pressure transducer. See Figure 3 for testing apparatus. The cannula (A in Figure 3) was an ordinary double-nares silastic nosepiece commonly used for chronic oxygen administration in clinical settings. The transducer (B in Figure 3) output was digitized, stored and analyzed to yield measures of sniff duration and magnitude. A computer program that measures area under the curve using the duration and magnitude of each sniff quantified air passage through the

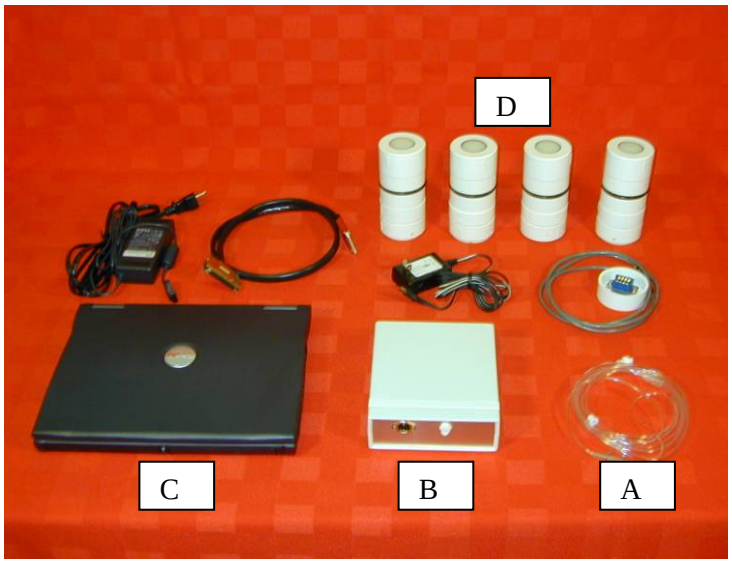

Figure 3. Sniff magnitude testing apparatus.

nose (C in Figure 3). Pressure for a sniff was recorded every 10 ms for up to 3 seconds. Only one sniff was measured such that transducer output information was not recorded after the first time a participant re-attains zero pressure. A sniff was defined as the pressure produced when a participant inhaled through her/his nostrils. See Figure 4 for a typical sniff to a malodor (dotted curve in figure) and a typical sniff to nonodorized air (solid curve in figure). The stimulus delivery system (D in Figure 3) consisted of 4 chambers containing either (a) no odor, (b) methylthiobutyrate (MTB; an organic compound with a putrid smell commonly identified as cabbage-like or fecal) at 1.0% volume/volume (v/v) diluted in odorless mineral oil, (c) MTB at 3.0% v/v, or (d) ethyl mercaptoproprionate (EMP) at 1.0% v/v (also a putrid odor commonly

labeled as skunky). Previous research indicated that MTB was the most effective odor at reducing a sniff compared to pleasant or neutral odors (Raudenbush et al., 1998) or to other

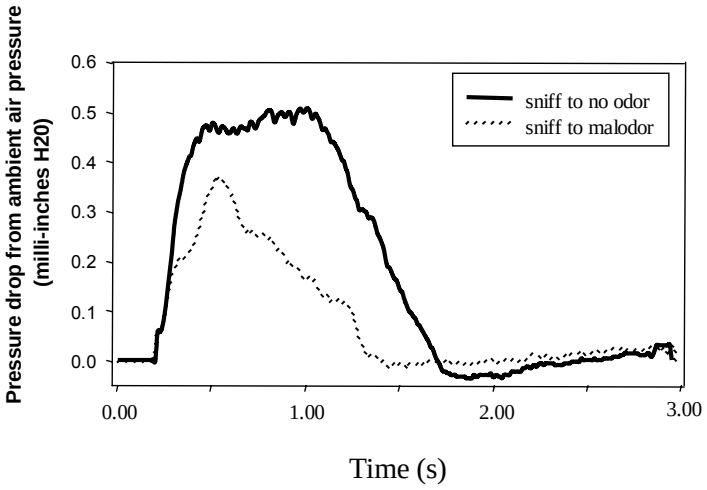

Figure 4. A typical sniff to a malodor and a typical sniff to nonodorized air.

malodors (Dulay, Gesteland, & Frank, 2000; Niergarth, Dulay, Gesteland, & Frank, 2003). Pilot studies indicated that MTB at 1.0% v/v does not produce notable nasal irritation (Dulay, Reinhard, Gesteland, & Frank, 2001; Raudenbush et al., 1998).

Participants were seated in front of the sniff device and the nasal cannula was fitted at the base of both nostrils (see Figure 5). Before testing, participants were told that they would be inhaling through both nostrils in an attempt to detect an odor, and that sometimes an odor would be present and sometimes not. Then, they were instructed to close their eyes, which reduced the likelihood of the use of visual cues. After a chamber was placed approximately 2.0cm below both nostrils by the experimenter, the command “sniff” was given, signaling a participant to inhale through her/his nostrils. Opening of the odor canister and exposure to a stimulus was triggered by the pressure change at the onset of a person’s sniff. At least two practice trials were given. Then, three trials were administered in which non-odorized air was presented. This served as the ‘no odor baseline’ that was compared to the malodor trials. Next, MTB at 1.0% v/v was presented three times. The dependent variable, the sniff magnitude ratio, was based on the average sniff magnitude and duration to the three MTB trials at 1.0% trials divided by the average sniff magnitude and duration to the three non-odorized air trials (mean of

three MTB trials / mean of three non-odorized air trials). If a participant scored at least one standard deviation away from the mean based on young adult normative data (Frank et al., 2003), a special protocol was administered in which a participant received three trials of MTB at 3.0% v/v and then three trials of EMP at 1.0% v/v[3]. This special protocol with a greater concentration of

Figure 5. Participant seated in front of the sniff device with the nasal cannula fitted at the base of both nostrils.

the same odorant and a different odorant allowed for the determination of (a) whether odor concentration was responsible for no sniff reduction to MTB at 1.0% v/v or (b) whether the specific odorant (MTB) was responsible for no sniff reduction. In all, 56% of the sample received the special protocol. The unit of measurement was the average sniff magnitude ratio for 3 trials of MTB at 1.0% v/v for all individuals. Previous research found that adaptation / habituation to MTB was not observed over as many as 12 consecutive trials with an inter-trial interval of 10 seconds in the concentration range similar to the present study's range (Niergarth et al., 2003).

[3] The six extra trials were used to further assess olfactory responses but did not provide information superior to 1.0% MTB (Niergarth et al., 2003).

University of Pennsylvania Smell Identification Test (UPSIT; Doty, 1995). The UPSIT is a self-administered test that assesses the ability to detect and identify odors using a four alternative, forced-choice format. Participants were instructed to scratch a one-inch patch containing a microencapsulated odor using a pencil, and then choose from 4 labels to indicate what the odor most smelled like. If participants were unsure, they were asked to guess. A different odor was encapsulated in each patch. Although the test was self-administered, the experimenter was always present to answer any questions or clarify how to perform the task. The final unit of measurement was the number of correctly identified odors out of 40 trials.

Two Alternative Forced-choice Phenyl Ethyl Alcohol Threshold (PEAT) Task (Doty et al., 1987). Olfactory thresholds for phenyl ethyl alcohol were assessed using a modified version of a two-alternative, forced-choice threshold task. The colorless phenyl ethyl alcohol was diluted with odorless mineral oil to form 12 concentrations (11 the weakest concentration and 0 the strongest) starting at 4.0% v/v increasing by 0.5 log steps per concentration. Testing began with the weakest concentration. Participants were given two plastic bottles, one bottle with phenyl ethyl alcohol and one bottle with odorless mineral oil, and asked to determine which bottle had a stronger odor. Participants placed the pop-top plastic bottle tip below both nostrils and squeezed on the bottle. Participants then indicated which of the bottles was believed to contain the stronger odor. An incorrect response led to an increased concentration on the next trial. A correct choice led to the presentation of the same concentration. Testing was halted when five correct choices in a row were made at the particular concentration. This final concentration represented the PEAT threshold dependent variable.

Non-Olfactory Neuropsychological Measures

American National Adult Reading Test (AMNART; Grober & Sliwinski, 1991). The AMNART was used to estimate premorbid verbal intelligence quotient (IQ), and to determine the relationship between verbal IQ and olfactory abilities. The AMNART consists of a list of

phonetically irregular words that increase in difficulty. The test is highly correlated with verbal IQ in healthy people (Blair & Spreen, 1989) and is relatively resistant to decline with dementing diseases (e.g., Sohlosser & Ivison, 1989). Test-retest reliability was found to be within the .92 to .98 range (Crawford, Stewart, Garthwaite, Parker, & Besson, 1988). The number of total errors on the task was the unit of measurement.

Dementia Rating Scale-2 (DRS-2; Jurica, Leitten, & Mattis, 2001; Mattis, 1988). The DRS-2 was used to estimate general cognitive ability of the sample and to assess the relationship between general cognitive level and olfactory abilities. The DRS-2 measures attention, initiation and perseveration, construction, conceptualization, and memory. The DRS-2 is sensitive to the effects of different disease processes (e.g., dementia; Kazniak, 1986), but has a ceiling effect that makes it relatively insensitive to normal aging variability (Vitaliano, Breen, Russo, Albert, Vitiello, & Prinz, 1984). Split-half reliability was found to be .90 (Gardner, Oliver-Munoz, Fisher, & Empting, 1981), and the test is highly correlated with other tests of general cognitive functioning (e.g., Bobholz & Brandt, 1993). The unit of measurement was the raw score sum of all 5 subscales. In addition, the raw score for the attention subscale was used as a measure of attention and concentration to determine the relationship between olfactory functioning and attentional abilities. Attention declines as a function of disease and aging processes (Plude, Schwartz, & Murphy, 1996).

Token Test of the Multilingual Aphasia Examination (Benton & Hamsher, 1978). The Token Test was used to quantify the ability to understand simple one- and two- step instructions, and to determine the relationship between comprehension level and olfactory test performance. The task involves following simple commands that require a participant to touch certain objects (circles and squares) that are different colors (red, white, yellow, blue, and green). The test correlates highly with other measures of auditory comprehension (Morley, Lundgren, & Haxby, 1979), and is sensitive to the effects of aphasia (Spreen & Risser, 1991)

and dementing processes (Swihart, Panisset, Becker, Beyer, & Boller, 1989), disorders that can impact verbal comprehension. Reliability was found to be within the .90 to .96 range (Spreen & Strauss, 1998). The unit of measurement was the raw score number of correct responses.

Short form of the Boston Naming Test (BNT-2nd edition, Kaplan, Goodglass, & Weintraub, 2001 which was derived from version 4 of Mack, Freed, Williams, & Henderson, 2001). The 15-item revised version of the BNT is a measure of semantic knowledge for visually presented penciled drawings and was used to assess one aspect (along with category fluency and verbal memory) of the relationship between verbal retrieval ability and olfactory test performance. Confrontation naming is sensitive to the effects of typical aging (Albert, Heller, & Milberg, 1988) and dementia (Storandt & Hill, 1989). Test-retest reliability was found to be within the .82 to .96 range (e.g., Huff, Collins, Corkin, & Rosen, 1986). The BNT is moderately to highly correlated with other measures of naming ability (e.g., Axelrod, Ricker, & Cherry, 1994). The unit of measurement was the total number of correct responses.

Category Fluency (Lezak, Howieson, & Loring, 2004; Rosen, 1980). Category fluency requires an available word knowledge base, intact retrieval ability, and rapid word generation based on semantic knowledge. The test was chosen as another aspect of verbal retrieval that was related to olfactory test performance. Category fluency declines as a part of the typical aging process (Fama, Sullivan, Shear, Cahn-Weiner et al., 1998) and is sensitive to disorders that influence semantic knowledge networks (Monsch, Bondi, Butters, Salmon, Katzman, & Thal, 1992). Reliability was found to be moderate to high (Harrison, Buxton, Husain, & Wise, 2000). The participant was given one minute to say as many words as possible that fell within a specified semantic category (animals, fruits, vegetables). The unit of measurement was the total number of words across categories.

Short form of the California Verbal Learning Test-II (CVLT-II; Delis, Kramer, Kaplan, & Ober, 2000). Episodic retrieval of words was assessed using the short-form version of the CVLT-II. The test was chosen to represent a third aspect of verbal retrieval ability. The CVLT-II short form incorporates a list-learning recall paradigm to measure memory for verbally presented words. Test performance declines as a function of typical aging (Delis et al., 2000) and is differentially sensitive to dementing processes (e.g., Massman et al., 1992). Test-retest reliability for this list-learning paradigm was found to be within the .90 to .96 range (Delis et al., 1990). The CVLT is moderately correlated with other measures of verbal memory (Woodard, Goldstein, Roberts, McGuire, 1999). The unit of measurement was the total number of correct words from trials 1- 4 with the range of possible scores from 0 to 36.

Letter-Number Sequencing (LNS), Digit Symbol-Coding and Symbol Search subtests of the Wechsler Adult Intelligence Scale-III (WAIS-III; Wechsler, 1997a). The LNS subtest is a measure of auditory working memory. The test was used to assess the relationship between working memory ability and olfactory abilities (along with the DRS-attention subtest). The test is moderately to highly reliable, loads onto a working memory/attention factor with other measures of attention, declines as a function of typical aging, and is differentially sensitive to a variety of neurocognitive disorders (Wechsler, 1997b). The Digit Symbol-Coding subtest measures visual motor coordination, visual sequencing, and psychomotor speed. The Symbol Search subtest is a measure of processing speed and accuracy. Both tests were used (along with the Trail Making Test) to estimate the role of cognitive processing speed in performance on olfactory tests. Both tests have been found to be highly reliable, load onto a processing speed latent factor with other measures of cognitive processing speed, and performance on the tests decline as a function of typical aging (Wechsler, 1997a) and various diseases (Lezak, Howieson, & Loring, 2004). The units of measurement were the raw score number of correct for each subtest.

Trail Making Test (TMT), part A (Army Individual Test Battery, 1944). The TMT was used to estimate cognitive processing speed ability. The TMT part A requires visual scanning and motor speed when connecting numbers that are randomly arranged on a page (Lezak et al., 2004). Test-retest reliability is within the .80 to .90 range (Spreen & Strauss, 1998). The test is sensitive to typical aging declines (Stuss, Stethem, Hugenholtz, & Richard, 1989) and neurocognitive deficits associated with different disorders (e.g., Greenlief, Margolis, & Erker, 1985). The unit of measurement was the time taken to complete the task.

Chapter III

Data Analyses

Initially, descriptive statistics (i.e., a search for outliers, influential data points, or data cleaning), assumptions (e.g., normality), and the calculation of Pearson product moment correlations among all olfactory and non-olfactory variables are presented. Then, a combined structural equation measurement modeling approach was used to test specific hypotheses. A two-step procedure was followed for modeling based in part on an approach recommended by Anderson and Gerbing (1988). In the first step, analysis of covariance structures was used to develop a measurement model among the latent constructs that demonstrated good fit to the data. Good fit refers to the idea that the covariance matrix of the actual data adequately corresponds, or fits, a theoretical covariance matrix. Statistical techniques described below provide an indication of goodness-of-fit. In the second step, the measurement model was modified so that it better represented the theoretical model of interest. This theoretical model was then tested and revised until a theoretically meaningful and good fitting model was found. Analyses were conducted using LISREL 8.3 with covariance structure models with multiple indicators for all latent constructs estimated with the maximum likelihood function (Jöreskog & Sörbom, 1999). This function reflects the difference between the observed covariance matrix and the matrix predicted by the model.

The initial measurement model consisted of three latent constructs: verbal retrieval, attention/working memory, and cognitive processing speed. A model of the relationship between the three measures of olfaction, the three cognitive domains, and chronological age is depicted in Figure 6. In the model, the 3 latent constructs are represented by neuropsychological measures defined in Table 2. The 3 cognitive constructs (identified by circles) had direct paths to the olfactory measures (SMT, UPSIT, PEAT), and chronological age had direct paths to the 3 cognitive domains and the 3 olfactory tasks. In the model, the Boston Naming Test (BNT in Figure 6), Letter Number

Sequencing (LNS), and the Trail Making Test (TMT) paths were constrained to be 1.0 based on the hypothesis that these measures best represent their respective latent constructs. Constraining

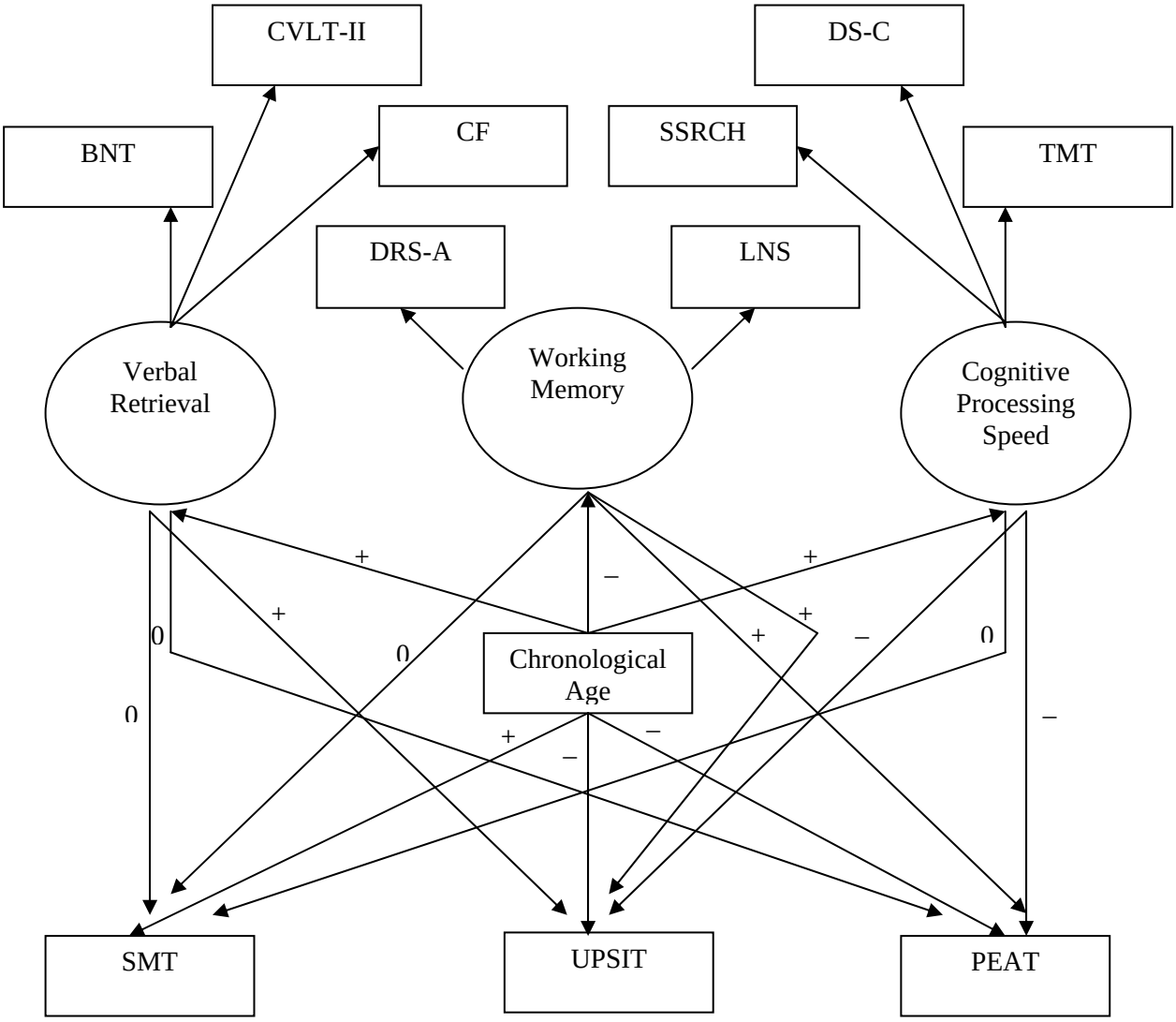

Figure 6. Theoretical structural model depicting the direction and magnitude of relationships among the olfactory and non-olfactory variables.

the path of the BNT, LNS, and TMT to their respective latent variables anchors the meaning of that dimension (latent construct) thereby allowing the remaining paths to be estimated (Bollen, 1989). Chronological age, the SMT, the UPSIT, and the PEAT were also constrained to 1.0. The error

variances for chronological age, the SMT, the UPSIT, and the PEAT were set to zero. The error terms for the 3 latent constructs were allowed to correlate among each other to permit other paths to be estimated. Further, the error terms among the 3 olfactory variables were allowed to correlate among each other. The errors among the latent factors were correlated at the same step in the causal chain because it was expected that they have other common causes not represented in the model.

It was hypothesized that each observed variable (defined in Table 2) would adequately represent its corresponding latent construct. Furthermore, it was hypothesized that the factor loadings between the olfactory tasks and the non-olfactory measures of cognition/processing speed would be significant depending on the cognitive complexity of the olfactory tasks. Finding that the cognitive domains have significant direct effects on an olfactory task while controlling for the effects of chronological age would strengthen the hypothesis that the task possesses a greater degree of cognitive complexity, and finding that there is no relationship between the domains and an olfactory task would suggest that the task is less cognitively demanding.

For all analyses, the χ^2 statistic and corresponding degrees of freedom, Critical N for a sample size of 200 (Hoelter, 1983), the Goodness of Fit Index (GFI; Tanaka & Huba, 1985), the goodness-of-fit index adjusted for degrees of freedom (AGFI), and the number of standardized residuals (SRs) with absolute values greater than 2.0 are reported as measures of model goodness-of-fit. A nonsignificant χ^2 statistic indicates good model fit. A value greater than .95 represented good fit for the GFI and a value greater than .90 represented good fit for the AGFI. Critical N represented the point at which a model's χ^2 statistic becomes statistically significant. The Critical N helped to estimate the influence of sample size when determining model fit, with approximately 5% of SRs with absolute values greater than 2.0 representing an acceptable number. Completely standardized path coefficients (factor loadings) were reported for all paths and depicted in each pictogram unless paths were non-significant in which case they were depicted with ns. Standardized path coefficients represent the strength of the relationship

between a manifest variable (or latent variable) and another manifest variable (or latent variable) in terms of standard deviation units.

Chapter IV

Results

There were no missing data. Using SPSS, out of range values, skewed distributions, kurtotic distributions, and outliers were assessed (SPSS, 1999). No out of range or outlier values were encountered. The DRS attention subtest was found to have a skewed and kurtotic distribution. Linear and cubic transformations did not improve the distribution for this measure.

Data means

Sample data means for the olfactory and non-olfactory tests, standard deviations (SD), z-scores, and raw score ranges are presented in Table 3. The z-scores were based on age

Table 3. Olfactory and non-olfactory test means, standard deviations (SD), scaled- and z-scores, and raw score ranges (N=138)

	Raw Score	SD	z-scores	Range
Sniff Magnitude Test	0.78	0.25		0.12 - 1.40
UP Smell Identification Test	27.90	7.02		6 - 38
PEA Threshold Test	5.22	2.75		0 - 11
ANART	109.25	11.38	-0.33	84 - 129
Dementia Rating Scale-2	132.20	8.72	-0.39	100 - 144
Token Test	41.32	2.87	0.23	33 - 44
Boston Naming Test	12.19	2.86	-0.53	5 - 15
Category Fluency	38.33	9.84	-0.03	9 - 60
CVLT-II Trials 1-4	6.73	1.33	-0.56	8 - 34
DRS Attention	35.46	1.65	0.39	26 - 37
Letter-Number Sequencing	7.60	3.03	-0.02	0 - 17
Digit Symbol - Coding	41.95	14.87	-0.28	6 - 93
Symbol Search	20.30	7.29	0.20	7 - 46
Trail Making Test - Part A	50.00	21.80	-0.23	18 - 120

UP = University of Pennsylvania; PEA = phenyl ethyl alcohol; ANART = National Adult Reading Test; DRS = Dementia Rating Scale; CVLT-II = short form version of the California Verbal Learning Test-II; Trail Making Test in seconds.

appropriate (and age/education in some cases) published norms: AMNART, Token Test and TMT (Ivnik, Malec, Smith, Tangalos, & Petersen, 1996); DRS-2 total and attention scores (Lucas, Ivnik, Smith, Bohac et al., 1998b); BNT (Kent & Luszcz, 2002); category fluency (Lucas, Ivnik, Smith, Bohac et al., 1998a); CVLT-II recall from trials 1-4 (Delis et al., 2000); and subtests of the WAIS-III (Wechsler, 1997a).The z-scores indicate that, as a group, the individuals in this sample performed in the average range on all non-olfactory neuropsychological tests compared to published norms.

Correlations

The correlation matrix for olfactory variables and measures of verbal intelligence (AMNART), general cognitive functioning (DRS-2), and verbal comprehension (Token Test) are presented in Table 4. Of note, the ability to comprehend simple one- and two-step commands and the level of general cognitive functioning were significantly associated with the UPSIT but not with the SMT. Further, the PEAT test was significantly associated with level of general cognitive functioning, and there was a trend approaching significance for verbal comprehension. The premorbid estimate of verbal intelligence was not associated with any of the olfactory measures.

Table 4. Correlation matrix among olfactory variables and measures of intelligence, general cognition and comprehension (N=138)

	SMT	PEAT	UPSIT
ANART	0.13	0.08	0.13
DRS-2	0.02	0.19**	0.37*
Token Test	0.01	0.16^{v}	0.34*

* = p < .001; ** = p < .05; ^{v} = p < .06.

The bottom-left portion of Table 5 shows the zero-order correlation matrix for the olfactory and nonolfactory variables used in the combined structural equation measurement model. The SMT was not significantly correlated with any of the non-olfactory measures (all p

values greater than .05). The moderate correlations among the olfactory tasks found in Table 5 replicate the pattern of correlations found in an independent sample (Frank et al., 2003). Performance on the UPSIT was related to performance on all of the non-olfactory cognitive tasks (correlations between .19 to .41, $p<0.05$ to .001). Performance on the PEAT was correlated with performance on the DRS-att (r =0.23, $p<.05$) and the TMT (r = -0.26, $p<0.01$), and approached significance for LNS (r =0.16, $p<0.06$). Older age was significantly associated with poorer performance on the SMT and UPSIT measures of olfactory ability (but not with the PEAT) and with LNS, DS-C and TMT.

Several additional analyses were conducted to assess the extent to which the correlations in Tables 4 and 5 were inflated by the inclusion of individuals with poorer test performance as a result of neurologic and psychiatric conditions, or as a result of poorer overall level of general cognitive functioning. First, the correlations excluding the individuals who self-reported the presence of a neurologic and psychiatric condition (n=26 excluded) showed no change in the pattern of significant results found in Tables 4 and 5. Second, correlations were computed among the tests with the individuals with a DRS-2 below 131 excluded (n=43 excluded) to determine the relationship among measures of olfaction and cognition in individuals without global cognitive impairment. Results indicated that the SMT was still not related to any of the cognitive variables. For the PEAT, the Token Test correlation no longer approached significance; however, the Dementia Rating Scale-II, the DRS-attention subtest, Letter Number Sequencing, and the Trail Making test remained significant. For the UPSIT, the Token Test, the Boston Naming Test, the CVLT-II, DRS-attention, Digit Symbol Coding, and Symbol Search correlations were no longer statistically significant; however, the Dementia Rating Scale-2, category fluency, Letter-Number Sequencing, and Trail Making Test remained significant with the UPSIT. Next, correlations were computed excluding individuals with a DRS-2 < 131 (n=43 excluded), self-reported neurologic conditions (n=5 excluded), and self-reported

Table 5. Correlation matrix among variables in the confirmatory factor analyses (bottom-left; N = 138), and matrix excluding individuals with possible cognitive deficits (top-right; N = 80)

	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.
1. SMT	X	*-0.45	**-0.32	0.08	-0.01	0.00	0.10	-0.05	-0.04	-0.09	0.02	***0.26
2. PEAT	*-0.40	X	*0.51	0.04	0.02	0.12	***0.23	***0.21	0.12	0.12	***-0.27	-0.03
3. UPSIT	*-0.36	*0.49	X	0.02	***0.26	0.01	-0.01	*0.32	0.09	0.10	***-0.24	***-0.26
4. BNT	0.06	0.12	*0.27	X	***0.26	0.11	-0.07	*0.36	*0.40	***0.24	*-0.41	0.04
5. Fluency	0.00	0.08	*0.41	*0.55	X	***0.25	**0.31	*0.47	*0.37	*0.35	*-0.34	-0.08
6. CVLT-II	-0.05	0.13	*0.27	*0.36	*0.55	X	0.09	*0.39	**0.30	*0.42	*-0.39	***0.25
7. DRS-att	0.04	**0.23	***0.19	*0.38	*0.35	***0.20	X	**0.27	0.07	0.14	-0.10	0.05
8. LNS	0.01	v0.16	***0.36	*0.58	*0.61	*0.60	*0.39	X	**0.29	*0.40	*-0.51	***-0.24
9. DS-C	0.05	0.14	**0.25	*0.55	*0.56	*0.57	*0.37	*0.59	X	*0.63	*-0.64	-0.13
10. SS	0.03	0.12	**0.22	*0.52	*0.57	*0.54	*0.40	*0.63	*0.77	X	*-0.45	-0.17
11. TMT	0.02	*-0.26	*-0.30	*-0.57	*-0.54	*-0.52	*-0.48	*-0.59	*-0.73	*-0.65	X	0.06
12. Age	**0.21	-0.09	**-0.25	-0.10	-0.12	v0.16	0.05	**0.21	***-0.17	***-0.19	0.12	X

* = p < .001; ** = p < .01; *** = p < .05; v = p < .06.

psychiatric conditions (n=10 excluded). With a new sample size of 80 participants, no significant change in the pattern of correlations was found when compared with just excluding individuals with a DRS-2 < 131. The correlation matrix among the tasks for the final analysis is presented in the top-right portion of Table 5.

The Initial and Revised Measurement Models

First, the proposal that the non-olfactory variables were representative of the 3 latent constructs (verbal retrieval, attention/working memory, cognitive processing speed) was tested. The initial analysis of the measurement model indicated that the DRS-attention variable was not a representative measure of attention/working memory based on the nonsignificant t-value obtained for the coefficient using LISREL. This finding is due, perhaps, to the fact that this subtest of the DRS-2 is quite easy for individuals who do not have substantial cognitive deficits. Given this, it was removed from the analysis as a variable and LNS was used as the sole indicator to represent attention/working memory. The observed error variance for LNS was set at 0 given that it was the only observed measure of the latent construct. The error variance was set at 0 because it must be assumed an item is measured without error when using a single indicator. An analysis of the covariance matrix for the respecified measurement model indicated good fit to the data. See Table 6 for the revised measurement model fit statistics. The Critical N (179) only approached the point that is desirable (200); however, all other fit indices indicated good fit.

The BNT, CVLT-II, and CF were found to be representative of the Verbal Retrieval (VR) cognitive construct. The relative size of the loadings differed with VR accounting for 58% of the variation in CF, but about 47% for the CVLT-II and 46% for the BNT. These findings might be expected given that besides verbal retrieval, each task differs greatly in the other types of cognitive processes (and underlying neurobiology involved) that must be intact for good performance. For example, CF relies on a person's initiative to generate words from an over-

learned semantic store without support from outside test cues, and the test is generally associated with left prefrontal cortex functions, whereas the CVLT-II relies on the presentation of new information that must be manipulated in working memory and relies more on intact left-hippocampal functioning. An argument could be made that any of these tests better represent the VR domain, but the present results indicate that in this sample CF better represents VR. The SSRCH, DS-C, and TMT were found to be representative of the Cognitive Processing Speed (CPS) construct. The CPS tasks also had variable factor loadings. This would be unexpected given that the 3 CPS tasks have the same task demands (do this as fast as you can) and tap the exact same underlying neurobiological processes (general CNS decline).

Table 6. Goodness-of-fit statistics (N = 138 for all analyses).

	χ^2	df	p value	Critical N	GFI	AGFI	SRs > |2.0|
Revised Measurement Model	18.40	12	0.104	179	0.963	0.914	3
Combined Structural Model	33.72	28	0.210	180	0.957	0.899	4
Cognitive Processing Speed Mode	8.45	8	0.391	322	0.983	0.939	1
Semantic Knowledge Model	5.62	8	0.690	486	0.988	0.959	0
Attention/Working Memory Model	model is saturated, so the fit is perfect						

GFI = Goodness-of-Fit index; AGFI = Adjusted Goodness-of-Fit index; SR = Standardized Residuals.

The Combined Structural Equation Measurement Model

Next, the fit of a model depicting the relationship between the 3 latent constructs, the 3 olfactory variables and chronological age was tested. Results indicated good fit (see Table 6 for the Combined Structural Model fit indices). Completely standardized factor loadings for the indicator variables are presented in Figure 7. Counter to the initial hypotheses, none of the

paths between the latent constructs to the olfactory tasks had significant factor loadings. R^2s for are in parentheses. Chronological age had the only significant paths. Specifically, chronological age had a significant factor loading with the SMT (i.e., .207), the UPSIT, and the 3 latent constructs. Importantly, an out of range value (i.e., greater than an absolute value of 1.0) suggested that there was an issue with multicollinearity. Specifically, the lack of effects of verbal retrieval, working memory, and cognitive processing speed on the olfactory variables may have resulted because the latent constructs were so intercorrelated that when any 2 variables were controlled for, much of the variation in the third variable was controlled for; and so on. To address this concern with multicollinearity, separate path models for each latent construct were analyzed.

Follow-up Individual Path Analyses

To investigate the impact of the possible effects of multicollinearity, individual path models for each latent cognitive construct were computed. When analyses were conducted in this manner, results fully supported the original hypotheses. Specifically, results indicated that verbal retrieval had a significant direct effect on the UPSIT (Figure 8a, i.e., factor load = 0.414), working memory had a significant direct effect on the UPSIT and, to a lesser extent, on the PEAT (Figure 8b; factor load = .324 on the UPSIT and = .147 on the PEAT), and cognitive processing speed had a significant direct effect on the UPSIT and, to a lesser extent, on the PEAT (Figure 8c; factor load = -.252 on the UPSIT and = -.169 on the PEAT). No construct significantly affected the SMT. Chronological age significantly affected the SMT and the UPSIT, but not the PEAT. Chronological age also had a significant effect on verbal retrieval, working memory, and cognitive processing speed. R^2's are in parentheses in Figures 8a, 8b, and 8c. See Table 6 for fit indices. The low amount of variance accounted for by all of the variables within the 3 models suggests that there are other factors missing that account for performance on the different olfactory tests. The non-significant amount of variance accounted

for by chronological age in PEAT performance was unexpected given that other studies have found a significant relationship. Further, the significant but low amount of variance accounted for by chronological age in SMT and UPSIT performance is lower than expected. However, the sample consisted of only older adults, which may have restricted the range of scores and thus led to lower correlations. The significant variance accounted for in UPSIT performance by Verbal Retrieval (17.1%), Working Memory (10.5%), and Cognitive Processing Speed (6.4%) are within an acceptable range. The significant variance accounted for in PEAT performance by Working Memory (2.1%) and Cognitive Processing Speed (2.9%) are low and suggest that the effect may only be found with larger sample sizes. Nonetheless, PEAT performance is influenced by cognition and cognitive processing speed, but only to a small degree.

Finding non-significant results with all 3 constructs in a model (Figure 7), and significant effects with individual path analyses, supported the proposal that the independent effects of each construct cannot be picked up (in one combined structural equation measurement model analysis) without a much larger sample, given the amount of multicollinearity among the cognitive constructs.

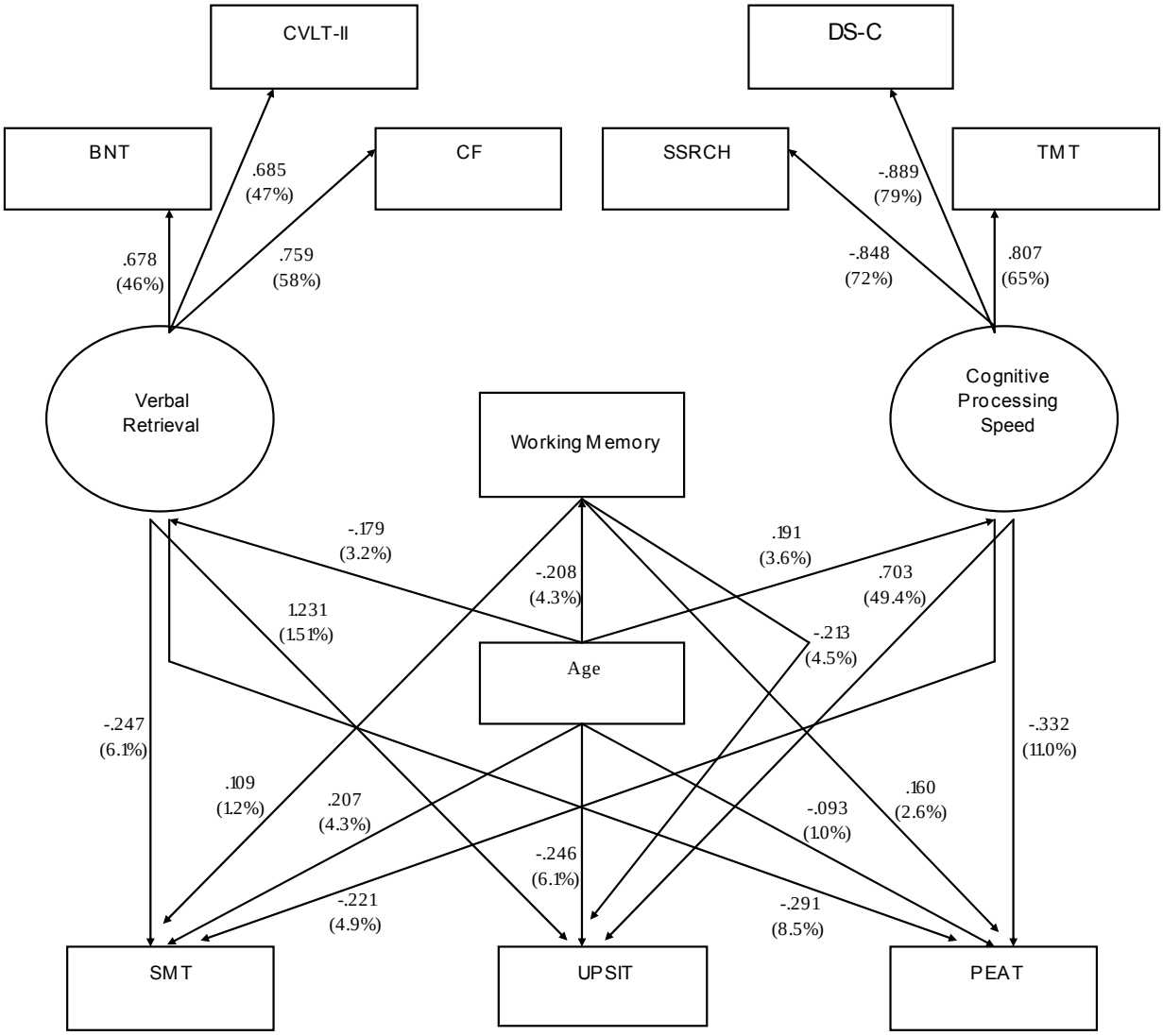

Figure 7. Full structural equation measurement model with completely standardized factor Loadings (N=138). R^2 are in parentheses.

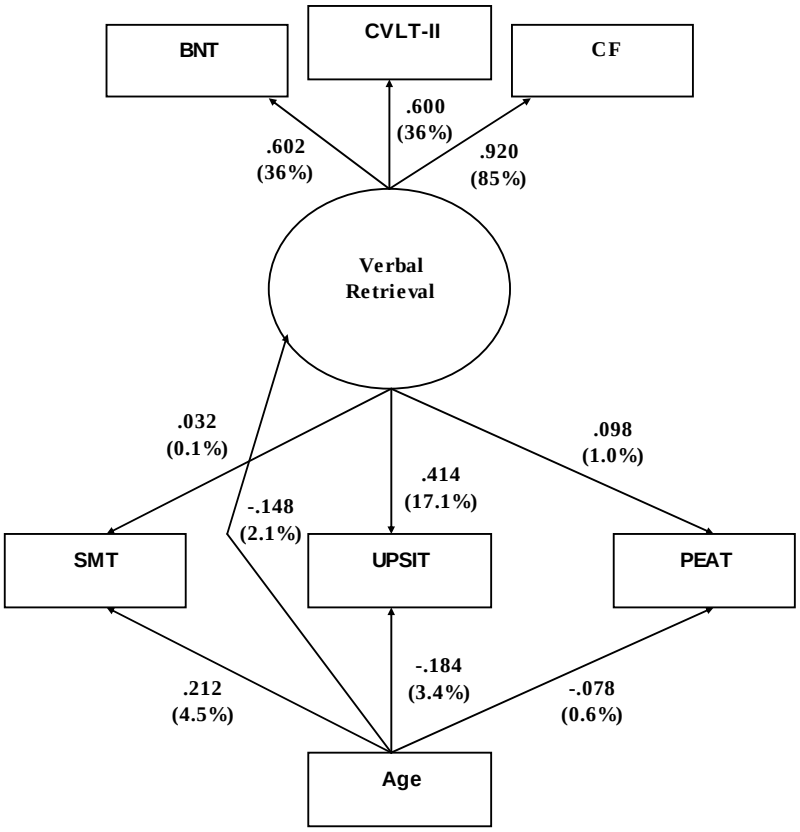

Figure 8a. Impact of verbal retrieval on different measures of olfactory functioning while controlling for the impact of age (N=138). R^2 are in parentheses.

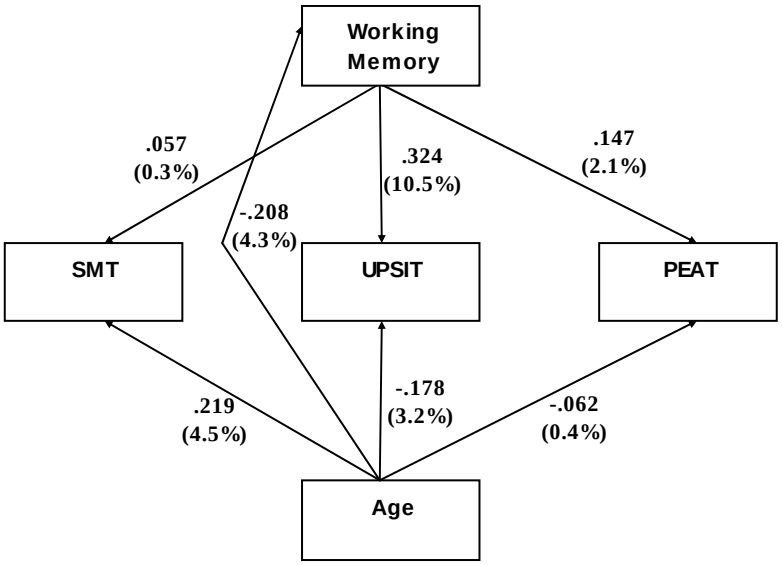

Figure 8b. Impact of working memory on olfactory functioning while controlling for the impact of age (N=138). R^2 are in parentheses.

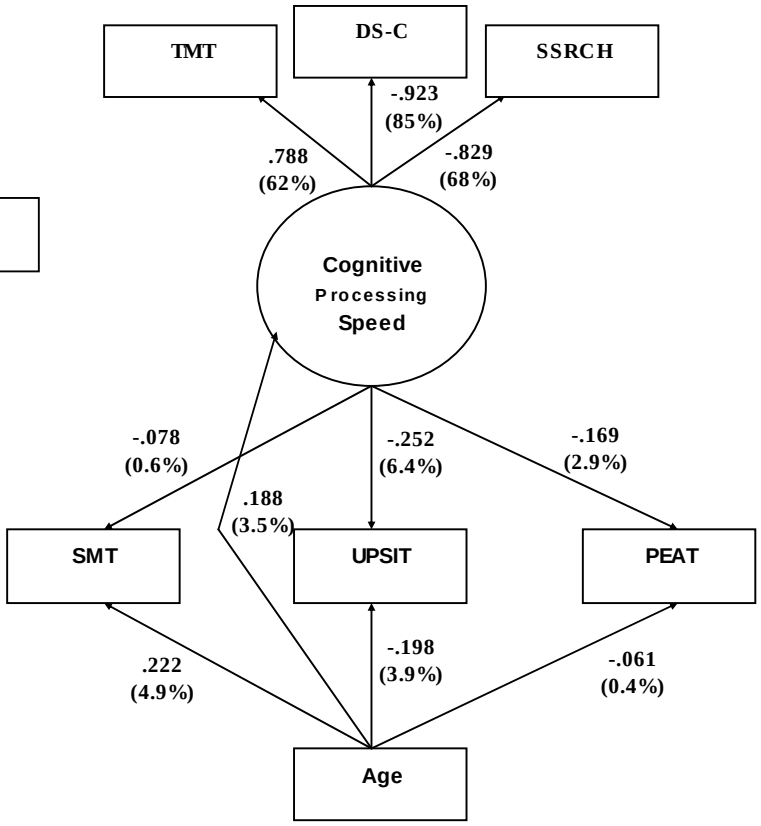

Figure 8c. Impact of cognitive processing speed on olfactory functioning while controlling for the impact of age (N=138). R^2 are in parentheses.

CHAPTER V

Discussion

Olfactory impairment is reportedly related to healthy aging as well as to a wide variety of neuropsychiatric disorders (Fedoroff et al., 1995; Gansler et al., 1998; Postolache et al., 1999; Razani et al., 1996; Rupp et al. 2003). However, the methods used to assess olfaction to date have typically been dependent on multiple cognitive abilities in addition to olfaction. Therefore, it is unclear whether the reported olfactory results are truly specific to this sensory ability or are instead largely or partially the result of the cognitive decrements associated with these conditions. The purpose of this study was to examine the differential relationships of three measures of olfaction hypothesized to have varying degrees of cognitive complexity with abilities in verbal information retrieval, working memory, and cognitive processing speed. The emphasis was on the novel Sniff Magnitude Test (SMT), which was hypothesized would be minimally influenced by cognition and cognitive processing speed. It was posited that the University of Pennsylvania Smell Identification Test (UPSIT) would be affected by poor verbal retrieval, working memory difficulties, and slow cognitive processing speed, and the Phenyl Ethyl Alcohol Threshold test (PEAT) would be affected by poor working memory ability and slow cognitive processing speed. Individual path analyses fully supported these *a priori* hypotheses.

Results supported the hypothesis that the SMT is minimally influenced by cognition given that the path analyses demonstrated no direct effect of verbal retrieval, attention/working memory and cognitive processing speed on SMT test performance (Figures 8a, b, and c). Support was also reflected in the fact that there were no significant correlations between the SMT and any of the non-olfactory cognitive measures (Tables 4 and 5), including measures of general cognition, comprehension, memory, language, attention, working memory, and cognitive processing speed. Results provide support for the divergent validity of the SMT as a measure of olfaction that does not measure overlapping variance associated with cognition and cognitive processing speed. Furthermore, the significant correlations between the SMT, UPSIT

and PEAT (Table 5) provide support for the convergent validity of the SMT as a measure of olfactory functioning (Frank et al., 2003). There is also face validity for the SMT as a measure of olfactory functioning given that study participants with a normal sense of smell routinely inhibited their sniff in response to a malodor in comparison to sniffs to non-odorized trials. Thus, the present study's results probably do not simply reflect the idea that the SMT is insensitive to olfactory loss and the other tasks are more sensitive given the demonstration of the convergent, divergent, and face validity of the SMT.

Results supported the hypothesis that the UPSIT is influenced by non-olfactory cognitive functioning given that the verbal retrieval, working memory, and cognitive processing speed constructs had significant direct effects on the UPSIT in the individual path analyses (Figures 8a, b, and c). Furthermore, poorer UPSIT performance was associated with lower general cognitive functioning (DRS-2) and impaired comprehension (Token test) (Tables 4). As predicted, the PEAT was found to be influenced by working memory and cognitive processing speed based on the path analyses, and general cognitive impairment was associated with poorer test performance based on correlational analysis.

The absence of a relationship between the SMT and cognition/cognitive processing speed is consistent with the proposal that sniff test procedures quantify the early olfacto-motor information processes involved with smelling a malodor (Johnson et al., 2003; Sobel et al., 1998b). The SMT may be an olfactory measure minimally influenced by non-olfactory cognitive functions because the sniff response does not require the explicit rating, categorization or memory of an odor stimulus, and no verbal response is required. Further support for the idea that the SMT is a simple sensori-motor measure comes from two studies. First, UPSIT scores of children and adolescents between the ages of 3 to 10 are poorer than those of young adults, but SMT scores are comparable across these ages (Frank et al., 2003, 2004). These findings are consistent with the hypothesis that lower odor identification scores of children are attributable to variations in memory/cognition and language/culture rather than olfactory abilities

(Cain, Stevens, Nickou, Giles, Johnston, & Garcia-Medina, 1995; Lehrner, Glück, & Laska, 1999). Second, recent research found that the reaction time of sniffs in response to odors is around 150 milliseconds, which is about half the amount of time necessary to register odorant-induced cortical evoked potentials (Johnson et al., 2003).

Consistent with the results of the present study, there is general agreement that a relationship exists between general cognitive impairment and poor odor identification ability in nondemented older adults (Brewer, et al, 1996; Danthiir et al., 2001; Finkel et al., 2001; Larsson et al., 2000; Morgan et al., 1995; Oberg et al., 2002; Royall et al., 2002; Stevens et al., 1998) and individuals with Alzheimer's disease, Down's syndrome, and human immunodeficiency virus (Graves et al., 1999; Gray et al., 2001; Larsson et al., 1999; Morgan et al., 1995; Murphy & Jinich, 1996; Serby et al., 1991). Others have found a significant relationship between measures of cognitive processing speed and odor identification test performance (Finkel et al., 2001; Larsson et al., 2000) and confrontation naming and odor identification test performance (Stevens et al., 1998) in non-demented older adults. The relationship between verbal retrieval with odor identification ability may represent overlapping structural and physiologic processing in olfactory-related CNS regions. For example, the relationship between verbal retrieval and odor identification abilities may reflect a dual sensitivity to the impact of aging and disease progression on the processing of semantic-related information. However, the relationships between auditory working memory, cognitive processing speed, general cognitive functioning, and the ability to understand instructions with odor identification ability are more difficult to link with olfactory-related CNS processing. One valid interpretation of the significant relationships with odor identification ability and these other cognitive functions is that the association reflects the unintended assessment of non-olfactory functions that inflates the appearance of olfactory losses.

Results from the present study are also consistent with other reports of a relationship between measures of cognition and odor detection sensitivity for nondemented older adults

(e.g., Dulay & Murphy, 2002) and within different patient populations (Larsson et al., 1999; Murphy et al., 1990; Murphy et al., 1999; Nordin & Murphy, 1996; Nordin et al., 1997; Razani et al., 1996). The finding that the SMT was not related to verbal retrieval, working memory or processing speed, but that the PEAT was related to working memory and cognitive processing speed, suggests that all olfactory sensitivity tasks per se do not inherently require a significant degree of cognitive processing. It is not intuitive that olfactory acuity should be related to cognitive functioning (Martzke et al., 1997); therefore a logical explanation for the findings in this study is that the relationship between measures of working memory and cognitive processing speed with the PEAT reflects the impact of non-olfactory cognitive deficits, which can emulate or exacerbate the appearance of olfactory losses when not taken into account. Evidence is building for the proposal that standard clinical tests of olfaction do not adequately discriminate between the different levels of olfactory information processing (i.e., early- versus higher-order olfactory processes), or between olfactory and non-olfactory information processes.

In contrast to the present study, some other researchers have reported nonsignificant relationships between measures of olfaction and cognition in nondemented older adults (Larsson et al., 1999, 2000), as well as in patients with Parkinson's disease (Doty, Deems, & Stellar, 1988; Doty, Riklan, Deems, Reynolds, & Stellar, 1989), Alzheimer's disease (Larsson et al., 1999; Serby et al., 1991), and schizophrenia (Kopala, Clark, & Hurwitz, 1989; Seidman, Talbot, Kalinowski, McCarley et al., 1992; Seidman, Goldstein Goodman, Koren, Turner, Faraone, et al. 1997; Stedman & Claire, 1998; Wu, Moy, Denlea, Kesslak et al., 1993). For example, researchers have reported that UPSIT performance was not correlated with measures of attention (Kopala, Clark, & Hurwitz, 1989; Seidman et al., 1992), visual memory (Wu et al., 1993), visual-spatial constructional ability (Seidman et al., 1992), and card sorting ability (Seidman et al., 1992, 1997) in individuals with schizophrenia. Other research found no relationship between measures of overall intelligence, verbal memory, motor speed, and visual recognition ability with the UPSIT and PEAT in individuals with Parkinson's disease (Doty et al.,

1988, 1989). Of note in the present study, the pattern of relationships between the 3 olfactory tests and non-olfactory cognitive variables were similar when excluding individuals with moderate to severe general cognitive impairment (N = 43 excluded, results displayed in top portion of Table 5), suggesting that the relationship between the UPSIT and PEAT with non-olfactory cognitive functions is robust.

Several explanations may be considered for the disparity between the findings noted above and the current study. These include the possibility of a restricted range of test scores due to limited sampling, the use of different cognitive and olfactory tests, and small sample sizes in previous studies. The conclusions about the strength of a relationship between two tests can vary depending on the range of values observed (Millsap, 1989). A restricted range of test scores can result from strict exclusion criteria, the inclusion of only patients at a particular stage of a disorder, or a small sample size (which can limit sampling a 'typical' population of interest). Many of the studies that have not found a relationship between measures of olfaction and cognition have restricted the range of test scores by limiting the study sample to patients with mild to moderate forms of a disorder[4], which is understandable given the difficulties in validly testing adults with severe cognitive impairment. For example, Larsson et al. (1999) did not find a relationship between general cognitive functioning and odor detection threshold ability in individuals with mild Alzheimer's disease (r = .04); however, others have found a relationship between a global measure of cognition and odor detection thresholds using a sample of patients across the mild to severe stages of Alzheimer's disease (r = .55; Murphy et al., 1990). As another example, Doty et al. (1988) reported that no relationship existed between a measure of visual recognition ability and the UPSIT in individuals with Parkinson's disease; however, 12 individuals were excluded from the final analyses because they failed a cognitive screening test.

[4] It is not the intention of this discussion to downplay the importance of valid exclusion criteria given the benefit that exclusion provides by improving the explanatory power when assessing specific disease or aging processes. However, it is important to point out that restricting sample variability decreases the explanatory power because the likelihood of finding significant associations that really exist can decrease. Replication helps to resolve this challenge.

Therefore, many of the individuals that could have possibly performed poorly on both the UPSIT and the visual test were excluded, thereby restricting the range of values.

The use of different cognitive measures can lead to different conclusions. For example, Seidman et al. (1992, 1997) found no relationship between the UPSIT and card sorting ability using the 'perseverative responses' measure of the Wisconsin Card Sorting Test (WCST) when testing individuals with schizophrenia. Others have found significant relationships between WCST and UPSIT performance using the 'number of correct categories' measure (Brewer et al., 1996) and using the 'failure to maintain set' measure (Stedman & Clair, 1998). In the present study, several cognitive tests were no longer related to the PEAT (Token test) or the UPSIT (the Token Test, the Boston Naming Test, the CVLT-II, Digit Symbol Coding, and Symbol Search) when individuals with possible cognitive problems were excluded from the correlational analyses (i.e., those with a DRS below 131 and individuals with self-report psychiatric / neurologic disorders). However, the general interpretation of the results remained the same given that other individual measures of working memory (Letter-Number Sequencing), cognitive processing speed (the Trail Making Test), and general cognitive impairment continued to remain or approach significance with the UPSIT and PEAT, and verbal retrieval (category fluency) remained significant with the UPSIT. If only one test would have been used in the present study to represent each of the cognitive domains, a different interpretation of the relationship between the UPSIT and PEAT with cognition/cognitive processing speed would have resulted. This demonstrates that both a restricted range of participants (i.e., excluding for reduced general cognitive status) and the use of different cognitive tests could influence the conclusions derived from between-test comparisons.

*S*mall sample sizes may have contributed to the findings of no relationship between measures of cognition and olfaction. For example, using exploratory factor analysis techniques, Doty et al. (1989) reported that UPSIT and PEAT performance were "independent of the other cognitive, memory, perceptual-motor, and neurological manifestations" of Parkinson's disease

(PD). Problematically, 26 measures were used in the factor analysis with a sample size of 58 individuals with UPSIT data and 38 individuals with PEAT data, and it is known that 'small sample size to variable ratios' increase the likelihood of creating unreliable factors that do not withstand cross-validation (Guadagnoli & Velicer, 1988). Sample size to variable ratios anywhere from 10:1 to 15:1 have been recommended (e.g., Park & Dudycha, 1974; Pedhazur, 1997), which is far greater than the sample size to variable ratio of 2.2 individuals per 1 variable for the UPSIT (and 1.5 individuals per 1 variable for the PEAT) used by Doty et al. (1989). Given the very small sample size to variable ratio, replication is necessary before a definitive conclusion can be drawn about the relationship among measures of cognition and olfaction in PD. Importantly, no study has attempted to replicate the findings of Doty et al. (1988) in the 17 years since the study was published even though the study is frequently cited as proof of independence among measures of olfaction and cognition in PD.

A measure minimally influenced by cognitive functioning such as the SMT could be used to address questions such as the extent to which poor olfactory test performance reflects actual olfactory impairments in patient populations that have moderate to severe cognitive limitations. This is particularly important given the restriction of range issues that can result when patients are excluded from studies because they cannot meet the minimal comprehension or task demands of a test. In this study, the inability to understand instructions (as reflected by the Token Test scores in the full sample) was related to poorer UPSIT and PEAT performance, but not SMT performance (Table 4). As expected, the relationship between the inability to understand instructions and poorer UPSIT and PEAT performance disappeared when individuals with general cognitive impairment were excluded from the correlational analyses. To date, the main control variable used to support the hypothesis that olfactory losses reflect the disease process and not poor comprehension (or different levels of task complexity) has been to attempt to match similar sensory or neuropsychological tasks. Several studies have reported that patients with Alzheimer's disease and Down's syndrome had the same taste thresholds

when compared to non-demented controls, but differed in olfactory functioning (e.g., Murphy & Jinich, 1996; Murphy et al., 1999). Similar results have been reported in patients with schizophrenia, Korsakoff's disease, and Alzheimer's disease on color, picture, and odor identification tests (Kopala, Good, Martzke, Hurwitz, 1995; Morgan et al., 1995; Vollmecke & Doty, 1985). However, problems exist with interpreting a dissociation of comparable performance on a control task and poor performance on an olfactory task between patient and control groups. One problem with interpreting the dissociation of comparable performance on a control task and poor performance on an olfactory task is that it is difficult to exactly match task complexity across sensory modalities for tastes, colors, and pictures with odor threshold and identification tests. For example, use of a color identification test as a matched task to odor identification ability is problematic because the color matching task is so simple. Even though the UPSIT is made simplier because verbal labels are provided, people still have great difficulty identifying odors because there are so many more perceptual markers to choose from for odors compared with colors (Richardson & Zucco, 1989). In this case where the control task is easier than the olfactory task, the "apparent dissociation may in fact reflect a psychometric artifact (Martzke et al., 1997)." Logically, a control task could be considered to have a similar level of complexity as an olfactory task if there were similar correlations between the control/olfactory tasks with a cognitive variable. This was not the case when Murphy & Jinich (1996) used the Dementia Rating Scale (DRS) as a covariate to examine the influence of general cognitive ability on odor and taste threshold ability between individuals with Down's syndrome and age-matched control participants. They originally found that individuals with Down's syndrome performed significantly poorer on an odor threshold test and a taste threshold test compared with controls, but that between-group differences disappeared on the taste threshold test, but not the odor threshold test, when cognitive ability was covaried. The authors interpreted the results as suggesting that the remaining between-group difference on the odor threshold test reflected "a true sensory impairment rather than an inability to perform a threshold task."

However, it is difficult to come to this conclusion because the correlation between the taste task and the DRS was not the same as the correlation between the olfactory task and the DRS. Statistical controls have been proposed as an indirect solution for controlling the impact of non-olfactory 'non-target' variables on the assessment of olfaction (Martzke et al., 1997). However, it is important that "the correlation between the covariate and target variable not differ across groups (Martzke et al., 1997)." Importantly, non-olfactory task demands may only explain a small part or no part of performance on olfactory tasks in patient populations with mild forms of cognitive impairment. However, comprehension difficulties can significantly influence test scores for patient populations with moderate to severe cognitive limitations (e.g., Bickel et al., 2000).

Future research could incorporate the SMT into the study of different patient populations to address the confounding factors associated with task demands. The test could also be used to differentiate individuals with olfactory deficits arising from the early stages of olfacto-motor information processing, as seen in individuals with deficits associated with the olfactory epithelium or olfactory bulb, from individuals with higher order olfactory deficits, as seen in individuals with neuroanatomical and neurophysiological changes associated with the neocortex and other higher-order projection areas. For example, the SMT could be used to study the early sensori-motor deficits that occur in individuals with different degenerative motor neuron diseases. Sobel and colleagues (2001) found that olfactory deficits in individuals with Parkinson's disease were in part attributable to an inability to generate a sufficient sniff. There is evidence that other tests of olfaction are sensitive in differentiating patients with neurodegenerative disorders that impact motor neuron pathways from control participants, but these tests are not specific in differentiating between motor neurodegenerative diseases (Connelly, Farmer, Lynch, & Doty, 2003; Liberini, Parola, Spano, & Antonini, 2000).

The SMT could also be used to assess the extent of peripheral olfactory losses in populations found to have comorbid detection sensitivity and identification losses, which include

nondemented older adults and individuals diagnosed with alcohol dependence, Alzheimer's disease, Down's syndrome, epilepsy, human immunodeficiency syndrome, Huntington's disease, Korsakoff's syndrome, Parkinson's disease, and schizophrenia. The SMT could also be used to differentiate early stage from later stage olfactory losses in the characterization of subgroups of individuals within a specific disorder. For example, there may be a subgroup of patients with moderate to severe forms of Alzheimer's disease who differ in their pattern of olfactory-related deficits. That is, some patients with moderate to severe Alzheimer's may have intact sensory-motor functioning with impaired odor identification abilities. Finally, characterization of an olfactory loss as more peripheral or central may be valuable when diagnosing olfactory problems not associated with neurodegenerative and neuropsychiatric disorders (e.g., upper respiratory infection, trauma, nasal sinus disease). For example, future studies could incorporate the SMT in an ENT physician office's assessment battery to determine the extent to which olfactory deficits reflect early sensory-stage losses versus the dysfunction of more central structures in patients who perform poorly on the UPSIT and thereby provide guidance (in conjunction with other medical tests) regarding whether referrals to a neurologist or memory-disorder specialist are appropriate. Comparing performance on the SMT and UPSIT could prove useful to efforts aimed at understanding the causes of olfactory system dysfunction in a number of neurodegenerative and neuropsychiatric disorders.

There were several limitations to the present study. First, we did not have an independent ENT evaluation that provided corroborating information about the general sinus health of this study's participants. Sinus blockage and general sinus disease are important factors that should be routinely and objectively screened in any olfactory study. Second, this study's broad inclusion criteria limit the generalizability to specific patient populations. Future studies could limit the type of patients included to better understand the specific relationships between cognition and olfaction in distinct patient populations. Third, and counter to having broad inclusion criteria, this study only included older adults. Given this, the magnitude of the

relationships among the measures of olfaction and non-olfactory measures of cognition may have been underestimated given the restricted of range of values. Future research should look at the relationship among these variables across the whole adult age range. Fourth, the etiologies related to cognitive impairment were not well defined by a neurologic or psychiatric evaluation, but rather we relied upon self-report. Corroborating information from a physician would have helped to better define the type of psychiatric / neurologic diagnoses for the patients included in this study. Fifth, this study did not control for the influence of medications, which can have an effect on the interpretation of both cognitive and olfactory functioning. Finally, the issue with multicollinearity that occurred in this study's structural modeling analysis suggests that much larger sample size would have been useful to reduce the impact of the collinearity.

In conclusion, measures of olfaction dependent on the ability to recognize and detect odors may overestimate olfactory loss. The SMT, however, which requires only that participants sniff odorants, is less dependent on higher-order cognitive and speed of information processing and therefore provides a valuable new tool for the better understanding of the relationship between olfaction and disease.

APPENDIX A

Appendix A. Equations for the models in Figure 8

	Beta	B	SE
Cognitive Processing Speed (CPS) Model			
CPS to SMT	-0.08	0.00	0.00
CPS to UPSIT	-0.25	-0.10	0.04
CPS to PEAT	-0.17	-0.03	0.01
Age to SMT	0.22	0.01	0.00
Age to UPSIT	-0.20	-0.20	0.07
Age to PEAT	-0.06	-0.03	0.03
Age to CPS	0.19	0.38	0.18
TMT to CPS	17.20	1.00	-
DS-C to CPS	-13.73	-0.80	0.07
SSRCH to CPS	-6.04	-0.35	0.03
Verbal Retrieval (VR) Model			
VR to SMT	0.03	0.00	0.01
VR to UPSIT	0.41	1.69	0.39
VR to PEAT	0.10	0.17	0.15
Age to SMT	0.21	0.00	0.00
Age to UPSIT	-0.18	-0.20	0.07
Age to PEAT	-0.08	-0.03	0.03
Age to VR	-0.15	-0.03	0.02
BNT to VR	1.72	1.00	-
CVLT-II to VR	2.91	1.69	0.30
CF to VR	9.05	5.26	0.88
Working Memory (WM) Model			
WM to SMT	0.06	0.00	0.01
WM to UPSIT	0.32	0.75	0.19
WM to PEAT	0.15	0.13	0.08
Age to SMT	0.22	0.00	1.00
Age to UPSIT	-0.18	-0.20	0.07
Age to PEAT	-0.06	-0.03	0.03
Age to WM	-0.21	-0.07	0.03

Beta = Standardized path coefficients; B = Unstandardized path regression coefficients; SE = standard error for B; smt = Sniff Magnitude Test; UPSIT = University of Pennsylvania Smell Identification Test; PEAT = Phenyl Ethyl Alcohol test; TMT = Trail Maki

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