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The Retrieval Deficit Memory Profile in Huntington's Disease: Reexamining Old Heuristics and Exploring New Ones

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The Retrieval Deficit Memory Profile in Huntington's Disease:
Reexamining Old Heuristics and Exploring New Ones

A dissertation submitted in partial satisfaction of the
requirements for the degree Doctor of Philosophy

in

Clinical Psychology

by

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2018

The Dissertation of Heather Marie Holden is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

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2018

DEDICATION

This dissertation is dedicated to my mother and my husband. Mom, thank you for your unconditional love and continuous support in everything I do. Thank you for making more sacrifices than I ever realized so that I could have a better life. More than anything, thank you for believing that I could do anything, and for inspiring me to believe the same.

Robert, thank you for being the most amazing husband and partner I ever could have asked for. Thank you for understanding the demands of this endeavor, for supporting me through all of its ups and downs, and for always believing in me. Above all else, thank you for making my dreams your own, and for making sacrifices in your life so that I would be able to achieve my goals.

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BOOK CHAPTERS

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PEER-REVIEWED PUBLICATIONS

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the California Verbal Learning Test-3: Clinical utility in Alzheimer's and Huntington's disease. *Journal of the International Neuropsychological Society*.

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Holden, H. M., Tierney, S. M., Graves, L. V., Woods, S. P., Herndon, A., Delis, D. C., . . . Gilbert, P. E. (in preparation). Subtle verbal memory deficits are detectable in premanifest Huntington's disease using the CVLT-II.

Graves, L. V., **Holden, H. M.**, Van Etten, E. J., Delano-Wood, L., Bondi, M. W., Salmon, D. P., . . . Delis, D. C. (in preparation). New intrusion analyses on the CVLT-3: Clinical utility in distinguishing patients with Alzheimer's or Huntington's disease.

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PRESENTATIONS

Graves, L. V., Holden, H. M., Van Etten, E. J., Delano-Wood, L., Bondi, M. W., Salmon, D. P., . . . Gilbert, P. E. (2018, February). *Novel recognition discriminability in Alzheimer's and Huntington's disease: New insights from the CVLT-3*. Poster session presented at the annual meeting of the International Neuropsychological Society, Washington, DC.

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Taylor, B. P., Van Etten, E. J., Graves, L. V., **Holden, H. M.**, Lopez, F. V., Nguyen, L., . . . Gilbert, P. E. (2017, February). *CVLT-II performance in Huntington’s disease and Parkinson’s disease*. Poster session presented at the annual meeting of the International Neuropsychological Society, New Orleans, LA.

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Graves, L. V., **Holden, H. M.**, Doyle, K. L., Delano-Wood, L., Bondi, M. W., Woods, S. P., . . . Gilbert, P. E. (2016, February). *Recognition discriminability in Huntington's and Alzheimer's disease*. Poster session presented at the annual meeting of the International Neuropsychological Society, Boston, MA.

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Sumida, C. A., Van Etten, E. J., Wagner, G. B., Hileman, J. B., **Holden, H. M.**, & Gilbert, P. E. (2015, February). *Who, when, and where: Age-related differences on a novel episodic-like memory task*. Poster session presented at the annual meeting of the International Neuropsychological Society, Denver, CO.

Holden, H. M., Nicoll, D. R., Pirogovsky, E., Woods, S. P., Filoteo, J. V., Gluhm, S., . . . Gilbert, P. E. (2014, February). *"Forgetting to remember" in Huntington's disease: A comprehensive study of laboratory, semi-naturalistic, and self-perceptions of prospective memory*. Poster session presented at the annual meeting of the International Neuropsychological Society, Seattle, WA.

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ABSTRACT OF THE DISSERTATION

The Retrieval Deficit Memory Profile in Huntington's Disease:
Reexamining Old Heuristics and Exploring New Ones

by

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Rationale: Memory dysfunction in Huntington's disease (HD) has been characterized as a primary retrieval deficit. Evidence for this conceptualization emerged from findings that individuals with HD demonstrate disproportionate improvement on recognition versus free recall. However, findings are mixed regarding memory

performance in HD, with some studies supporting the recall/recognition discrepancy and others demonstrating similar levels of impairment in these processes. The present study aimed to improve understanding of memory in HD by examining two possible explanations for the inconsistent findings: 1) different operational definitions of the retrieval deficit profile may result in mixed findings regarding the nature of memory dysfunction in HD, and 2) neurocognitive mechanisms underlying memory dysfunction in HD may vary as a function of the level of global cognitive impairment. **Design:** The present study used archival data from the California Verbal Learning Test-II. The first aim included 27 individuals with Alzheimer's disease (AD), 39 individuals with HD, and 70 healthy adults (HA). Various contrasts of recall and recognition were used in a discriminant function analysis to determine if one was superior in discriminating between groups. The second aim included 72 individuals with HD. Using a previous discriminant function algorithm, individuals were classified as having one of three memory profiles: normal, encoding deficit, or retrieval deficit. Logistic regression analysis was conducted to determine if overall cognitive impairment, measured by the Dementia Rating Scale, predicted memory profile. **Results:** In the first aim, the contrast of Total Recognition Discriminability - Trial 5 Recall was superior to other contrasts in distinguishing between groups and resulted in a correct classification rate of 77.6%. In the second aim, memory profiles of HD patients were classified as: normal profile = 7%, encoding deficit = 33%, and retrieval deficit = 60%. For individuals classified with memory impairment, global cognitive impairment did not predict memory profile. **Relevance:** Refining characterization of memory dysfunction in HD may help resolve inconsistencies in the literature and enhance understanding of the cognitive sequelae of this neurodegenerative

disease. Improved understanding of the course of memory impairment in HD may inform interventions to target specific neurocognitive mechanisms at different stages of the disease.

CHAPTER 1: INTRODUCTION

Overview of Huntington's Disease

Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder caused by an expansion of CAG (cytosine-adenine-guanine) repeats within the coding region of the IT15 gene on chromosome 4 (Huntington's Disease Collaborative Research Group, 1993). The CAG repeat encodes the protein huntingtin and is found in normal lengths in all people. Repeat lengths of 39 or more will result in manifest HD if the person lives an average lifespan (Paulsen & Mikos, 2008). Due to the autosomal dominant nature of the disorder, every child born to a parent with HD has a 50% chance of inheriting the disease. Currently, it is estimated that 30,000 individuals in the U.S. have manifest HD and another 200,000 are at-risk of inheriting the disease (Huntington's Disease Society of America).

HD usually manifests in middle adulthood and is characterized by motor abnormalities, psychiatric symptoms, and cognitive dysfunction. Chorea is the primary motor disturbance in HD and consists of involuntary writhing or jerking movements (Vonsattel & DiFiglia, 1998). Other motor abnormalities include dysarthria, dystonia, gait disturbance, and oculomotor dysfunction. Psychiatric symptoms include depression, increased suicide risk, obsessive thinking, and compulsive behaviors (Paulsen & Mikos, 2008). Depression is highly prevalent in HD (i.e., up to 60% of patients) and may precede the onset of motor symptoms (Folstein, Franz, Jensen, Chase, & Folstein, 1983). Less common psychiatric symptoms include mania and psychosis (Paulsen & Mikos, 2008). HD is also associated with behavioral and personality changes, including increased irritability and anger outbursts. Apathy, or diminished motivation, is also common in HD

and is distinct from depression (Levy et al., 1998). Cognitive dysfunction in HD will be discussed below in detail. The triad of motor, psychiatric, and cognitive symptoms in HD leads to increasing functional dependence as the disease progresses.

Neuropathology of HD

Early pathology in HD is localized to the neostriatum (caudate and putamen) and includes dendritic and neuronal loss, gliosis, and atrophy (Brodal, 1981; Vonsattel & DiFiglia, 1998; Vonsattel et al., 1985). Loss of neurons in the striatum is associated with decreased GABAergic and cholinergic activity (McGeer & McGeer, 1976; Spokes, 1980; Cummings, 1986). At later stages of the disease, other subcortical structures are affected, including globus pallidus, thalamus, subthalamic nucleus, and white matter (Vonsattel, 2000). Cortical neurons, particularly those with extensive striatal connections, also deteriorate as the disease progresses (Sanberg & Coyle, 1984).

Structural neuroimaging techniques have revealed volume loss in striatum (Backman, Robins-Wahlin, Lundin, Ginovart, & Farde, 1997; Bamford, Caine, Kido, Cox, & Shoulson, 1995; Jernigan, Salmon, Butters, & Hesselink, 1991; Rosas et al., 2001; Starkstein et al., 1992), frontal lobes (Backman et al., 1997; Starkstein et al., 1992), thalamus and medial temporal lobe structures (Jernigan et al., 1991), as well as white matter abnormalities (Jernigan et al., 1991). Positron emission tomographic (PET) scans have shown both dopamine receptor binding deficits and reduced metabolism in caudate and putamen (Backman et al., 1997; Berent et al., 1988). Furthermore, these structural and metabolic changes are associated with cognitive dysfunction (for review, see Montoya, Price, Menear, & Lepage, 2006), motor symptoms (Kuwert et al., 1990; Young et al., 1986), and functional decline (Young et al., 1986).

Neuropathology in the striatum and other subcortical structures results in disruption to important circuits connecting these structures to the frontal lobes (Cummings, 1986, 1993). There are five anatomically segregated, but parallel, frontal-subcortical circuits, each of which is named for the region of the frontal cortex from which it originates: 1) motor, 2) oculomotor, 3) dorsolateral prefrontal, 4) lateral orbitofrontal, and 5) anterior cingulate (Alexander, DeLong, & Strick, 1986). In general, these circuits originate in the frontal cortex, connect to the striatum, project from striatum on to the globus pallidus and substantia nigra, from these to structures to the thalamus, and finally, project from the thalamus back to the frontal lobe (Cummings, 1993). Structures with afferent projections to or efferent projections from specific circuits are anatomically and functionally related.

Within each circuit, there are two pathways, the direct pathway that connects the striatum to the globus pallidus interna/substantia nigra complex; and the indirect pathway, which connects striatum to globus pallidus externa, then subthalamic nucleus, and back to the globus pallidus interna/substantia nigra complex (Alexander & Crutcher, 1990; Cummings, 1993). Chorea in Huntington's disease results from dysfunction in the indirect pathway of the motor circuit. Specifically, decreased GABAergic activity in the putamen results in a reduced inhibitory signal from the globus pallidus interna/substantia nigra to the thalamus, with a net effect of increased excitatory signals from the thalamus to the motor cortex (Paulsen & Mikos, 2008). Dysfunction in other frontal-subcortical circuits may contribute to cognitive dysfunction and psychiatric symptoms in HD (Cummings, 1993; Mega & Cummings, 2001; Paulsen & Mikos, 2008). Disruption of the dorsolateral prefrontal circuit is associated with executive dysfunction and motor

programming abnormalities. Orbitofrontal circuit dysfunction leads to personality changes, including increased irritability, impulsivity, labile mood, and disinhibition. Damage to this circuit may also result in mood disorder and/or obsessive-compulsive disorder. Finally, disruption of the anterior cingulate circuit is associated with decreased motivation and apathy (Cummings, 1993; Mega & Cummings, 2001; Paulsen & Mikos, 2008).

Cognitive Function in HD

The cognitive sequelae of HD often are extensive and include deficits in many cognitive domains (for reviews, see Dumas, van den Bogaard, Middelkoop, & Roos, 2013; Salmon & Filoteo, 2007).

Executive Function. Executive dysfunction is prominent and widespread in HD and is thought to result from damage to frontal-subcortical circuits. Executive function refers to a set of higher-level cognitive functions that includes abilities such as planning, organization, reasoning, cognitive flexibility, and conceptualization. Individuals with HD demonstrate deficits in planning (Watkins et al., 2000), task switching (Aron et al., 2003; Rich, Troyer, Bylsma, & Brandt, 1999), and novel problem solving (Savage, 1997). On the twenty questions test, individuals are presented with an array of stimuli and are asked to identify a preselected target with as few yes/no questions as possible. Success on the task depends on asking questions related to the more abstract, conceptual properties of the stimuli (e.g., is it living?) in an effort to eliminate as many stimuli as possible with one question. HD patients were impaired on this test due to a propensity to ask less efficient questions (e.g., does it sting?) related to concrete properties of the stimuli (Stout et al., 1996). HD patients also exhibit a decline in response inhibition, the ability to

inhibit responses that are not needed or are inappropriate (Beste, Saft, Andrich, Gold, & Falkenstein, 2008). Additional executive function deficits include poor judgment and decision making (Stout, Rodawalt, & Siemers, 2001) and a tendency to perseverate with a particular response strategy even when it is not rewarded (Lange, Sahakian, Quinn, Marsden, & Robbins, 1995). On global screening measures, HD patients consistently perform more poorly on the items or subscales sensitive to executive dysfunction, including serial sevens on the Mini-Mental State Exam (Folstein, Folstein, & McHugh, 1975), the initiation and perseveration subscale of the Dementia Rating Scale (Mattis, 1988; Paulsen et al., 1995; Salmon, Kwo-on-Yuen, Heindel, Butters, & Thal, 1989), and a subgroup of attention/executive function items on The Montreal Cognitive Assessment (Gluhm et al., 2013; Nasreddine et al., 2005). Furthermore, screening instruments that include assessments of executive function have been shown to be particularly sensitive to cognitive impairment in HD (Gluhm et al., 2013; Mickes et al., 2010).

Attention and Working Memory. Evidence also suggests that attention and working memory are impaired in HD. Studies using standardized neuropsychological instruments have revealed that these deficits are evident early in the disease (Josiasen, Curry, and Mancall, 1983) and HD patients are significantly more impaired on attention and concentration indices than Alzheimer's disease (AD) patients matched for dementia severity (Troster, Jacobs, Butters, Cullum, & Salmon, 1989). Investigations of more specific aspects of attention have revealed that HD patients have particular difficulty with shifting attention, especially in the later stages of the disease (Lawrence, Sahakian, Quinn, Marsden, & Robbins, 1995). Furthermore, individuals with HD are able to maintain and shift attention in response to external cues, but are impaired when vigilance

and attentional shifts requires internal regulation (Sprenelmeyer, Lange, & Homberg, 1995).

Visual Cognition. Visuospatial deficits also are apparent in HD. Individuals with HD have exhibited impaired figure copying, which was characterized by omission errors and distorted spatial relationships between elements of the picture (Caine, Bamford, Schiffer, Shoulson, & Levy, 1986). Similarly, on a clock drawing test, HD patients were impaired on both command and copy conditions and performance was characterized by graphic, spatial, and planning errors (Rouleau, Salmon, Butters, Kennedy, & McGuire, 1992). Individuals with HD also are impaired on the Benton Judgment of Line Orientation Test (Benton, Sivan, Hamsher, Varney, & Spreen, 1994), suggesting that visuospatial deficits persist even when speed and motor demands of a task are minimized (Corey-Bloom et al., 2016). In a study comparing visual perceptual and spatial abilities in HD and AD, individuals with HD exhibited deficits on visuospatial tasks that required manipulation in relation to the individual (e.g., map test), but were not impaired on visuoconstructive tasks that required manipulation of objects in relation to an external referent (e.g., complex figure copy), whereas AD patients exhibited the opposite effect. This double dissociation was attributed to the role of the frontal cortex in personal orientation and the parietal cortex in extra personal orientation (Brouwers, Cox, Martin, Chase, & Fedio, 1984). This distinction was further supported by a study that demonstrated individuals with HD accurately performed mental rotation of visual objects, but were significantly slower than controls, whereas AD patients were quick to respond but inaccurate (Lineweaver, Salmon, Bondi, & Corey-Bloom, 2005). More general visuospatial dysfunction appears to be related to dementia associated with basal ganglia

dysfunction (e.g., HD and Parkinson's disease (PD) dementia); however, specific impairments in person-centered spatial judgment are unique to HD (Mohr, Claus, & Brouwers, 1997).

Language. With the exception of deficits in speech production resulting from dysarthria, language function appears to be relatively well preserved in HD. Some deficits have been shown on language tasks, but they appear to be more related to dysfunction in other cognitive processes necessary for successful performance. For example, two different types of verbal fluency tasks are commonly used in clinical and research settings. Phonemic fluency tasks require that the individual name as many words as they can think of that start with a particular letter (e.g., F,A,S). Semantic fluency tasks require generation of words that belong to a particular semantic category (e.g., animals). A number of studies have found that AD patients are impaired on category fluency but not letter fluency tasks, whereas HD patients are equally impaired on both (e.g., Butters, Granholm, Salmon, Grant, & Wolfe, 1987; Hodges, Salmon, & Butters, 1990). It is thought that the specific category deficit in AD results from a breakdown of semantic knowledge, whereas in HD, impaired performance is related to difficulty with effortful systematic retrieval of information stored in memory (Butters et al., 1987; Hodges et al., 1990; Salmon & Filoteo, 2007). Another important distinction can be drawn on the basis of visual confrontation naming tasks. While HD patients have exhibited deficits on these tasks, the nature of the errors is qualitatively different from that in AD. Individuals with HD make more errors related to perceptual misjudgments (e.g., mushroom for umbrella), whereas individuals with AD make semantically based errors (e.g., animal for camel; Hodges, Salmon, & Butters, 1991).

Other Domains. Two other cognitive deficits deserve mention before proceeding to memory dysfunction. First, HD patients demonstrate consistent deficits in psychomotor speed (e.g., Snowden, Craufurd, Griffiths, Thompson, & Neary, 2001) and cognitive slowing has been shown to be independent of general slowing due to motor abnormalities (Aron et al., 2003). Second, individuals with HD are impaired in their ability to recognize emotions, and in particular, negative emotions like disgust (Bora, Velakoulis, & Walterfang, 2016).

General Memory. Memory dysfunction is prominent in HD, occurs early in the disease, and is evident across a vast array of abilities. Before proceeding to an in-depth discussion of episodic memory deficits, more general memory findings will be reviewed here.

Squire (1982; see also Squire & Zola-Morgan, 1991) proposed that memory can be divided into two anatomically distinct systems. Declarative (explicit) memory is available to conscious awareness and includes memory for information and events that we encounter in everyday experience. In contrast, nondeclarative (implicit) memory is not consciously accessible and is demonstrated only through performance; examples include procedural or skill learning, classical conditioning, and priming. Even in severe cortically based amnesic disorders, implicit memory remains intact. Implicit memory is often assessed with motor skill (e.g., pursuit rotor) and cognitive skill (e.g., mirror-reading) tasks. Implicit memory is evident through improved performance with practice, despite no conscious recollection of having completed the task. Priming tasks also reveal implicit learning and memory through facilitation of performance after prior exposure to stimuli. Comparisons of HD and AD patients on implicit memory tasks have revealed important

dissociations in the types of memory affected (and preserved) in these distinct neurological disorders. A number of studies have revealed that HD patients are impaired on procedural/skill learning tasks (Gabrieli, Stebbins, Singh, Willingham, & Goetz, 1997; Heindel, Butters, & Salmon, 1988; Martone, Butters, Payne, Becker, & Sax, 1984), but not on priming tasks, including priming for words (Shimamura, Salmon, Squire, & Butters, 1987), pictures (Heindel, Salmon, & Butters, 1990), and contextual learning (van Asselen et al., 2012). In contrast, priming in AD is impaired but procedural/skill learning is preserved (e.g., Heindel, Salmon, Shults, Walicke, & Butters, 1989), suggesting these two types of implicit memory are mediated by distinct brain regions.

Anterograde amnesia refers to loss of memory for new information (e.g., recent events, word list presented 20 minutes ago), while retrograde amnesia refers to loss of memory for previously stored information (e.g., events in remote past). Individuals with AD demonstrate temporally graded loss of remote memories, such that memory loss for more recent years is more profound than that for years in the more distant past. This pattern of loss is thought to result from ineffective consolidation that relies on medial temporal lobe and neocortical areas affected in AD (Beatty, Salmon, Butters, Heindel, & Granholm, 1988; Sadek et al., 2004). In contrast, remote memory loss in HD is equally severe across decades, suggesting the deficit lies in the retrieval of previously stored information (Beatty et al., 1988; Sadek et al., 2004).

Finally, HD patients demonstrate impairment on a number of memory tasks that are thought to be reliant on frontal lobes and/or frontostriatal circuits affected in the disease. Source memory refers to memory for where information originated (e.g., doctor, spouse), rather than the content of the information itself. Individuals with HD have

demonstrated source memory impairments across a number of paradigms, including remembering the source of verbal information (Brandt, Bylsma, Aylward, Rothlind, & Gow, 1995), as well as visual and olfactory stimuli (Pirogovsky et al., 2007). HD patients also have exhibited deficits in temporal order memory, or memory for the sequence in which events occurred. Further, these deficits were more pronounced for stimuli presented closer together in time due to increased interference from overlapping temporal representations (Nicoll et al., 2013). Finally, prospective memory is the ability to remember to perform an intended action at some point in the future (McDaniel & Einstein, 2000), or “remembering to remember.” Individuals with HD were impaired on both laboratory and semi-naturalistic prospective memory tasks, despite intact recognition memory for the intended actions (Nicoll et al., 2014).

Episodic Memory in HD

A multitude of studies have examined episodic memory function in HD. In addition to comparing performance of HD patients to cognitively healthy adults, many studies have compared memory dysfunction in HD with that of alcoholic Korsakoff’s syndrome (KS), a prototypical amnesic syndrome, and/or Alzheimer’s disease (AD). AD and KS patients exhibit very similar patterns of spared and impaired memory functions, likely due to the involvement of the same underlying memory system (Delis et al., 1991); thus, more recent studies have focused on comparisons between HD and AD. In HD, the primary locus of pathology is the neostriatum (Cummings & Benson, 1983), whereas in AD, medial temporal lobe structures are a primary region of neuropathological changes (Hyman, Van Hoesen, Damasio, & Barnes, 1984). Although neuropathology is not entirely restricted to these areas, comparisons of memory function in these two groups

have led to important dissociations of the type of memory processes affected by primary subcortical versus cortical pathology and have contributed greatly to our understanding of the respective memory systems.

There is extensive evidence of episodic memory impairment in HD. Individuals with HD demonstrate poor learning, characterized by a flat learning rate and deficits in overall level of immediate recall (Delis et al., 1991; Kramer et al., 1988; Lundervold, Reinvang, & Lundervold, 1994; Massman, Delis, Butters, Dupont, & Gillin, 1992; Massman, Delis, Butters, Levin, & Salmon, 1990). HD patients consistently exhibit impairments in delayed recall, in both verbal (Delis et al., 1991; Lundervold et al., 1994; Massman et al., 1992; Massman et al., 1990) and visual (Hodges et al., 1990; Pirogovsky et al., 2015) paradigms. Additionally, they exhibit a strong recency effect, decreased recall consistency, and inefficient use of higher-level encoding and retrieval strategies, such as semantic clustering (Delis et al., 1991; Lundervold et al., 1994; Massman et al., 1992; Massman et al., 1990). Individuals with HD commit more errors than healthy adults, including repetitions (perseverations) and intrusions (Beatty & Butters, 1986; Lundervold et al., 1994; Massman et al., 1990). The error profile tends to be qualitatively different than that of AD and/or KS patients, with HD patients generating more perseverative errors, but less intrusion errors (Delis et al., 1991). Additionally, elevated intrusion errors are sometimes limited to cued recall trials (Massman et al., 1990). In contrast to deficient learning and overall level of recall, individuals with HD generally demonstrate intact retention (Lundervold et al., 1994; Massman et al., 1990; Troster et al., 1993). Regarding yes/no recognition, results are mixed, with some studies demonstrating normal recognition and others demonstrating impaired performance, albeit

to a lesser extent than AD/KS patients (Delis et al., 1991; Kramer et al., 1988). When recognition is impaired in HD, there is a tendency to make increased false positive errors, though again, to a lesser extent than AD/KS patients (Kramer et al., 1988). The discrepant findings with regard to recognition memory will be discussed in greater detail below.

Much of the work on memory dysfunction in HD has sought to elucidate the specific neurocognitive mechanisms underlying this impairment. Early investigations focused on deficient encoding and/or storage processes as a potential source of memory dysfunction in HD. Initial evidence supporting this hypothesis came from studies demonstrating that individuals with HD did not benefit from increased rehearsal time (Meudell, Butters, & Montgomery, 1978), predistractor delays (Butters & Grady, 1977), reduced proactive interference (Butters, Tarlow, Cermak, & Sax, 1976), or in-depth processing of stimuli (Biber, Butters, Rosen, Gerstman, & Mattis, 1981).

Despite these initial findings, a number of subsequent studies found evidence to suggest that encoding and storage processes were not impaired in HD. On a word list-learning task, HD patients demonstrated a better rate of learning and lower rate of forgetting compared to individuals with KS, despite similar levels of impairment on free recall (Butters, Wolfe, Granholm, Martone, 1986; Butters, Wolfe, Martone, Granholm, & Cermak, 1985). Beatty and Butters (1986) utilized two paradigms to assess the encoding abilities of HD patients. In the first study, they assessed recall and recognition for words that were both high and low in imageability. Although HD patients were impaired relative to controls in their overall level of recall, they demonstrated similar improvement in performance for highly imageable words, suggesting they were able to benefit from

more elaborate encoding. The second study assessed susceptibility to interference. Proactive interference results when prior learning interferes with new learning; release from proactive interference occurs when reducing interference effects (e.g., semantically unrelated stimuli) results in improved performance. Individuals with encoding problems should not demonstrate sensitivity to and/or release from proactive interference because prior information has not been encoded well enough to interfere with new learning. In this second study, HD patients exhibited normal release from proactive interference, suggesting they were able to encode semantic features of the stimuli (Beatty & Butters, 1986).

Many studies also have demonstrated that HD patients are able to successfully retain information they have learned (Lundervold et al., 1994; Massman et al., 1990; Troster et al., 1993), suggesting that consolidation and storage processes also are intact in individuals with HD. Together, this evidence argued against deficient encoding and storage processes as the primary underlying mechanism of memory impairment in HD. In response to findings emerging at the time, attention quickly turned to retrieval deficits as a potential source of memory dysfunction in HD.

Early experimental studies demonstrated intact recognition memory for words used in a mirror-reading task (Martone et al., 1984) and pictorial information (Butters, 1984), as well as better recognition versus free recall for events from personal history (Caine, Hunt, Weingartner, & Ebert, 1978). Furthermore, individuals with HD performed better on recognition tasks for verbal versus nonverbal stimuli (Moss, Albert, Butters, & Payne, 1986) and benefitted from use of a verbal encoding strategy for visual information (Butters, 1984), presumably due to their intact language abilities.

Butters and colleagues (1985) were the first to assess recognition and recall performance using the same assessment measure. On a modified version of the Rey Auditory Verbal Learning Test (RAVLT; Lezak, 1983; Rey, 1964), HD patients demonstrated better recognition performance than amnesic patients, despite comparable levels of impairment on free recall. Many subsequent studies have demonstrated a similar effect, with HD patients exhibiting greater than normal improvement on recognition testing versus free recall (Butters et al., 1986; Delis et al., 1991; Lundervold et al., 1994; Massman, Delis, & Butters, 1993; Massman et al., 1990; Moss et al., 1986), and in some cases, demonstrating normal or near normal recognition performance (Butters, 1984; Moss et al., 1986).

As part of a larger study examining memory profiles in depressed patients, Massman and colleagues (1992) compared performance of HD patients, AD patients, and healthy controls on the California Verbal Learning Test (CVLT; Delis, Kramer, Kaplan, & Ober, 1987). Several CVLT variables were selected for analysis based on the likelihood that they would maximally discriminate the three groups: 1) Trials 1-5 Total, which was expected to distinguish the control group from the clinical groups; 2) Cued Recall Intrusions, which was expected to differentiate the AD group from the other two groups; and 3) a contrast between Total Recognition Discriminability and Trial 5 Recall, which was expected to separate the HD group from the other two groups. Using discriminant function analysis, the researchers demonstrated that the combination of these three variables successfully discriminated the three groups. Importantly, the contrast between recognition and recall significantly enhanced differentiation of HD patients from AD patients and healthy controls. Filoteo (personal communication, 2016)

extended these findings by deriving a new discriminant function algorithm using the same three variables from the second edition of the CVLT (CVLT-II; Delis, Kramer, Kaplan, & Ober, 2000).

Taken together, these studies suggest that memory impairment in HD is characterized by an inability to initiate systematic retrieval strategies when searching for information that has been successfully stored in memory. These findings led to the widely accepted belief that the primary neurocognitive mechanism underlying memory dysfunction in HD is a retrieval deficit.

Despite a wealth of evidence supporting this idea, two primary findings have led to arguments against the hypothesis of a primary retrieval deficit in HD. First, a number of studies have demonstrated that recognition memory is not intact in HD (Beatty & Butters, 1986; Butters et al., 1986; Delis et al., 1991; Kramer et al., 1988; Lang, Majer, Balan, & Reischies, 2000; Lundervold et al., 1994; Massman et al., 1992; Massman et al., 1990) and some suggest this is indicative of problems with encoding (Lundervold et al., 1994) and/or storage (Caine et al., 1986). Most would agree that mildly impaired recognition, along with other characteristics of memory dysfunction in HD (e.g., flat learning rate, intrusions on delayed recall) suggest that HD patients may have at least mild encoding deficits (Massman et al., 1990; Delis et al., 2000). However, there also is evidence to suggest that HD patients can improve encoding if they are instructed to utilize cues that are provided for them (Granholm & Butters, 1988). Thus, these deficits in HD may be due to an inability to initiate efficient encoding strategies, rather than deficient encoding mechanisms per se (Massman et al., 1990).

Despite the possibility that mild encoding deficits may be present, it is important to note that the hypothesis of a retrieval deficit did not arise from evidence that recognition memory is *preserved* in HD. Rather, this hypothesis emerged in response to evidence that HD patients demonstrate disproportionate improvement in recognition versus free recall, both when compared with AD patients (e.g., Delis et al., 1991) and healthy adults (e.g., Massman et al., 1990). Nonetheless, some studies have failed to find any improvement in recognition testing versus free recall, which is the second (and potentially more problematic) finding calling into question the validity of the retrieval deficit hypothesis.

In one study, researchers used a word list learning task and found that recognition was not only impaired in HD patients, but was more severely impaired than free recall. The authors used these findings to argue against the retrieval deficit hypothesis and suggest that recognition performance may be a sensitive measure capable of detecting early cognitive decline in this population (Lang et al., 2000). Delis and colleagues (2005) were interested in examining the utility of a new recall discriminability index on the California Verbal Learning Test-Second Edition (CVLT-II; Delis et al., 2000), which measures level of correct recall relative to intrusion rate. Using the recall discriminability index, HD patients exhibited less severe impairment in recall than AD patients, in contrast to prior findings of similar levels of impairment in the two groups. Given that the new discriminability measure revealed less impaired recall scores in the HD group, the researchers hypothesized that HD patients might not exhibit an improvement in recognition. In a post hoc analysis, the contrast of recall discriminability versus recognition discriminability was examined in HD patients and there was no difference in

performance (i.e., no improvement on recognition). Thus, the authors hypothesized that memory dysfunction in HD may actually be characterized by an encoding/storage deficit, rather than a primary retrieval deficit as previously thought (Delis et al., 2005). Finally, a meta-analysis of 48 studies examining episodic memory in HD found no significant difference in effect sizes for recall or recognition deficits. This finding held even when comparing effect sizes only in the 13 studies that assessed recall and recognition in the same sample of subjects (Montoya, Pelletier, et al., 2006).

In summary, there are mixed findings with regard to the retrieval deficit hypothesis in HD, with some studies supporting the recall/recognition discrepancy and others demonstrating similar levels of impairment in these memory processes. The proposed study seeks to examine two possible explanations for the inconsistent findings.

One potential explanation for the current discrepancies in the literature is that different operational definitions of the retrieval deficit profile across studies may result in discrepant conclusions regarding the nature of memory dysfunction in HD. These different operational definitions can arise from variations in the definition of recall, or recognition, or both. Some studies have compared immediate recall and recognition (e.g., Lang et al., 2000), others have compared recall on the final learning trial to delayed recognition (Delis et al., 1991; Massman et al., 1992), and still others have compared performance on both delayed recall and recognition (Massman et al., 1990; Zizak et al., 2005). These varying methods for capturing recall and recognition processes may result in different conclusions regarding whether or not HD patients demonstrate improvement on recognition testing, and whether this improvement is markedly different from that seen in AD and/or healthy adults. For example, comparing Trial 5 recall to recognition on

the CVLT not only captures any improvement on recognition, but also serves as a measure of retention, as the recognition trial occurs after a delay (Massman et al., 1992). In contrast, if one compares performance on the long delay free recall trial to recognition on the CVLT, any differences in retention are already accounted for and the contrast will only reflect improvements in performance as a function of the recognition format. Thus, the Trial 5 versus recognition contrast may better capture differences between HD patients, who have intact retention and benefit from a recognition format, and AD patients, who demonstrate rapid forgetting and no benefit from recognition testing.

There are also many diverse ways for measuring recognition memory, which could subsequently impact conclusions. For example, three commonly used assessments of verbal learning and memory utilize different types of distractors on recognition testing. The RAVLT (Lezak, 1983; Rey, 1964) is different from the Hopkins Verbal Learning Test-Revised (HVLT-R; Brandt & Benedict, 2001) and the CVLT (Delis et al., 1987, 2000) in that the set of target words are all unrelated. As such, this instrument employs a set of 15 distractor words that are also unrelated to target words. In contrast, the target words on the HVLT-R are comprised of three semantic categories, with four words from each category. The recognition test includes six distractor words that are semantically related to the target words and six distractors that are semantically unrelated. Thus, performance on this test may be affected by increased false positive errors in response to semantically related distractors, a phenomenon typically seen in individuals with mild encoding problems (Delis et al., 2000).

Finally, the CVLT-II (Delis et al., 2000) includes various measures of recognition discriminability, each with a different set of distractors. Source Recognition

Discriminability (SRD) on the CVLT-II is a measure of the ability to endorse target items and reject items from the interference list. Novel Recognition Discriminability (NRD) reflects the ability to endorse target items and reject distractor items that are novel (i.e., not from the target or interference list). However, NRD also includes semantically related and unrelated distractor items, and in this way, is similar to recognition discriminability on the HVLT-R. Finally, Total Recognition Discriminability (TRD) on the CVLT-II includes the 16 distractors from the interference list plus the 16 distractors from the NRD measure, and as such, measures the ability to reject various types of distractors. In a study comparing the new CVLT-II indices in HD and AD, Fine et al. (2008) found that the two patient groups were similarly impaired on source recognition discriminability, but the HD group outperformed the AD group on novel and total recognition discriminability. The authors suggest that comparable recognition performance using the SRD index is likely a function of source memory deficits in HD. Importantly, while NRD and TRD scores were both better in HD, the effect size was larger for NRD versus TRD, suggesting that the NRD may be the best CVLT-II index for differentiating between AD and HD patients (Fine et al., 2008).

As outlined, the lack of consistent definitions for recall and recognition across studies may have some bearing on the inconsistent findings in the extant literature. Importantly, the aforementioned discussion does not address differences in formulas for computation of the recognition score and how those might yield different conclusions regarding recognition memory in AD and HD (e.g., Brandt, Corwin, & Krafft, 1992; Graves et al., 2017). The current project will utilize the same d' formula for all measures of recognition, thus these variations will not be discussed in this paper.

However, the impact of these different formulas on the recall/recognition contrast is an important topic for future investigation.

A second possible explanation for the inconsistent findings is that there may be considerable heterogeneity in the memory profiles in HD, with only a subset of HD patients demonstrating a primary retrieval deficit. Zizak et al. (2005) compared the prevalence of the retrieval-deficit profile (RDP) in two disorders arising from frontal-striatal dysfunction, HD and PD. The RDP in this study was characterized by a z-score discrepancy between recognition discriminability and long delay free recall on the CVLT (Delis et al., 1987). Using a discrepancy score of ≥ 2 (conservative approach), they found that only 37% of the HD sample demonstrated the RDP. Even when using less stringent criteria of ≥ 1 for the discrepancy score, still only 63% of the HD patients were characterized as having a retrieval deficit. Furthermore, the authors found that the prevalence of the RDP in HD differed as a function of the level of global cognitive functioning. HD patients were split into normal or impaired groups based on age-corrected scores on the Dementia Rating Scale (DRS; Mattis, 1988) and significant differences were found in the rate of the retrieval profile between the two groups. In the normal cognition group, only 13% had the RDP, whereas 44% exhibited this profile in the impaired group.

In addition, in the aforementioned meta-analysis (Montoya, Pelletier, et al., 2006), when HD patients were split into two groups based on dementia severity, there was a significantly larger effect size for recall compared to recognition in the mild dementia subgroup, suggesting that deficits in recall are more severe than those in recognition in the earlier stages of dementia. There were no differences in recall and recognition

impairment in the moderate/severe dementia subgroup (Montoya, Pelletier, et al., 2006). Thus, it may be that the profile of memory dysfunction in HD is not static. Primary retrieval deficits may characterize memory impairment at earlier stages of the disease process, whereas encoding difficulties may emerge as the disease progresses and neuropathology becomes more widespread.

Summary and Purpose of the Present Study

In summary, there is a wealth of historical evidence to suggest that the primary neurocognitive mechanism underlying memory dysfunction in HD is a retrieval deficit. The strongest support for this hypothesis came from studies demonstrating a disproportionate improvement on recognition testing versus free recall. However, several recent investigations have failed to find a recall/recognition discrepancy, and thus, have called into question the validity of this characterization of memory dysfunction in HD. The purpose of the present study was to improve understanding of the memory profile in HD by examining two possible explanations for the inconsistent findings.

First, discrepant findings in the extant literature may exist, in part, due to different operational definitions of the retrieval deficit profile. Specifically, varying methods for measuring recall and/or recognition may have resulted in different conclusions regarding the underlying mechanism of memory dysfunction in HD. Early studies found that the contrast between the final learning trial (Trial 5) and recognition discriminability was a sensitive measure for discriminating between individuals with HD and AD (Delis et al., 1991; Massman et al., 1992). Since the recognition trial occurs after a delay, this particular contrast may measure retention, in addition to improvement in performance with a recognition format (Massman et al., 1992). Thus, this contrast may be particularly

sensitive to differences between AD patients that have poor retention and fail to demonstrate improvement on recognition trials, and HD patients that have intact retention and benefit from a recognition format. Evidence suggests that particular recognition indices also may have greater power in detecting differences between HD and AD patients. On the CVLT-II, group differences are greatest on the NRD index, which includes no distractors from the interference list. In contrast, both SRD and TRD recognition indices include List B distractor items, which may hinder performance in HD patients susceptible to source memory deficits (Fine et al., 2008). The present study aimed to compare a number of distinct contrasts using different measures of recognition and recall from the CVLT-II in an effort to determine whether one was superior to the others in differentiating memory function in HD from that in AD and healthy adults.

Second, there may be significant heterogeneity in the profile of memory dysfunction in HD, and further, the neurocognitive mechanisms underlying this dysfunction may vary as a function of the overall level of cognitive impairment. An original study (Zizak et al., 2005) and a meta-analysis (Montoya, Pelletier, et al., 2006) have already provided some support for this hypothesis. The present study sought to extend these important findings in two ways. First, the prior studies found that only a subset of HD patients exhibited the retrieval deficit profile; however, in those that do not have this profile, the exact nature of memory function is still unclear. The present study aimed to further characterize the memory profile in individuals that do not exhibit the prototypical retrieval profile. Second, the prior studies split HD patients into groups based on cut points on the DRS, whereas the present study used the DRS as a quantitative variable. It was hypothesized that this approach would allow for a more nuanced

understanding of how the memory profile in HD changes as the overall level of global cognitive impairment changes.

Specific Aims of the Present Study

Aim 1. To examine whether one contrast of recognition and recall on the CVLT-II is superior to others in distinguishing memory function in HD from that in AD and healthy adults.

Aim 1, Hypothesis 1. It was hypothesized that prior findings would be replicated, to a large extent, in that the combination of three CVLT-II variables (Trials 1-5 Total, Cued Recall Intrusions, and *some* recognition/recall contrast) would differentiate the HD, AD, and healthy adult groups.

Aim 1, Hypothesis 2. It was hypothesized that the specific recognition/recall contrast that would best discriminate between the HD group and other two groups would be Novel Recognition Discriminability versus Trial 5 Recall.

Aim 2. To examine whether there is heterogeneity in the neurocognitive mechanisms of memory dysfunction in HD, and further, whether the level of global cognitive impairment predicts the type of memory profile.

Aim 2, Hypothesis 1. It was hypothesized that in HD patients that exhibit memory dysfunction (i.e., not a normal profile), there would be a mix of encoding and retrieval profiles.

Aim 2, Hypothesis 2. It was hypothesized that the total DRS score would predict the type of memory profile in HD, such that as DRS score increased (less severe global impairment), the odds of having a retrieval profile would increase.

Chapters 1 - 4, in part will be prepared for submission for publication of the material. Holden, Heather M.; Filoteo, J. Vincent; Corey-Bloom, Jody; Delano-Wood, Lisa; Sadler, Melody; Gilbert, Paul E. The dissertation author was the primary investigator and author of this material.

CHAPTER 2: METHODS

Archival Data

All CVLT-II data were extracted from archival databases at the respective sites described below. The data were collected as part of larger neuropsychological batteries in conjunction with ongoing research studies. Testing batteries at all sites were administered using standardized procedures by trained research assistants or psychometrists.

Participants

Individuals with HD ($n = 72$) were participants in the Huntington's Disease Clinical Research Program at the University of California, San Diego. All HD patients were diagnosed with definite HD by a senior staff neurologist on the basis of unequivocal motor signs and a positive family history for HD. In addition, all HD participants had a CAG repeat length greater than 39 ($M=44.46$, $SD=3.37$)¹, indicating that all carried the fully penetrant genetic mutation for HD. HD patients were administered the Unified Huntington's Disease Rating Scale (UHDRS; Huntington Study Group, 1996) by a senior staff neurologist. The UHDRS includes a Total Motor Score (TMS) ranging from 0-124, with higher scores suggestive of more severe motor impairment. The mean TMS was 37.41 ($SD=16.56$)¹.

Individuals with AD ($n = 27$) were participants in ongoing research studies at the Shiley-Marcos Alzheimer's Disease Research Center (ADRC) in La Jolla, California. These individuals were diagnosed with probable Alzheimer's disease based on criteria established by the National Institute of Neurological and Communicative Disorders and

¹ Missing CAG data for 3 participants and TMS score for 4 participants

Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) workgroup (McKhann et al., 1984; McKhann et al., 2011).

The healthy adult comparison group ($n = 70$) was made up of participants in the Huntington's Disease Clinical Research Program ($n = 23$) and seronegatives from the HIV Neurobehavioral Research Center ($n = 9$), both at the University of California, San Diego. The remaining healthy adult participants ($n = 38$) were participants in ongoing studies at the Center for Healthy Aging and Neurodegenerative Disease Research at San Diego State University. Exclusion criteria for all participants in the study included a history of neurological disorders (with the exception of HD for the HD participants or AD for the AD participants), a formal diagnosis of a psychiatric disorder (with the exception of mood or anxiety disorder for the HD or AD participants), or history of traumatic brain injury. All participants gave informed written consent for participation approved by the Institutional Review Boards of the University of California, San Diego and/or San Diego State University.

Analyses for Aim 1 utilized the healthy comparison group ($n = 70$), the AD participants ($n = 27$), and a subset of the HD sample ($n = 39$) matched to the AD sample for overall dementia severity. Table 1 provides a summary of demographic variables for these three groups, as well as DRS Total Score for the HD and AD groups. A one-way analysis of variance (ANOVA) revealed no significant differences between the HD and AD groups on DRS Total Score, $F_{(1,64)} = 1.90, p = .17$. There also were no significant differences between the three groups in mean education level, $F_{(2,133)} = 1.20, p = .31$. A one-way ANOVA did reveal significant age differences between the groups, $F_{(2,133)} = 46.13, p < .01$. This difference was expected based on the differences in typical age of

onset for HD and AD. Further, given the large difference in mean age between the HD ($M=50$) and AD ($M=77$) groups, it was not possible to create a comparison group that was similar to both groups in age. Finally, a chi-square analysis revealed significant differences in sex percentages between the three groups, $\chi^2(136) = 9.04, p < .05$.

Importantly, all analyses used standardized scores on the CVLT-II, which correct for age and gender. Analyses for Aim 2 utilized only the HD participants ($n = 72$); disease characteristics for these individuals are described above.

Assessments

California Verbal Learning Test-Second Edition (CVLT-II; Delis et al., 2000).

All participants were administered the CVLT-II using standardized procedures. The test includes two lists, each of which consists of 16 words drawn evenly from four semantic categories. The individual is presented with the target list (List A) over five learning trials, immediately followed by one presentation of the interference list (List B).

Immediately after the presentation of List B, short delay free and cued recall trials for List A are administered. After a 20-minute delay, during which nonverbal tasks are administered, long delay free and cued recall of List A is assessed. Finally, a yes/no recognition trial for the target list is administered. The assessments were scored using the CVLT-II scoring software (Delis & Fridlund, 2000). Standardized scores from the CVLT-II, corrected for age and gender, were used for all analyses. The measures of interest for the current study are described in Table 2.

Dementia Rating Scale (DRS; Jurica, Leitten, & Mattis, 2001; Mattis, 1988).

The DRS was administered using standardized procedures and scored either by hand or using the scoring software. The DRS yields a total score of overall level of cognitive

functioning and five subscale scores for specific abilities (e.g., Attention, Memory). Since standardized scores are not available for individuals under the age of 56, raw scores were used. The total score was used in all analyses and ranges from 0-144.

Statistical Analyses

Aim1. The proposed discriminant function analysis (DFA) included eight CVLT-II variables as predictors of membership in a diagnostic group. Predictors included Trials 1-5 Total, Total Cued Recall Intrusions, and six contrasts of recognition versus recall. The following six recognition/recall contrasts were of interest: a) Total Recognition Discriminability (TRD) - Trial 5 Recall, b) TRD – Long Delay Free Recall (LDFR), c) TRD - LDFR Discriminability, d) Novel Recognition Discriminability (NRD) - Trial 5 Recall, e) NRD – LDFR, and f) NRD - LDFR Discriminability. The diagnostic groups were individuals with HD (n = 39), individuals with probable AD (n = 27), and a comparison group of healthy adults (n = 70). Estimates of the necessary sample size for DFA are based on a subject to variable ratio. Recommendations for the minimum sample size range from 4-5 cases per independent variable (Garson, 2012) up to 10 cases per predictor (Scott C. Roesch, personal communication, 2009). With 136 subjects and 8 variables, the subjects to variable ratio was satisfactory.

Prior to conducting the DFA, data from the six contrasts of recognition and recall were checked for multicollinearity. Several indices were consulted, including the Pearson correlation coefficient for each pair of contrasts, and tolerance and variance inflation factors for sets of contrasts that used the same recall or recognition variable. Any Pearson r greater than .90 and/or several Pearson r values greater than .80 was considered problematic (Garson, 2012). Tolerance values $< .10$ and variance inflation factors (VIF) $>$

10 are indicative of extreme redundancy among a set of variables; in the current study, a more conservative cutoff of tolerance $< .20$ and VIF > 5 was used (Kline, 2011). If several of these indices were above cutoffs established above, the variable set was reduced to a smaller, less redundant set of contrasts.

Data were checked for outliers using studentized deleted residuals for each variable that would ultimately be entered in the DFA. Studentized deleted residuals with absolute values > 3 were considered indicative of outliers in a particular diagnostic group (Judd, McClelland, & Ryan, 2009) and data for these individuals were not used in the final analyses. The homogeneity of covariance assumption was evaluated using Box's M test, with a significant p -value indicative of unequal population covariance matrices. If the Box's M test was significant, the analyses were conducted again using separate-groups covariance matrices. If the results from analyses using separate-groups covariance matrices were comparable to those using within-groups covariance matrices, then results from analyses using within-groups covariance matrices were described in the results section (Garson, 2012), as this approach allowed for cross-validation of classification results.

In the DFA, numerous indices were examined to determine the utility of the CVLT-II variables in discriminating between the three diagnostic groups. First, the overall model was examined to determine if there were any significant discriminant functions. Second, the F test of Wilks' Lambda was examined for each of the independent variables to determine if the variable contributed significantly to the discriminant functions. Third, standardized canonical discriminant function coefficients (i.e., discriminant function weights) were examined for each significant discriminant

function. The larger the absolute value of a standardized coefficient, the greater that variable's relative contribution to determining scores on the function, and values larger than an absolute value of .30 are considered good (Klecka, 1980). Fourth, structure coefficients (i.e., discriminant function loadings) for each discriminant function also were examined and represent the Pearson product-moment correlation between the independent variable and the discriminant function, thus serving as a measure of how closely the variable and function are related. Finally, classification statistics were examined to determine how well the model predicted group membership. The classification rate was compared to the percent that would have been correctly classified by chance alone. Since the sample sizes in each diagnostic group were not equal, this criterion classification percentage was determined by: 1) multiplying the prior probability of being in a particular group by the group size, 2) summing these products for all groups, and 3) dividing the result by the total size of all three groups (Garson, 2012). Thus, in the current study, the calculation was as follows: $[(70 * .515) + (39 * .287) + (27 * .199)] / 136 = .39$, indicating 39% of individuals in this study would have been correctly classified by chance alone. A more stringent approach to determining the criterion classification percentage involves determining the hit rate if all cases were classified into the most numerous category (Garson, 2012). In the current study, this would be the hit rate if all cases were classified as healthy adults, which equates to 51% of individuals being correctly classified.

As the sample was not large enough to permit independent-sample cross-validation, the leave-one-out classification method was used to cross-validate the initial

classification results. This method estimates coefficients for each given case based on all other observations in the sample (Garson, 2012).

Aim 2. Using a previously derived discriminant function algorithm with Trials 1-5 Total, Total Cued Recall Intrusions, and TRD - Trial 5 Recall (J. Vincent Filoteo, personal communication, 2016), each individual with HD was classified as having one of three memory profiles: normal, retrieval deficit, or encoding deficit. For those individuals that were classified as having memory impairment (i.e., encoding deficit or retrieval deficit) a logistic regression analysis was conducted with memory profile as the outcome and Total DRS score as the predictor. The odds ratio for Total DRS score was examined, which provides an estimate of the factor by which the odds of having a retrieval deficit profile change for every one-point increase in Total DRS score.

Estimates of the necessary sample size for logistic regression analysis are based on a subject to variable ratio. Based on Monte Carlo simulations, a minimum of 10 “events” per variable is recommended (Peduzzi, Concato, Kemper, Holford, & Feinstein, 1996), with “events” referring to the smaller number of the two possible outcomes (e.g., encoding or retrieval). Other guidelines suggest 20-50 subjects per variable (Tabachnik & Fidell, 2013). The current model included one predictor variable and an initial sample of 72 individuals; thus, sample size requirements were met for even the most conservative guidelines (i.e., 50 subjects per variable).

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CHAPTER 3: RESULTS

Aim 1

Primary analyses. Data were first checked for multicollinearity using the indices previously described. Pearson r correlation coefficients were above .90 for two contrasts: 1) TRD - Trial 5 Recall and NRD - Trial 5 Recall ($r = .93$), and 2) TRD - LDFR Discriminability and NRD - LDFR Discriminability ($r = .90$). In addition, the Pearson r correlation between the contrasts of TRD - LDFR and NRD - LDFR was above .80 ($r = .88$). As expected, given the strong correlations between these pairs of contrasts, tolerance values were low and VIFs were high. Tolerance for TRD - Trial 5 Recall and NRD - Trial 5 Recall was .15 and the VIF was 6.57. Tolerance for TRD - LDFR Discriminability and NRD - LDFR Discriminability was .19 and the VIF was 5.38. Finally, tolerance for TRD - LDFR and NRD - LDFR was .23 and the VIF was 4.42. Since the same contrasts using either TRD or NRD were highly redundant, the decision was made to reduce the set of recall/recognition contrasts to three, utilizing only either TRD or NRD. Given that TRD is the standard measure of recognition discriminability, and this measure has been used consistently across prior CVLT studies, this variable was selected as the recognition measure for final analyses.

Data for the final set of three TRD contrasts also were checked for multicollinearity. All Pearson r correlations, tolerance values, and VIFs for the three contrasts were within the predetermined acceptable range. The Pearson r correlations for the three contrasts ranged from .45 - .76: TRD - T5 Recall and TRD - LDFR ($r = .70$), TRD - T5 Recall and TRD - LDFR Discriminability ($r = .45$), and TRD - LDFR and TRD - LDFR Discriminability ($r = .76$). Tolerance for TRD - T5 Recall was .492 and

VIF was 2.03. Tolerance for TRD - LDFR was .26 and VIF was 3.88. Finally, tolerance for TRD - LDFR Discriminability was .40 and VIF was 2.48.

For each of the five variables that were used in the discriminant function analysis, studentized deleted residuals were examined to identify outliers. There were no identified outliers for the variable Trials 1-5 Total or Total Cued Recall Intrusions. One individual in the AD group was identified as an outlier with respect to scores on both the TRD - Trial 5 Recall contrast and the TRD - LDFR contrast. Another individual in the AD group was identified as an outlier with respect to scores on the TRD - LDFR Discriminability contrast. Thus, these two individuals were excluded from the final analyses. In all following discriminant function analyses, the Box's M test was significant, indicating the population covariance matrices were unequal. However, in each case the analyses were conducted using separate-groups covariance matrices and the results were almost identical, with the largest discrepancy in classification percentage only 1.5%. Thus, results from analyses using within-groups covariance matrices are reported.

The initial DFA included Trials 1-5 Total, Total Cued Recall Intrusions, and all three TRD contrasts. Two discriminant functions were calculated, with a combined $\chi^2(10) = 180.98, p < .001$. After removal of the first function, the second function also was significant, with $\chi^2(4) = 26.95, p < .001$. The two discriminant functions accounted for 90.8% and 9.2%, respectively, of the between-group variance. The F test of Wilks' Lambda indicated that three of the five independent variables contributed significantly to the discriminant functions: 1) Trials 1-5 Total, $F_{(2,131)} = 131.47, p < .001$, 2) Total Cued Recall Intrusions, $F_{(2,131)} = 29.51, p < .001$, and 3) TRD - Trial 5 Recall contrast, $F_{(2,131)} = 4.32, p < .05$. The TRD - LDFR contrast, $F_{(2,131)} = 1.04, p = .36$, and TRD - LDFR

Discriminability contrast, $F_{(2,131)} = 1.02, p = .36$, were both nonsignificant. The standardized discriminant function coefficients for the first function were as follows: (a) Trials 1-5 Total = .977, (b) Total Cued Recall Intrusions = -.167, (c) TRD - T5 Recall = .425, (d) TRD - LDFR = -.341, (e) TRD - LDFR Discriminability = .232. The structure coefficients for the first function were as follows: (a) Trials 1-5 Total = .930, (b) Total Cued Recall Intrusions = -.397, (c) TRD - T5 Recall = -.025, (d) TRD - LDFR = -.083, (e) TRD - LDFR Discriminability = .033. The standardized discriminant function coefficients for the second function were as follows: (a) Trials 1-5 Total = .347, (b) Total Cued Recall Intrusions = .676, (c) TRD - T5 Recall = -.930, (d) TRD - LDFR = .902, (e) TRD - LDFR Discriminability = -.082. The structure coefficients for the second function were as follows: (a) Trials 1-5 Total = .284, (b) Total Cued Recall Intrusions = .618, (c) TRD - T5 Recall = -.527, (d) TRD - LDFR = .015, (e) TRD - LDFR Discriminability = .237. Overall, 79.9% of the sample was correctly classified into their diagnosis group and 77.6% were correctly classified in cross-validation, both of which exceed the value for classification based on chance (39%). The combined results of all indices evaluated suggest that the best predictors for distinguishing between the three groups were Trials 1-5 Total, Total Cued Recall Intrusions, and the contrast of TRD - Trial 5 Recall.

A second DFA was conducted using only these three variables. Two discriminant functions were calculated, with a combined $\chi^2(6) = 171.74, p < .001$. After removal of the first function, the second function also was significant, with $\chi^2(2) = 18.78, p < .001$. The two discriminant functions accounted for 93.5% and 6.5%, respectively, of the between-group variance. The F test of Wilks' Lambda indicated that all three independent variables contributed significantly to the discriminant functions: 1) Trials 1-

5 Total, $F_{(2,131)} = 131.47, p < .001$, 2) Total Cued Recall Intrusions, $F_{(2,131)} = 29.51, p < .001$, and 3) TRD - Trial 5 Recall contrast, $F_{(2,131)} = 4.32, p < .05$. The standardized discriminant function coefficients for the first function were as follows: (a) Trials 1-5 Total = 1.029, (b) Total Cued Recall Intrusions = -.097, (c) TRD - T5 Recall = .316. The structure coefficients for the first function were as follows: (a) Trials 1-5 Total = .943, (b) Total Cued Recall Intrusions = -.397, (c) TRD - T5 Recall = -.028. The standardized discriminant function coefficients for the second function were as follows: (a) Trials 1-5 Total = .330, (b) Total Cued Recall Intrusions = .814, (c) TRD - T5 Recall = -.419. The structure coefficients for the second function were as follows: (a) Trials 1-5 Total = .272, (b) Total Cued Recall Intrusions = .787, (c) TRD - T5 Recall = -.642. Classification results for the original grouped cases and cross-validated grouped cases are presented in Table 3. Overall, 77.6% of the sample was correctly classified into their diagnosis group and 76.9% were correctly classified in cross-validation, both of which exceed the value for classification based on chance (39%). The combined results of all indices evaluated suggest that these three indices successfully discriminated between the three groups.

The group means for each of the three discriminant function indices are displayed in Table 4. These group means revealed that the TRD - T5 Recall contrast did not capture marked improvement in recognition in the HD group, on average ($M = .23$). Further examination of this contrast in the HD group found that only a subset of the HD group ($12/39 = 31\%$) demonstrated ≥ 1 z-score improvement on TRD versus Trial 5 Recall. A paired-samples t-test comparing TRD to Trial 5 Recall was not significant in this group, $t_{(38)} = .24$. Further, the group means revealed that the AD group did more poorly on TRD versus Trial 5, on average ($M = -.56$). Further examination of this contrast in the AD

group found that a subset of the AD group (12/25 = 48%) demonstrated ≤ 1 z-score decline on TRD versus Trial 5 Recall. A paired-samples t-test comparing TRD to Trial 5 Recall was significant in this group, $t_{(24)} < .05$. Thus, in the current sample, it appears the TRD - Trial 5 contrast captured poorer performance on TRD versus Trial 5 Recall in the AD group, rather than improved performance on TRD versus Trial 5 Recall in the HD group. This decline in performance in the AD group may have been in part due to poor retention, as the recognition trial occurs after a delay (Massman et al., 1992). Importantly, while the HD group did not demonstrate improvement in recognition on average, approximately 1/3 of this group did demonstrate this pattern.

Exploratory analyses. Based on these findings, an exploratory discriminant function analysis was conducted with separate indices of retention (i.e., poorer recall after a delay) and retrieval (i.e., improvement on recognition versus free recall). The contrast of LDFR - Trial 5 Recall was used to represent retention and the contrast of TRD - LDFR was used to represent retrieval. Two discriminant functions were calculated, with a combined $\chi^2(8) = 180.16, p < .001$. After removal of the first function, the second function also was significant, with $\chi^2(3) = 27.01, p < .001$. The two discriminant functions accounted for 90.7% and 9.3%, respectively, of the between-group variance. The F test of Wilks' Lambda indicated that three of the four independent variables contributed significantly to the discriminant functions: 1) Trials 1-5 Total, $F_{(2,131)} = 131.47, p < .001$, 2) Total Cued Recall Intrusions, $F_{(2,131)} = 29.51, p < .001$, and 3) LDFR - Trial 5 Recall contrast, $F_{(2,131)} = 9.78, p < .05$. The TRD - LDFR contrast was not significant, $F_{(2,131)} = 1.04, p = .36$. The standardized discriminant function coefficients for the first function were as follows: (a) Trials 1-5 Total = 1.023, (b) Total Cued Recall

Intrusions = $-.100$, (c) LDFR - T5 Recall = $.290$, (d) TRD - LDFR = $.203$. The structure coefficients for the first function were as follows: (a) Trials 1-5 Total = $.938$, (b) Total Cued Recall Intrusions = $-.399$, (c) LDFR - T5 Recall = $.062$, (d) TRD - LDFR = $-.084$. The standardized discriminant function coefficients for the second function were as follows: (a) Trials 1-5 Total = $.327$, (b) Total Cued Recall Intrusions = $.653$, (c) LDFR - T5 Recall = $-.645$, (d) TRD - LDFR = $.072$. The structure coefficients for the second function were as follows: (a) Trials 1-5 Total = $.278$, (b) Total Cued Recall Intrusions = $.621$, (c) LDFR - T5 Recall = $-.779$, (d) TRD - LDFR = $.016$. Classification results for the original grouped cases and cross-validated grouped cases are presented in Table 5. Overall, 79.9% of the sample was correctly classified into their diagnosis group and 78.4% were correctly classified in cross-validation, both of which exceed the value for classification based on chance (39%). The combined results of all indices evaluated suggest that Trials 1-5 Total, Total Cued Recall Intrusions, and the contrast of LDFR - Trial 5 Recall discriminated the three groups, but the contrast of TRD - LDFR did not contribute significantly to classification.

Aim 2

Primary analyses. Using a previously derived discriminant function algorithm with Trials 1-5 Total, Total Cued Recall Intrusions, and TRD - Trial 5 Recall (J. Vincent Filoteo, personal communication, 2016), each individual with HD was classified as having one of three memory profiles: normal, encoding deficit, or retrieval deficit. Based on this algorithm, the memory profiles of 72 HD patients were classified as follows: a) normal profile = $5/72$ (7%), b) encoding deficit profile = $24/72$ (33%), and c) retrieval deficit profile = $43/72$ (60%).

For the 67 individuals classified as having memory impairment, a logistic regression analysis was conducted with type of profile (encoding deficit or retrieval deficit) as the outcome and Total DRS score as the predictor. The model was not significant, $\chi^2(1) = 2.01, p = .16$. DRS Total score did not predict the type of memory profile, Wald $z(1) = -1.31, p = .19$, odds ratio (OR) = .972.

Exploratory analyses. Since the level of global cognitive impairment did not predict the type of memory profile, exploratory analyses were conducted to determine if a measure of global learning and memory impairment, Trials 1-5 Total on the CVLT-II, might be more sensitive to differentiating between those with a retrieval deficit profile and those without. Since this index was used to derive the original discriminant function algorithm, and thus to characterize memory profiles in this sample, it was not appropriate to use it as a predictor of these same memory profiles. Instead, new memory profiles were assigned to all 72 HD patients based only on the contrast of TRD - Trial 5 Recall. The following classifications were used based on scores on this contrast: 1) ≤ -0.5 = decline on recognition, 2) $0 - 0.5$ = no/minimal improvement, and 3) ≥ 1 = improvement on recognition.

Polynomial contrast codes were used to compare the three groups on Trials 1-5 Total and Trial 5 Recall. The first contrast compared those with improvement on recognition to the other two groups combined. The second contrast compared those in the “no/minimal improvement” group to those in the “decline on recognition” group. There were no significant differences between the three groups in Total DRS score, $F_{(2,69)} = .80, p = .45$. There were significant differences between the three groups on Trials 1-5 Total, $F_{(2,69)} = 7.04, p < .01$. Those who demonstrated improvement on recognition had

significantly lower scores on Trials 1-5 Total, on average, than the other two groups, $F_{(1,69)} = 7.63, p < .01$. Additionally, individuals who showed no/minimal improvement on recognition had significantly lower scores on Trials 1-5 Total than those who declined on recognition, $F_{(1,69)} = 6.05, p < .05$. There also were significant differences between the three groups on Trial 5 Recall, $F_{(2,69)} = 11.79, p < .001$. Those who demonstrated improvement on recognition had significantly lower scores on Trial 5 Recall to start, on average, than the other two groups, $F_{(1,69)} = 15.59, p < .001$. Additionally, individuals who showed no/minimal improvement on recognition had significantly lower scores on Trial 5 Recall than those who declined on recognition, $F_{(1,69)} = 7.36, p < .01$.

The two groups that did not demonstrate improvement on recognition (i.e., no/minimal improvement group and decline on recognition group) were then combined into one group. A logistic regression analysis was conducted with type of profile (improvement on recognition or not) as the outcome and Trials 1-5 Total as the predictor. The model was significant, $\chi^2(1) = 7.55, p < .01$. Trials 1-5 Total did predict the type of memory profile, Wald $z(1) = -2.52, p < .05$, odds ratio (OR) = .932. Thus, as Trials 1-5 Total increased, the odds of having a retrieval profile (i.e., improvement on recognition) decreased by a factor of .932.

Chapters 1 - 4, in part will be prepared for submission for publication of the material. Holden, Heather M.; Filoteo, J. Vincent; Corey-Bloom, Jody; Delano-Wood, Lisa; Sadler, Melody; Gilbert, Paul E. The dissertation author was the primary investigator and author of this material.

CHAPTER 4: DISCUSSION

Historically, memory dysfunction in HD has been characterized as a primary retrieval-based deficit. The most striking evidence for this conceptualization emerged from findings that individuals with HD demonstrate disproportionate improvement on yes/no recognition testing versus free recall, suggesting that memory impairment results from an inability to initiate systematic retrieval strategies when searching for information that has been successfully encoded and/or stored. However, findings are mixed with regard to memory performance in HD, with some studies supporting the recall/recognition discrepancy and others demonstrating no improvement on recognition testing. The purpose of the current study was to examine two possible reasons for the discrepant findings: 1) different operational definitions of the retrieval deficit may result in inconsistent findings, and 2) the neurocognitive mechanisms (e.g., encoding, retrieval) underlying memory impairment in HD may vary as a function of severity of global cognitive impairment.

Aim 1

Operational definitions of the retrieval deficit profile have been inconsistent across prior studies, with variations in the indices used to characterize recall, recognition, or both. The first aim of the current study was to determine if a particular contrast of recall and recognition on the CVLT-II is better at differentiating memory performance in individuals with HD, individuals with AD, and healthy adults. The results revealed that the contrast of TRD - Trial 5 Recall, when combined with Trials 1-5 Total and Total Cued Recall Intrusions, was superior to other contrasts at discriminating the three groups, and resulted in a correct classification rate of 77.6% (76.9% on cross-validation). These

results provide partial support for the hypotheses set forth in the current study. It was hypothesized that prior findings of Massman and colleagues (1992) would be replicated to some extent, but that the NRD - Trial 5 Recall contrast would emerge as the best measure for differentiating the HD group from the other two groups.

The six recognition/recall contrasts examined varied based on either the recognition discriminability index (NRD or TRD) or the recall index (Trial 5, LDFR, or LDFR Discriminability). NRD reflects the ability to endorse the 16 target items and reject 16 distractor items that are novel (i.e., not from the target or interference list). The 16 distractor items on the NRD index include eight semantically related and eight semantically unrelated words. TRD includes the 16 distractors from the interference list plus the 16 distractors from the NRD measure, and as such, measures the ability to reject various types of distractors. It was hypothesized that NRD would serve as a superior measure of recognition, as it reduces source interference and results in greater differences in recognition performance between HD and AD than TRD (Fine et al., 2008). However, the current findings revealed that varying the indices of recognition discriminability did not make a difference. When using the same recall index, pairs of contrasts using either NRD or TRD shared a high proportion of variance. Thus, while HD patients may gain some additional benefit from the NRD format, the difference was negligible in identifying the best recall/recognition contrast. Since pairs of contrasts using either NRD or TRD were highly redundant, the final set of contrasts included comparisons of the three recall measures with only one recognition discriminability measure. TRD was selected as the recognition measure, since it is the traditional measure of recognition

discriminability and is the measure that has been used consistently across prior CVLT studies.

In evaluating various recall measures, it was hypothesized that Trial 5 would be superior to the others in differentiating between the three groups. Trial 5 Recall was chosen because a comparison of performance on this initial learning trial with performance on *delayed* recognition not only captures improvement on recognition versus recall, but also may serve as a measure of retention (Massman et al., 1992). In contrast, when comparing performance on *delayed* recall and *delayed* recognition, any differences in retention are already accounted for and the contrast reflects only improvements in performance as a function of the recognition format. Thus, it was hypothesized that a comparison of Trial 5 recall to recognition would better capture differences between HD patients, who have intact retention and benefit from a recognition format, and AD patients, who demonstrate rapid forgetting and no benefit from recognition testing. The current findings supported this hypothesis, as the TRD - Trial 5 contrast emerged as the best recall/recognition contrast for discriminating between the three groups.

Further investigation of the TRD - Trial 5 contrast in the HD and AD groups revealed an interesting and unexpected finding. An examination of the group means revealed that the HD patients did not demonstrate improvement on TRD versus Trial 5, on average. Further, as a group, the AD patients showed a significant decrease in performance on Trial 5 compared to TRD. Thus, in the current sample, it appears the TRD - Trial 5 contrast captured poorer performance on recognition versus recall in the AD group, rather than improved performance on recognition versus recall in the HD

group. There are a number of possible explanations for the decline in performance in the AD group. First, performance on Trial 5 does not account for the number of intrusions generated on this trial. AD patients tend to generate a high number of intrusions on recall trials, and thus, obtain additional correct responses by chance alone (Delis et al., 2005). Thus, performance on Trial 5 in AD may be overestimated because it is not capturing level of correct recall relative to rate of intrusions. In contrast, TRD does account for the false positive rate on recognition, and thus, may have been more sensitive in measuring true recognition abilities. Second, decline in performance in the AD group may have been in part due to poor retention, as the recognition trial occurs after a delay (Massman et al., 1992).

Prior studies using the CVLT have demonstrated improvement on recognition versus recall in individuals with HD, as well as better TRD in HD patients compared with AD patients (Delis et al., 1991; Massman et al., 1990; Massman et al., 1992). Zizak and colleagues (2005) found that only 37% of HD patients exhibited improvement on recognition when using a conservative discrepancy score of ≥ 2 z-score difference; however, when using less stringent criteria of ≥ 1 for the discrepancy score, approximately 63% of the HD patients were characterized as having a retrieval deficit. In the current study, only 31% of the HD group demonstrated ≥ 1 z-score improvement on TRD compared with Trial 5 Recall. The inconsistent findings in the current study may be explained, in part, by differences in the way the TRD index is derived on the original CVLT and CVLT-II. The original CVLT used a nonparametric formula to calculate recognition discriminability, which represented the proportion of correct responses. The CVLT-II utilizes a parametric formula, which represents the absolute difference in

standard deviation units between the hit rate and false positive rate. While the parametric formula is better suited for unequal numbers of targets and distractors, it may not fully capture the magnitude of false positive errors (see Graves et al., 2017 for complete discussion). In addition, the original CVLT included only eight List B distractors and eight semantically related distractors, whereas the CVLT-II includes 16 of each type of distractor. Individuals with frontal-system dysfunction are more prone to source memory errors (Fine et al., 2008) and semantic confusion errors (Baldo, Delis, Kramer, & Shimamura, 2002). Graves and colleagues (2017) found no differences between AD and HD patients on standardized TRD scores as calculated on the CVLT-II. Comparable performance in these two groups may have resulted because TRD scores on the CVLT-II did not sufficiently capture the magnitude of false positive errors in the AD group and because increased source and semantic interference negatively impacted performance in the HD group (Graves et al., 2017). Thus, differences in recognition discriminability between the two groups may be less salient using CVLT-II TRD scores, and further, HD patients may demonstrate worse recognition performance on the CVLT-II compared to the original CVLT.

A current study in our laboratory (Graves et al., accepted) examined recognition performance in these two groups using a new recognition measure, List A vs. Novel/Unrelated Recognition Discriminability, on the CVLT-3 (Delis, Kramer, Kaplan, & Ober, 2017). This index is considered a purer measure of recognition discriminability, as it includes no List B or semantically related distractors. Findings from this study revealed that this new index, which minimizes source and semantic interference, may be more sensitive to differences in recognition performance in AD and HD, particularly in

those with moderate dementia severity (Graves et al., under review). Taken together, the results of these CVLT studies suggest TRD scores on the CVLT-II may be particularly susceptible to the types of errors made by HD patients, and as such, may reflect poorer recognition than original CVLT TRD scores or more pure measures of recognition on the CVLT-3.

Since the contrast of TRD - Trial 5 Recall may have captured poor retention in the AD group, and a subset of the HD patients did show improvement on recognition, an exploratory analysis was conducted to examine the utility of two separate indices representing these mechanisms. Retention (i.e., poorer recall after a delay) was represented by the contrast of LDFR - Trial 5 Recall and retrieval (i.e., improvement on recognition versus free recall) was represented by the contrast of TRD - LDFR. In a separate sample, Filoteo (personal communication, 2016) utilized these two indices, along with Trials 1-5 Total and Total Cued Recall Intrusions, and found that the set of four variables successfully discriminated between HD patients, AD patients, and healthy adults. In the current study, these four indices also provided good classification of individuals into correct diagnostic groups, with a total of 79.9% correctly classified (78.4% on cross-validation). This is a slight increase in classification rate (+2.3%) over the original set of three variables, which was driven by improved classification of AD patients. However, while the overall set of variables performed well in discriminating the three groups, the contrast of TRD - LDFR did not contribute significantly to the model. This suggests that, in the current sample, a measure of retention performed comparably to a measure of retrieval in differentiating the three groups. It is important to note that this

may be a unique finding in the current sample, given the relatively low rate of improvement on recognition in the HD group compared with other studies.

The present study replicated prior findings of Massman and colleagues (1992) and Filoteo (personal communication, 2016) in supporting the utility of Trials 1-5 Total, Total Cued Recall Intrusions, and TRD - Trial 5 Recall indices on the CVLT in discriminating between HD patients, AD patients, and healthy adults. Further, the present study demonstrated that different recall/recognition contrasts are not interchangeable and do not perform comparably in delineating characteristics of memory performance in these groups. Specifically, the contrast of TRD - Trial 5 Recall was superior to other contrasts in distinguishing between the three groups, which may be due to the ability of this contrast to capture multiple neurocognitive mechanisms. An improvement in TRD compared to Trial 5 Recall may represent a retrieval-based deficit, while a decline in performance from Trial 5 to TRD may to some extent capture poor retention, albeit to a lesser extent than a more pure retention measure such as LDFR - Trial 5 Recall. The results from the current study suggest that inconsistent findings regarding the retrieval deficit in HD may arise in part due to different operational definitions across studies. Discrepancies in the measurement of free recall may be particularly impactful, but variations in the recognition measures utilized also may have an effect. Though some diverse recognition measures may yield similar performance in HD, there is evidence to suggest that recognition indices that minimize source and semantic interference may be particularly sensitive to differences in recognition abilities in HD and AD patients (Fine et al., 2008; Graves et al., 2017; Graves et al., under review).

Importantly, while the contrast of TRD - Trial 5 Recall has been identified as the best for distinguishing between HD patients, AD patients, and healthy adults, the question remains as to whether it is the best contrast for characterizing a “retrieval deficit profile.” One might argue that identification of a retrieval-based deficit requires only an improvement on recognition versus free recall, thus any contrast that measures such a discrepancy would be appropriate. Based on the findings of the present study, and others before it (e.g., Massman et al., 1992), it is suggested that the “retrieval deficit profile” is not only represented by better recognition versus recall, but also by preserved retention that is not evident in individuals with consolidation deficits.

Aim 2

The second aim of the current study was to examine whether there is heterogeneity in the neurocognitive mechanisms of memory dysfunction in HD, and further, whether the level of global cognitive impairment predicts the type of memory profile (i.e., encoding deficit or retrieval deficit). Using a previously derived discriminant function algorithm (J. Vincent Filoteo, personal communication, 2016), each individual with HD was classified as having one of three memory profiles: normal, retrieval deficit, or encoding deficit. A small percentage of HD patients ($5/72 = 7\%$) were classified as having a normal memory profile. As hypothesized, in HD patients that exhibited memory impairment ($N = 67$), there was a mix of memory profiles, with 36% ($24/67$) demonstrating an encoding deficit profile and 64% ($43/67$) demonstrating a retrieval deficit profile. These findings are consistent with those of Zizak and colleagues (2005), who also found that only a subset of individuals with HD demonstrated a retrieval deficit profile. In that study, at most 63% of HD patients were classified as having a retrieval

deficit, and this was using more liberal criteria for defining the profile. One unique aspect of the current study, and the study by Zizak and colleagues (2005), is that each individual was classified with a particular memory profile, rather than examining differences in recall and recognition at a group level. In both of these studies, significant heterogeneity was observed, with only a subset of individuals with HD exhibiting a retrieval profile. Prior studies that compared these memory constructs at a group level may have inadvertently obscured important individual variability. Thus, methodological differences alone may explain some of the inconsistent findings in the extant literature.

Prior findings have suggested that the prevalence of the retrieval deficit profile in HD may vary based on the severity of global cognitive impairment. Zizak and colleagues (2005) split HD patients into unimpaired and impaired groups based on age-corrected scores on the DRS and found a higher rate of the retrieval deficit profile in those with global cognitive impairment. A meta-analysis examined recall and recognition across levels of dementia severity and found greater deficits in recall compared with recognition in the mild dementia group but no differences in the two memory constructs in the moderate/severe dementia group (Montoya, Pelletier, et al., 2006). Based on these findings, it was postulated that the profile of memory dysfunction in HD may change over the course of the disease. Specifically, it was hypothesized that primary retrieval deficits may characterize memory impairment at earlier stages of the disease process, whereas deficits in other memory mechanisms (e.g., encoding, consolidation) might emerge as the disease progresses. The present results did not provide support for this hypothesis, as Total DRS score did not predict the type of memory profile. In contrast to prior findings, the findings from the current study suggest that severity of global

cognitive impairment does not distinguish between those that demonstrate a retrieval deficit profile and those that do not.

There are several key differences between prior studies and the current study that make direct comparison of findings difficult. First, Zizak and colleagues (2005) identified the presence or absence of the retrieval deficit profile based on a contrast of recall and recognition, whereas the current study utilized a discriminant function algorithm with multiple CVLT-II indices to classify individuals into memory profile groups. Second, the prior study used the original CVLT, whereas the current study used the CVLT-II. As previously discussed, differences in the calculation of TRD between the two editions of the test may result in discrepant findings regarding recognition abilities in HD (Graves et al., 2017; Graves et al., under review). Third, in the prior study, HD patients were split into unimpaired and impaired groups based on age-corrected DRS scores, whereas the current study used raw DRS scores as a continuous variable. There was no normative data available for the age range of HD patients in the current study, thus it is difficult to ascertain whether the samples were comparable in range of dementia severity. Also of note, the current study and prior study by Zizak and colleagues (2005) examined differences in recall and recognition at the individual level. In contrast, the meta-analytic study (Montoya, Pelletier, et al., 2006) examined group means in recall and recognition across a multitude of studies, which may have obscured heterogeneity in memory profiles within the groups. Given the limited number of studies examining the retrieval profile as a function of global cognitive impairment, it is prudent to refrain from drawing definitive conclusions until studies with more similar methodology are available for comparison.

One possible explanation for the inconsistent findings across studies, and nonsignificant findings in the present study, is that the DRS may not be the most sensitive measure for assessing severity of cognitive dysfunction in HD. A recent review commissioned by the International Parkinson and Movement Disorder Society evaluated the use of specific cognitive assessment instruments in HD (Mestre et al., 2018). Of the 14 instruments evaluated, the Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005) was the only one that met more rigorous standards to be “recommended” for assessing severity of cognitive impairment in HD. Among the reasons the MoCA was recommended for use in HD, this measure: 1) has established psychometric properties in this population, 2) samples more cognitive domains than the MMSE, 3) has high sensitivity and specificity in detecting cognitive impairment in HD, and 4) is sensitive in detecting cognitive dysfunction across a range of disease severity. The DRS met enough criteria to be classified as “suggested” for assessing severity of cognitive dysfunction in HD, but the committee noted a lack of psychometric validation in this population (Mestre et al., 2017). One study revealed that only two DRS subscales (Initiation and Attention) accounted for significant variance in the level of functional impairment in HD (Peavy et al., 2010). Total scores on the MoCA, as well as scores across five cognitive domains sampled, are useful in detecting cognitive impairment across a range of symptom severity in HD (Gluhm et al., 2013). Further, the MoCA may be more sensitive to cognitive impairment in HD than the MMSE (Bezdicek et al., 2013). The MoCA also has been shown to differentiate between memory profiles in HD and AD, based on the availability of cued recall and recognition trials (Van Liew et al., 2016). Thus, while the DRS has

some utility in assessing cognitive function in HD, there are other measures that may be more sensitive in assessing the severity of cognitive dysfunction in this population.

There were no other measures of global cognitive impairment available in the current study; however, exploratory analyses evaluated the utility of an index of global learning and memory function, Trials 1-5 Recall, in distinguishing between those with a retrieval deficit profile and those without. Since this variable was used to derive the original discriminant function algorithm, and thus to characterize memory profiles in the preliminary analyses, it was not appropriate to use it as a predictor of these same memory profiles. Instead, new memory profiles were assigned to all 72 HD patients based only on the contrast of TRD - Trial 5 Recall. HD patients were classified into one of three groups (decline, no improvement, improvement) based on performance on TRD compared to Trial 5 Recall. The cutoff for improvement in performance was ≥ 1 z-score difference. The present findings revealed no differences between the three groups in Total DRS scores. However, the groups did differ on Trials 1-5 Recall, in that those with improvement on recognition (i.e., retrieval deficit profile) had lower scores, on average, than those who did not demonstrate improvement. This finding was opposite of what was expected, as prior studies have suggested that the retrieval deficit is more prevalent in individuals with more mild cognitive impairment (Montoya, Pelletier, et al., 2006). Further, individuals who demonstrated improvement on recognition also had lower scores on Trial 5 Recall, on average, than those who did not improve on recognition testing. Thus, it appears that the individuals who improved on recognition testing were more impaired on recall initially. This finding is consistent with that of Zizak and colleagues

(2005) who also found that HD patients with the retrieval deficit profile had worse initial recall than those who did not display this profile.

An additional exploratory analysis collapsed the “decline” and “no improvement” groups into one group, characterized as those without a retrieval deficit profile. A logistic regression analysis revealed that Trials 1-5 Recall significantly predicted the type of memory profile (i.e., retrieval deficit or not). Specifically, as Trials 1-5 Recall scores increased, the odds of having a retrieval deficit profile decreased. Again, this is contrary to prior findings, and to the original hypothesis of the current study, that individuals with milder cognitive impairment demonstrate a retrieval deficit. These findings warrant further investigation, as this is the first study to utilize a single measure of global learning and memory impairment, rather than global cognitive impairment, as a predictor of the retrieval deficit profile. The current findings suggest that individuals with a retrieval deficit profile may have more severe memory impairment than those without, but they may not be more cognitively impaired overall.

As hypothesized, the present study revealed heterogeneity in the neurocognitive mechanisms of memory impairment in HD, with only 64% of memory-impaired individuals demonstrating a retrieval deficit profile. These findings are consistent with a prior study that also examined differences in recall and recognition at an individual level. This methodology may be preferable to examining these constructs at a group level, which may obscure significant variability in memory profiles in this population. In contrast to prior findings, results from the current study did not support the hypothesis that the type of memory dysfunction (i.e., primary encoding or retrieval deficit) varies as a function of the level of global cognitive impairment. However, it is possible that these

inconsistent findings may be explained by methodological differences or utilization of a less sensitive measure of cognitive dysfunction in HD. Additional analyses revealed that a measure of global learning and memory function did distinguish between those that demonstrate a retrieval deficit profile and those that do not. Contrary to expectations, those with a retrieval deficit profile were found to have more severe global memory impairment and worse initial recall than those who do not display this profile. Thus, the severity of memory impairment specifically, rather than global cognitive impairment, may better explain the heterogeneity in memory profiles observed in HD.

Limitations

Several limitations of the current study should be addressed. First, the DRS was utilized to characterize dementia severity. As previously discussed, there may be more sensitive measures for assessing severity of cognitive dysfunction in HD. Additionally, raw DRS scores were used to match AD and HD individuals for level of dementia severity. While this is a common approach in memory disorders literature, the HD cohort is significantly younger than the AD cohort. Thus, similar raw scores on this measure may not reflect a similar level of dementia severity. Age-corrected scores would have provided a better measure of the true level of impairment, but norms are not available for the age range in the current HD sample.

For Aim 1, the overall classification rates were close to twice that which would be expected by chance alone, which indicates good classification. However, these classification percentages were still lower than those of prior studies, which were generally around 90%. Possible reasons for poorer discrimination in the current study have been discussed, including variations in the calculation of TRD on the CVLT-II.

However, these discrepancies may also reflect something unique about the current sample. Finally, the current sample of AD patients is relatively small, and further, is smaller than the other two groups. Future investigations with larger samples of AD patients would be helpful in determining if the current results can be replicated.

Future Directions

Findings from the current study highlight several avenues for future research. First, future investigations could aim to identify other predictors of memory profiles in HD, including other indices of disease severity and neuropathological changes. Further, while the current results suggest that global cognitive impairment does not explain heterogeneity in memory dysfunction in HD, other studies could investigate this question using more sensitive measures of cognitive impairment in this population. Second, future studies could aim to enhance understanding of memory dysfunction in those individuals that do not demonstrate a retrieval deficit profile. Prior research suggests some of these individuals may exhibit normal memory functioning, while others may have predominant encoding or consolidation difficulties. Further, while a subset of individuals may demonstrate comparable recall and recognition performance, this group also may be heterogeneous. For example, a z-score discrepancy of zero would have markedly different interpretations for an individual performing in the normal range versus someone in the impaired range. Third, future studies could examine the prevalence of the retrieval deficit profile in HD using purer measures of recognition, such as the List A vs. Novel/Unrelated on the CVLT-3. Finally, future investigations could investigate the functional implications for different types of memory dysfunction and begin to develop interventions that target specific neurocognitive mechanisms.

Summary

The present study contributes to the extant literature in several important ways. First, the present findings revealed that not all contrasts of recall and recognition are equally effective in distinguishing between memory performance in HD patients, AD patients, and healthy adults. On the CVLT-II, the contrast of TRD - Trial 5 Recall yielded the best discriminatory power, which may be due to the ability of this contrast to capture both retrieval and retention processes. Second, the current study provided additional evidence that there is heterogeneity in the neurocognitive mechanisms underlying memory dysfunction in individuals with HD, with only about 2/3 of individuals demonstrating the classic “retrieval deficit profile.” Third, methodological similarities in the two studies that have identified this heterogeneity suggest that examining recall and recognition discrepancies at the individual level may provide the most precise means for characterizing memory dysfunction in HD. Fourth, findings from the current study suggest that the severity of global cognitive impairment may not explain variability in memory profiles in HD, though additional studies are needed to resolve inconsistent findings. Fifth, preliminary findings suggest that individuals who demonstrate a retrieval deficit profile may have more severe memory impairment than those who do not display this profile. Finally, severity of overall memory impairment, rather than global cognitive impairment, may better explain variability in memory dysfunction in HD.

The present study enhances understanding of memory dysfunction in HD and may help to address some of the inconsistent findings in the extant literature. Findings from the current study offer important insights about the most sensitive measures and approaches for characterizing memory dysfunction in HD. The current findings also

highlight the heterogeneity and complexity of memory dysfunction in HD and suggest possible constructs for explaining some of this variability. Improved understanding of the course of memory dysfunction in HD may inform interventions that can target specific neurocognitive mechanisms at different stages of the disease. Finally, Huntington's disease has historically served as the prototypical model for memory dysfunction resulting from subcortical pathology. Thus, enhanced understanding of the nature of memory dysfunction in HD has far reaching implications for understanding of other neurological disorders and memory function in general.

Chapters 1 - 4, in part will be prepared for submission for publication of the material. Holden, Heather M.; Filoteo, J. Vincent; Corey-Bloom, Jody; Delano-Wood, Lisa; Sadler, Melody; Gilbert, Paul E. The dissertation author was the primary investigator and author of this material.

TABLES

Table 1. *Characteristics of Huntington's disease patients, Alzheimer's disease patients, and healthy adult comparison group*

Variable	HD (n=39)	AD (n=27)	HA (n=70)
Sex (% men)	35.9%	70.4%	40.0%
Age (years)	50.10 (10.67)	77.33 (8.31)	59.38 (12.68)
Education (years)	14.13 (2.10)	14.89 (2.87)	14.71 (1.99)
DRS Total Score	121.72 (7.39)	119.19 (7.25)	---

Note. Data represent means and standard deviations. HD = Huntington's disease patients, AD = Alzheimer's disease patients, HA = Healthy Adult Comparison Group. DRS = Dementia Rating Scale.

Table 2. *Description of relevant CVLT-II Variables*

Variable	Description
Trial 5 Recall	Number of List A words recalled on the final learning trial
Trials 1-5 Total	Total number of List A words recalled across Trials 1-5
Short Delay Free Recall (SDFR)	Number of List A words recalled immediately after presentation of List B (w/o repeat presentation of List A)
Short Delay Cued Recall	Number of List A words recalled with semantic cues immediately after Short Delay Free Recall
Long Delay Free Recall (LDFR)	Number of List A words recalled after a 20-minute delay
Long Delay Cued Recall	Number of List A words recalled with semantic cues immediately after Long Delay Free Recall
Total Cued Recall Intrusions	Total number of nontarget words reported on short- and long- delay cued recall trials
LDFR Discriminability	Total recall on LDFR after accounting for intrusion rate
Total Recognition Discriminability	d' measure of ability to endorse target words and reject all 32 distractor words ¹
Novel Recognition Discriminability	d' measure of ability to endorse target words and reject the 16 distractor words that do not appear on either list ¹

¹ There are four categories of distractor words: 1) *List B shared category* – eight words from List B that are from categories represented on both lists; 2) *List B nonshared category* – eight words from List B that are from unique categories (i.e., not found on List A); 3) *Neither List Prototypical* – eight words that are not found on either list, but are prototypical members of categories on List A; 4) *Neither List Unrelated* – eight words that are not found on either list and are not semantically related to categories on either list

Table 3. Classification results for original and cross-validated groups using Trials 1-5
 Total Recall, Total Cued Recall Intrusions, and TRD - Trial 5 Recall contrast

		Predicted Group			
		Group	Healthy Adults	HD Patients	AD Patients
Original ^a	Count	HA	62	3	5
		HD	1	29	9
		AD	2	10	13
	Percent	HA	88.6	4.3	7.1
		HD	2.6	74.4	23.1
		AD	8.0	40.0	52.0
Cross-valid ^b	Count	HA	62	3	5
		HD	1	28	10
		AD	2	10	13
	Percent	HA	88.6	4.3	7.1
		HD	2.6	71.8	25.6
		AD	8.0	40.0	52.0

^a 77.6% of original grouped cases correctly classified

^b 76.9% of cross-validated grouped cases correctly classified

Note. HA = Healthy Adults, HD = Huntington's disease patients, AD = Alzheimer's disease patients; TRD = Total Recognition Discriminability

Table 4. *Group data for Trials 1-5 Total Recall, Total Cued Recall Intrusions, and TRD - Trial 5 Recall contrast*

Variable	HD (n=39)	AD (n=25)	HA (n=70)
Trials 1-5 Total Recall	29.02 (10.08)	34.32 (12.63)	60.24 (9.83)
Total Cued Recall Intrusions	1.14 (1.61)	2.32 (2.23)	-.11 (.78)
TRD - Trial 5 Recall	.23 (1.20)	-.56 (1.18)	-.14 (.92)

Note. Data represent means and standard deviations. HD = Huntington's disease patients, AD = Alzheimer's disease patients, HA = Healthy Adults.

Table 5. Classification results for original and cross-validated groups using Trials 1-5 Total Recall, Total Cued Recall Intrusions, LDFR - Trial 5 Recall contrast, and TRD - LDFR contrast

		Predicted Group			
		Group	Healthy Adults	HD Patients	AD Patients
Original ^a	Count	HA	62	3	5
		HD	1	30	8
		AD	2	8	15
	Percent	HA	88.6	4.3	7.1
		HD	2.6	76.9	20.5
		AD	8.0	32.0	60.0
Cross-valid ^b	Count	HA	62	3	5
		HD	1	29	9
		AD	2	9	14
	Percent	HA	88.6	4.3	7.1
		HD	2.6	74.4	23.1
		AD	8.0	36.0	56.0

^a 79.9% of original grouped cases correctly classified

^b 78.4% of cross-validated grouped cases correctly classified

Note. HA = Healthy Adults, HD = Huntington's disease patients, AD = Alzheimer's disease patients; LDFR = Long Delay Free Recall, TRD = Total Recognition Discriminability

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