TEMPORAL ORDER MEMORY DYSFUNCTION IN
HUNTINGTON’S DISEASE

A Thesis
Presented to the
Faculty of
San Diego State University

In Partial Fulfillment
of the Requirements for the Degree
Master of Arts
in
Psychology

by
Adrienne Elena Collazo

Fall 2010
SAN DIEGO STATE UNIVERSITY

The Undersigned Faculty Committee Approves the
Thesis of Adrienne Elena Collazo:

Temporal Order Memory Dysfunction in
Huntington’s Disease

Paul Gilbert, Chair
Department of Psychology

Linda Gallo
Department of Psychology

Sarah Mattson
Department of Psychology

Roger Simmons
School of Exercise and Nutritional Sciences

November 19th, 2010
Approval Date
DEDICATION

This thesis is dedicated to my father, Richard Collazo. Your love and wisdom has helped get me through all of the ups and downs, so that I may continue to stay focused and awake. I am so grateful to have you as a friend and mentor. Thank you for supporting me in my quest for an independent and professional life.
ABSTRACT OF THE THESIS

Temporal Order Memory Dysfunction in Huntington’s Diseases
by
Adrienne Elena Collazo
Master of Arts in Psychology
San Diego State University, 2010

Huntington’s disease (HD) is a genetically inherited neurological condition marked by motor, cognitive, and behavioral disturbances. The identification of novel indicators of disease progression are important for the diagnosis and assessment of HD. Findings from previous studies involving humans and animals with lesions in the frontal cortex suggest that the frontal lobes play a major role in memory for the temporal order of sequences of events. Since HD results in damage to the frontostriatal circuits, temporal order memory may be particularly sensitive to neuropathological degeneration in HD and may serve as a cognitive marker of disease progression. In the present study, HD patients and normal controls were administered a visuospatial temporal order memory task on a computerized radial eight-arm maze. On the study phase of each trial, participants were presented with a random sequence of circles shown one at a time at the end of each of the eight arms. On the choice phase, participants were presented with a circle at the end of two of the study phase arms and were asked to choose the circle that occurred earliest in the sequence. In order to vary temporal interference, parametric manipulations of the temporal metric were carried out by systematically changing the temporal separation lag between the two circles in the choice phase. Prior research demonstrates that temporal order memory is superior for items occurring further apart in a sequence than items that are temporally closer in time. This temporal lag effect is assumed to occur because there is greater temporal interference between temporally proximal items in a sequence than temporally distal items. The data indicated that HD patients were significantly impaired on the temporal order memory task compared to controls. The data also revealed that overall performance improved as temporal separation lag increased. Normal controls outperformed HD patients on the 0, 4, and 6 temporal separation lag trials; however, there were no significant between group differences on the 2 temporal separation lag trials. These results indicate that temporal order memory is impaired in HD patients even when temporal interference is minimal. The present findings, combined with a previously published study from our lab, suggest that temporal order memory tasks may serve as an early marker of phenoconversion to manifest HD and a useful measure of disease progression.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>CHAPTER</th>
<th>PAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABSTRACT</td>
<td>v</td>
</tr>
<tr>
<td>LIST OF TABLES</td>
<td>viii</td>
</tr>
<tr>
<td>LIST OF FIGURES</td>
<td>ix</td>
</tr>
<tr>
<td>ACKNOWLEDGMENTS</td>
<td>x</td>
</tr>
<tr>
<td>1 INTRODUCTION</td>
<td>1</td>
</tr>
<tr>
<td>Neuropathology</td>
<td>2</td>
</tr>
<tr>
<td>Motor Impairment</td>
<td>4</td>
</tr>
<tr>
<td>Cognitive Disturbances</td>
<td>5</td>
</tr>
<tr>
<td>Behavioral Problems</td>
<td>6</td>
</tr>
<tr>
<td>Premanifest HD</td>
<td>8</td>
</tr>
<tr>
<td>Temporal Order Memory in HD</td>
<td>9</td>
</tr>
<tr>
<td>2 METHODS</td>
<td>11</td>
</tr>
<tr>
<td>Participants</td>
<td>11</td>
</tr>
<tr>
<td>Temporal Order Memory Task</td>
<td>12</td>
</tr>
<tr>
<td>Neuropsychological Measures</td>
<td>15</td>
</tr>
<tr>
<td>3 RESULTS</td>
<td>16</td>
</tr>
<tr>
<td>Temporal Order Memory Task</td>
<td>16</td>
</tr>
<tr>
<td>Neuropsychological Measures</td>
<td>18</td>
</tr>
<tr>
<td>Section</td>
<td>Page</td>
</tr>
<tr>
<td>----------------------------------------------</td>
<td>------</td>
</tr>
<tr>
<td>Pearson $r$ Correlations</td>
<td>20</td>
</tr>
<tr>
<td>4 DISCUSSION</td>
<td>22</td>
</tr>
<tr>
<td>Limitations</td>
<td>29</td>
</tr>
<tr>
<td>Conclusion and Implications</td>
<td>30</td>
</tr>
<tr>
<td>REFERENCES</td>
<td>31</td>
</tr>
</tbody>
</table>
LIST OF TABLES

Table 1. Mean (± Standard Error) Demographics for HD Patients and Normal Controls ........................................ 12

Table 2. Results From a 2 x 4 ANOVA With Group (HD Patients, Normal Controls) as the Between Groups Factor and Lag (0, 2, 4, 6) as the Within Groups Factor ........................................ 16

Table 3. Results From One-Way ANOVAs With Group (HD Patients, Normal Controls) as the Between Groups Factor and the Standardized Neuropsychological Measures as the Within Groups Factor ............................. 19

Table 4. Pearson $r$ Correlations Between Performance on the Temporal Order Memory Task and Performance on the Standardized Neuropsychological Measures With Significant Differences Between Groups (HD Patients, Normal Controls) .................................................. 21
LIST OF FIGURES

PAGE

Figure 1. Computer adaptation of the 8-arm radial maze in the temporal order task ........................................... 12

Figure 2. Sample phase temporal sequence displaying the locations of the circle on the 1st through 8th arm in a random sequence ................. 13

Figure 3. Choice phase temporal sequence displaying a 6 temporal separation lag trial, a 2 temporal separation lag trial, and a 0 temporal separation lag trial .......................................................... 14

Figure 4. Mean percent correct performance as a function of temporal separation lag for HD patients and normal controls ................................. 17
ACKNOWLEDGMENTS

I would like to thank my committee members, Paul Gilbert, Linda Gallo, Sarah Mattson, and Roger Simmons. Your input, time, and efforts are greatly appreciated. I would like to especially thank Paul for always believing in me and pushing me to reach my potential. Without your guidance I would not be on the path to becoming a clinical psychologist. I would also like to thank my research assistant Corey Hightower for helping to test controls and make this body of work possible. Thank you to Jody Goldstein for being such a crucial element in this project’s success by providing me with contacts for recruitment. I would like to express my gratitude to all my lab mates who have been wonderful friends and a pleasure to work with throughout this amazing experience. Finally, I would like to thank all of my family and friends who are my pillar of support and my reason for continuing to strive to reach my goals.
CHAPTER 1

INTRODUCTION

Huntington’s disease (HD) is a severe, progressive degenerative neurological condition. Symptoms that stem from the disorder include motor impairments, cognitive decline, and psychiatric manifestations. In 1993, it was discovered that the offspring of a parent carrying the genetic mutation, referred to as the Huntingtin gene, have a 50% chance of inheriting the fully penetrant disease. The mutated gene takes form as an expansion of the three nucleotides cytosine, adenine, and guanine (CAG) on the small arm of chromosome 4 (Huntington’s Disease Collaborative Research Group, 1993). The average person has anywhere from 10 to 26 CAG repeats, whereas individuals with 39 or more repeats will develop HD in their lifetime. Age of onset of HD typically occurs between 35 and 44 years of age, but can vary dramatically. Previous research has shown paternal heritance and CAG repeat length as possible predictors of onset age (Brandt et al., 1996; Myers, 2004; Swami et al., 2009). Unfortunately, there is no cure for HD, and on average, an afflicted individual dies within 15-17 years after symptoms develop (Aubeeluck & Wilson, 2008). Approximately 4 to 10 people per 100,000 in the United States currently live with HD, and about 250,000 are at risk (Leegwater-Kim & Cha, 2004). Therefore, it is critical that studies are conducted to better understand this disease.
NEUROPATHOLOGY

Extensive widespread atrophy of the brain is the hallmark gross pathological symptom in HD, with the most affected area being the striatum (Bates, Harper, & Jones, 2002). Deterioration of the striatum generally proceeds in a dorsal to ventral, medial to lateral, and anterior to posterior fashion. Early in the disease, damage to the medial and tail areas of the caudate nucleus can be documented, with further detrimental changes occurring in the globus pallidus, putamen, and the nucleus accumbens in later HD (Alexander & Crutcher, 1990). Along with severe damage to the striatum, previous data supports evidence of deterioration in the cerebral cortex as well as abnormalities in the diencephalon, hippocampus, surrounding parahippocampal cortices, and the cerebellum (Braak & Braak 1992; de la Monte, Vonsattel, & Richardson, 1988). Increased size of the lateral ventricles is also one of the major indications of atrophy in HD (Vonsattel et al., 1985). Cell loss in the form of striatal medium spiny neurons in the caudate nucleus and putamen is the first to be observed, along with a build-up of astroglia (Sharp & Ross, 1996). Interestingly, medium aspiny neurons are conserved even though they contain large amounts of the huntingtin protein, suggesting that medium aspiny neurons may be unaffected by the mutation (Sapp et al., 1997). The loss of medium spiny neurons results in a decrease in gamma-aminobutyric acid (GABA), which leads to a decrease of inhibitory signals to the globus pallidus and the thalamus, and an increase in excitatory signals to the motor cortices (Harris et al., 1996; O’Shea, 1997; Perry, Hansen, & Kloster, 1973; Walker, 2007). Striatal dysfunction also is evidenced by a decrease in dopamine (D2) receptor binding (Leenders, Frackowiak, Quinn, & Marsden, 1986).
Deterioration of the basal ganglia and consequent degeneration of frontal-striatal circuitry is suspected to be a primary cause of the motor, cognitive, and behavioral symptoms in HD (Brandt & Butters, 1997; Cummings, 1993). A number of the cognitive deficits displayed in HD may be a result from damage to the dorsolateral prefrontal circuit. Patients with lesions in the dorsolateral prefrontal cortex demonstrate similar cognitive deficits in executive functioning as HD patients. For example, patients demonstrate difficulty maintaining or shifting sets, decreased verbal fluency, exhibit weak spatial working memory, and poor planning skills (Benton, 1968; Malloy & Richardson, 1994; Milner, Petrides, & Smith, 1985). Due to the afferent and efferent connections between the basal ganglia and the frontal lobes (Alexander, DeLong, & Strick, 1986), the vast majority of pathological studies have focused on investigating the frontal lobes in HD. Decreased projections from the basal ganglia affect the cortical areas of the HD brain, resulting in a diminished prefrontal cortex volume (Montoya, Price, Menear, & Lepage, 2006; Selemon, Rajkowska, & Goldman-Rakic, 2004). Aylward et al. (1998) used magnetic resonance imaging (MRI) and found a decrease in frontal lobe volume in HD patients experiencing moderate symptoms, but not in patients experiencing mild symptoms. The largest decrease in frontal lobe volume was seen in white matter. It has been suggested that frontal lobe atrophy may be a consequence of retrograde degeneration subsequent to striatal pathology (Hedreen, Peyser, Folstein, & Ross, 1991), yet others contend that deterioration of the frontal lobe is a primary pathology in HD (review in Selemon et al., 2004).

A study carried out by Macdonald and Halliday (2002) revealed degeneration of long projecting SMI32 immunopositive pyramidal neurons in the primary motor cortex, suggesting that HD negatively affects the corticostriatal pathways. Moreover, lessening of
short projecting pyramidal neurons in the premotor cortex also was discovered (Sotrel, Williams, Kaufman, & Myers, 1993). Neurophathological changes in HD brains also were found to affect the function of the entorhinal cortex, and in turn the hippocampus, due to the transfer of information between the two structures in later HD (Braak & Braak, 1992). Overall neurodegeneration of the brain as a result of HD eventually causes the affected brain to weigh as little as 25% less than the average brain at death (Andrews & Brooks, 1998).

**MOTOR IMPAIRMENT**

Of all the motor symptoms associated with HD, chorea is the most prominent, and manifests itself early in the disease as an amplification of usual restlessness and a change in facial expressions (O’Shea, 1997; Walker, 2007). Initially, HD patients may be able to conceal these symptoms, but as the disease progresses chorea becomes involuntary (extrapyramidal), and is even more pronounced in HD patients when triggered by stress, depression, and anxiety (Rosenblatt, Ranen, Nance, & Paulsen, 1999). In later stages of HD, chorea is replaced by bradykinesia, characterized by acute slowness of movement, and rigidity. Dystonic movements, which are muscle contractions that distort the body, also are observed in later HD (Aubeeluck & Wilson, 2008). Eventually, HD patients become emaciated, spastic, and bedridden (O’Shea, 1997).

Additional abnormalities include deficits in fine motor skills such as oculomotor problems, which are widely seen in the affected HD population (Leigh, Newman, Folstein, Lasker, & Jensen, 1983). Atrophy of the basal ganglia is thought to be the cause of a noticeable decrease in saccades in HD, along with a weakened ability to maintain stable fixation (Lasker & Zee, 1997; Pelsch, Hoffman, Armstrong, Pari, & Munoz, 2008). Due to
continuous loss of muscle control, difficulties in swallowing known as dysphagia (Leopold & Kagel, 1985), and speech articulation with irregular movements of the jaw known as dysarthria (Podoll, Caspary, Lange, & Noth, 1988) are observed in HD. Disturbances in motor speed and gait are exhibited throughout the disease, and serve as good measures of the progression of HD (Folstein, Franz, Jensen, Chase, & Folstein, 1983).

**COGNITIVE DISTURBANCES**

Often the dementia in HD begins with executive dysfunction. Daily tasks involving organization, planning, controlling emotions, and attention become increasingly difficult to perform as the disease progresses (Hakimian, 2000; Josiassen, Curry, & Mancall, 1983). Extensive atrophy of the brain leads to further cognitive dysfunction including diminished motivation, difficulties with abstract reasoning, and a gradual decrease in speed of information processing (Aubeeluck & Wilson, 2008; Lineweaver, Salmon, Bondi, & Corey-Bloom, 2005; Ward et al., 2006). Due to the nature of these cognitive deficits and the deterioration of the frontal-subcortical connections, HD is generally thought of as a subcortical dementia. In contrast, individuals suffering from Alzheimer’s disease experience amnesia, agnosia, apraxia, and aphasia, known as cortical dementia (Montoya, Price, et al., 2006; Zakzanis, 1998).

The major memory deficits observed in HD patients may stem from impairment of organization during information retrieval. Prior research has shown a dissociation between recall and recognition memory in HD, revealing that HD patients have difficulty with tests of recall (e.g., free recall of word lists, paired associate learning). In contrast, recognition memory has been shown to remain roughly intact (Butters, Wolfe, Martone, Granholm, &
Other memory impairments that are associated with HD involve deficits in episodic memory, short-term and long-term memory, and procedural memory (Aubeeluck & Wilson, 2008; Montoya, Pelletier, et al., 2006; Montoya, Price, et al., 2006). Problems related to memory are noticeable throughout the disease and may serve as an early marker of cognitive dysfunction in HD (Pirogovsky et al., 2009).

Individuals with HD also have difficulty with verbal fluency tasks (Alexander, Benson, & Stuss, 1989). Studies revealed that HD patients show poor performance on both semantic and phonemic fluency, with a larger impairment in semantic fluency (Henry, Crawford, & Phillips, 2005; Zakzanis, 1998). Another characteristic of cognitive decline in HD is the apparent lack of ability to shift or allocate attention (Hanes, Andrewes, & Pantelis, 1995; Lawrence et al., 1996), which is especially obvious when it is necessary to internally control attentional shifts (Sprengelmeyer, Lange, & Homberg, 1995). Visuospatial deficiencies exhibited by HD patients become more profound in the later stages of the disease, and include deficits in personal orientation and spatial manipulation (Brouwers, Cox, Martin, Chase, & Fedio, 1984; Mohr, Brouwers, Claus, Mann, & Fedio, 1991). Overall performance on tests of language show that comprehension remains mostly intact, but participation in lengthy conversation and initiation of verbal communication tends to diminish (Brandt & Butters, 1997).

**Behavioral Problems**

In addition to cognitive dysfunction, individuals diagnosed with HD struggle with myriad of behavioral symptoms as the brain deteriorates over time. Major depression is one
of the most common psychiatric problems found in HD and is characterized by a steady low
mood, decrease in energy, irregular sleep, low self-esteem, feelings of remorse, and a reduced
desire for food (Paulsen et al., 2005). Prior studies have linked depression with dysfunction
in frontal cortices in HD (Mayberg, 2001; Mayberg et al., 1992). Irritability and often
aggression are displayed by affected individuals, and are considered to be a consequence of
depression, or possible side effects of medications prescribed to treat HD symptoms (Harper,
1996).

Also apathy is a frequent behavioral disturbance exhibited in HD patients. Apathy is
generally observed in the middle to later stages of HD, and is distinguished by a lack of
motivation, and a loss of interest in activities associated with daily life (Rosenblatt et al.,
1999). In a study by Kingma, Van Duijn, Timman, Van Der Mast, and Roos (2008),
symptomatic and premanifest HD gene carriers were found to be significantly more irritable,
 apathetic, and depressed than individuals in the control group. Furthermore, evidence to
support apathy as a strong marker of disease progression is supported by the finding that
premanifest HD gene carriers demonstrated notably less apathy than individuals with
manifest HD.

In certain cases, HD patients may suffer from emotional blunting and withdrawal,
which are observed in both schizophrenia and HD. The appearance of these symptoms may
sometimes occur prior to the manifestation of motor symptoms, and lead to a misdiagnosis of
schizophrenia, as opposed to an accurate identification of manifest HD (Rosenblatt et al.,
1999). Hypossexual desire is often a symptom of HD. One study reported 62% of HD patients
having experienced a significant decrease in libido (Fedoroff, Peyser, Franz, & Folstein,
1994). Less frequently, patients may experience psychotic symptoms, such as delusions and
hallucinations in later stages of the disease (Folstein & Folstein, 1983). Increased rates of suicide have been documented in individuals who show early signs of the HD, but have not been diagnosed, and occur in about 7% of cases cross culturally (O’Shea, 1997).

**PREMANIFEST HD**

As mentioned earlier, the autosomal dominant expansion of the CAG trinucleotide repeat is responsible for HD. In essence, if one parent has the mutated HD gene, their children have a 50% chance of receiving the gene. The 1993 discovery of the genetic mutation has made it possible for at-risk offspring of individuals with HD to have their genetic status tested with 99% accuracy (Huntington’s Disease Collaborative Group, 1993). The ability to identify individuals who are premanifest gene carriers for HD has led to several studies examining the neuropathological symptoms and changes that are experienced by individuals who carry the mutated HD gene, but do not yet display clinically diagnosable symptoms of the disease. Typically, HD is diagnosed when an individual begins to show signs of motor impairment, but studies also have found evidence of cases where cognitive dysfunction appeared before motor symptoms of the disease (Hahn-Barma et al., 1998; Kirkwood et al., 1999; Pirogovsky et al., 2007; Pirogovsky et al., 2009).

Previous neuropsychological investigations have revealed the development of measurable cognitive changes before clinical onset of HD (Diamond et al., 1992; Foroud et al., 1995; Hahn-Barma et al., 1998; Lawrence et al., 1998; Lemiere, Decruyenaere, Evers-Kiebooms, Vandenbussche, & Dom, 2002; Paulsen, Ready, Hamilton, Mega, & Cummings, 2001; Paulsen, Zhao, et al., 2001; Pirogovsky et al., 2009; Snowden, Craufurd, Thompson, & Neary, 2002); however, other studies comparing gene carriers and normal controls have
failed to find significant differences in cognitive functioning (de Boo et al., 1997; Brandt, Shpritz, Codori, Margolis, & Rosenblatt, 2002). Most of the cognitive deficits in premanifest gene carriers may be associated with executive functioning, such as difficulties found in sustained attention and planning initiation (Hahn-Barma et al., 1998; Kirkwood et al., 1999; Lemiere et al., 2002; Pirogovsky et al., 2009). Gene carriers perform poorly on tasks that have shown to be related to frontal lobe functioning such as digit symbol, picture arrangement, source memory, verbal fluency, and block span tasks (Foroud et al., 1995; Kirkwood et al., 1999; Lawrence et al., 1998; Lemiere et al., 2002; Pirogovsky et al., 2007; Pirogovsky et al., 2009). Therefore, studies that identify cognitive disturbances in premanifest gene carriers may help to identify cognitive biomarkers for phenocoversion to HD.

**TEMPORAL ORDER MEMORY IN HD**

The function of temporal order memory is to aid in the organization of events as they occur in time. Temporal order memory may require executive function processes, which are impaired in HD, and are necessary to carry out normal activities such as coordinating future activities. Episodic memory also is dependent upon temporal order memory in that it is necessary in the process of arranging and recalling the sequence of experiences in daily life (Gilbert, Kesner, & Lee, 2001). Fuster (2001) proposed that the prefrontal cortex plays a major role in “temporal integration of information for the attainment of prospective behavioral goals” (p. 323). It is hypothesized that the prefrontal cortex is important in the organization of events because of its role in the mediation of cross-temporal contingencies
Thus, the prefrontal cortex may temporally structure pieces of information that are dispersed spatially across cortical networks.

Prior studies have focused on examining temporal order memory in humans, primates, and rats. Findings have shown that humans and animals with lesions in the frontal lobe experienced significant difficulty performing tasks involving temporal order memory (Chiba, Kesner, & Gibson, 1997; Inoue & Mikami, 2006; Kesner, Hopkins, & Fineman, 1994; McAndrews & Milner, 1991; Milner, Corsi, & Leonard, 1991; Ninokora, Mushiake, & Tanji, 2004). These results indicate that the activity of the frontal cortex may aid in the temporal structuring of sequences of events. HD affects the frontostriatal circuits, thus, tests of temporal order memory may be particularly sensitive to cognitive deficits associated with HD. A study by Pirogovsky et al. (2009) demonstrated that premanifest gene carriers for HD close to estimated disease onset performed significantly worse on a temporal order memory task compared to premanifest gene carriers further from estimated disease onset and normal controls. Gene carriers close to estimated disease onset were not impaired relative to controls on most tasks of executive function, but demonstrated memory impairment on the HVLT-R Hopkins Verbal Learning Test—Revised. These results support that the temporal order memory task may be especially sensitive to neuropathological impairment even in individuals who carry the HD gene, but do not meet diagnostic criteria. To date, no studies have examined temporal order memory in the HD patient population. The present study investigated the effects of manifest HD on temporal order memory.
CHAPTER 2

METHODS

PARTICIPANTS

There were a total of 20 participants in the study, including participants with clinically diagnosed HD \( n = 10 \), and age-gender-education matched normal controls \( n = 10 \). Eight female, and 12 male participants were recruited. Originally, 10 HD patients and 10 normal controls were tested, but due to administrative error, 2 normal controls were excluded from further analysis. Two age-gender-education matched controls from an existing database in Dr. Paul Gilbert’s lab were randomly selected to replace the individuals excluded from the analysis. The individuals completed all tests with the exception of the BDI-II and the VSLT. Mean participant ages and years of education are provided in Table 1. One-way analysis of variance tests with group (HD patients, normal controls) as the independent variable, revealed that there were no significant differences between groups for age \( F(1, 18) = .000, p = 1.00 \), or years of education completed \( F(1, 18) = .323, p = .577 \). All participants were provided with written informed consent, and all procedures were approved by San Diego State University and the University of California San Diego prior to participation. Testing required approximately 2 to 2.5 hours for each individual, and participants were compensated $20 an hour for their time and effort.
Table 1. Mean (± Standard Error) Demographics for HD Patients and Normal Controls

<table>
<thead>
<tr>
<th></th>
<th>Gender (F/M)</th>
<th>Age (Yrs)</th>
<th>Education (Yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HD patients</td>
<td>4/6</td>
<td>49.2 ± 7.32</td>
<td>15.2 ± 2.49</td>
</tr>
<tr>
<td>Controls</td>
<td>4/6</td>
<td>49.2 ± 7.01</td>
<td>14.7 ± 1.25</td>
</tr>
</tbody>
</table>

**TEMPORAL ORDER MEMORY TASK**

The participants were tested on a task developed by Pirogovsky et al. (2009). Participants were seated in a chair approximately 60 cm from a 59 cm (diagonal) computer monitor. At the beginning of each trial, participants were prompted to focus on the monitor where a computerized version of the radial 8-arm maze was shown. The computerized 8-arm maze consists of 8 arms extending from a center like spokes on a wheel (Figure 1).

Figure 1. Computer adaptation of the 8-arm radial maze in the temporal order task.
The 8-arm maze appeared on the computer screen with a diameter of approximately 30 cm. The participants were told that a circle would appear at the end of each arm one at a time in a random sequence. The experimenter then instructed participants to remember the sequence in which the circles were presented on the arms. Each trial consisted of a sample phase followed by a choice phase. On the sample phase, a gray circle (3 cm diameter) appeared at the end of a randomly selected arm (Figure 2). The circle appeared for 2 s and then the entire display was masked for 2 s by a gray mask to eliminate after image effects. Then another circle appeared at the end of a different randomly selected arm for 2 s followed by a 2 s mask. This continued until a gray circle had been presented at the end of each of the 8 arms once in a random sequence that varied on each trial.

![Figure 2. Sample phase temporal sequence displaying the locations of the circle on the 1st through 8th arm in a random sequence.](image)

On the choice phase, the participants were presented simultaneously for 5 s with two circles, one at the end of one of the sample phase arms and the other at the end of another sample phase arm (Figure 3). The participants were asked to indicate which circle appeared
Figure 3. Choice phase temporal sequence displaying a 6 temporal separation lag trial, a 2 temporal separation lag trial, and a 0 temporal separation lag trial.

earliest in the sequence. Temporal separations of 0, 2, 4, and 6 lags were randomly selected for each choice phase and represented the number of circles that occurred in the sample phase sequence between the two circles presented simultaneously in the choice phase. For example, on a 6 lag temporal separation, participants were presented with two circles on the choice phase that occurred with six circles between them on the sample phase sequence (e.g., 1st circle presented vs. 8th circle presented). On a 2 lag temporal separation, two circles were presented on the choice phase that occurred with two circles between them on the sample phase sequence (e.g., 2nd circle presented vs. 5th circle presented). Following each sample phase sequence, three choice phases were conducted involving three of the four temporal separations (Figure 3). A total of 16 different sample phase sequences were presented with three choice phases for each sequence. As a result, there were a total of 12 choice phase trials for each of the four temporal separations. A 15 s inter-trial interval was implemented between each trial. Participant responses were recorded by the experimenter.
NEUROPSYCHOLOGICAL MEASURES

Participants were administered the Dementia Rating Scale (DRS; Mattis, 1976) to assess global cognitive function. Participants also were asked to complete the Beck Depression Inventory-II (BDI-II; Beck, Steer, & Brown, 1996), which was used to assess the presence and severity of depression. Verbal memory was evaluated using the Hopkins Verbal Learning Test—Revised (HVLT-R; Brandt & Benedict, 1997) and the Verbal Paired Associates Subtest from the Wechsler Memory Scale—Third Edition (WMS-III; Wechsler, 2002). The Visual Spatial Learning Test (VSLT; Malec, Ivnik, & Hinkeldey, 1991) was administered to evaluate nonverbal visuospatial memory. The Color-Word Interference Test and Verbal Fluency subtests of the Delis Kaplan Executive Function System (D-KEFS; Delis, Kaplan, & Kramer, 2001) were used to assess executive function. Visuopspatial perception was measured by administering the Benton Judgment of Line Orientation Test (Benton, Sivan, Hamsher, Varney, & Spreen, 1994).
CHAPTER 3

RESULTS

TEMPORAL ORDER MEMORY TASK

A mixed model 2 x 4 analysis of variance (ANOVA) with group (HD patients, normal controls) as a between group variable and temporal separation lag (0, 2, 4, 6) as the within group variable was used to analyze the data from the temporal order task, as shown in Table 2. Analysis revealed a statistically significant main effect of temporal separation lag, \( F(3, 54) = 5.73, p < .01 \). A Newman-Keuls post hoc comparison test of the significant main effect of temporal separation lag showed that performance on the 0 temporal separation lag was significantly lower than performance on 4 and 6 temporal separation lags \( (p < .05) \). Performance on the 2 temporal separation lag was significantly lower than performance on the 4 and 6 temporal separation lags \( (p < .05) \); however, no significant differences were detected between the 0 and 2 temporal separation lags or the 4 and 6 temporal separation lags (see Figure 4).

Table 2. Results From a 2 x 4 ANOVA With Group (HD Patients, Normal Controls) as the Between Groups Factor and Lag (0, 2, 4, 6) as the Within Groups Factor

<table>
<thead>
<tr>
<th></th>
<th>( F  )</th>
<th>( (df) )</th>
<th>( p )</th>
<th>Observed Power</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group</td>
<td>9.2</td>
<td>(1, 18)</td>
<td>&lt;.01</td>
<td>0.818</td>
</tr>
<tr>
<td>Lag</td>
<td>5.73</td>
<td>(3, 54)</td>
<td>&lt;.01</td>
<td>0.934</td>
</tr>
<tr>
<td>Group X Lag</td>
<td>6.11</td>
<td>(3, 54)</td>
<td>( \leq .001 )</td>
<td>0.948</td>
</tr>
</tbody>
</table>
There was also a significant main effect of group, $F(1, 18) = 9.20, p < .01$, indicating that normal controls outperformed HD patients on the task. A significant group X temporal separation lag interaction also was detected, $F(3, 54) = 6.11, p \leq .001$. A Newman-Keuls post hoc comparison test of the group X temporal separation lag interaction revealed that normal controls outperformed HD patients on the 0, 4, and 6 temporal separation lags ($p < .05$). However, no group differences were detected on the 2 temporal separation lag. Within the control group, participants performed significantly better on the 4 and 6 temporal separation lags compared to the 0 and 2 temporal separation lags ($p < .05$). However, there were no significant differences across lag within the HD group, indicating that performance did not improve as a function of temporal separation lag (see Figure 4).
NEUROPSYCHOLOGICAL MEASURES

One-way ANOVAs were conducted to assess performance between groups (HD patients, normal controls) on each of the standardized neuropsychological measures. The results of these analyses are provided in Table 3. On average, HD patients performed significantly worse on the DRS than did the normal controls, $F(1, 18) = 21.59, p < .001$. On average, the HD patients were significantly more depressed than the normal controls, $F(1, 16) = 5.56, p < .05$. Normal controls also outperformed HD patients on all subscales of the Hopkins Verbal Learning Test-Revised (HVLT-R): trial one recall, $F(1, 18) = 21.26, p < .001$, trial two recall, $F(1, 18) = 100.66, p < .001$, trial three recall, $F(1, 18) = 43.22, p < .001$, total immediate, $F(1, 18) = 63.65, p < .001$, delayed recall, $F(1, 18) = 49.95, p < .001$, retention percentage, $F(1, 18) = 6.67, p < .05$, and recognition, $F(1, 18) = 15.15, p < .001$, and most subscales of the Visual Spatial Learning Test (VSLT): designs recognized, $F(1, 16) = 11.41, p < .01$, correct positions, $F(1, 16) = 10.61, p < .01$, correct position and design, $F(1, 16) = 15.71, p < .001$, recall correct positions, $F(1, 16) = 7.96, p < .05$, and recall correct position and design, $F(1, 16) = 12.54, p < .05$. In addition, normal controls outperformed HD patients on all subscales of the D-KEFS Color-Word Interference Test: color naming, $F(1, 18) = 27.24, p < .001$, word reading, $F(1, 18) = 23.0, p < .001$, inhibition, $F(1, 18) = 17.36, p < .001$, and inhibition/switching, $F(1, 18) = 13.31, p < .01$. Also normal controls outperformed HD patients on all subscales of the D-KEFS Verbal Fluency Test: letter fluency, $F(1, 18) = 7.25, p < .05$, category fluency, $F(1, 18) = 31.28, p < .001$, and category switching, $F(1, 18) = 21.43, p < .001$. Also, significant main effects of group for the immediate recall, $F(1, 18) = 17.8, p < .01$, and the delayed recall, $F(1, 18) = 39.53, p < .001$, subscales of the WMS-III Verbal Paired Associates Test were revealed. Finally, results
Table 3. Results From One-Way ANOVAs With Group (HD Patients, Normal Controls) as the Between Groups Factor and the Standardized Neuropsychological Measures as the Within Groups Factor

<table>
<thead>
<tr>
<th></th>
<th>HD Patients Mean (SD)</th>
<th>Controls Mean (SD)</th>
<th>F</th>
<th>(df)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DRS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>132.4 (6.1)</td>
<td>141.7 (1.6)</td>
<td>21.59</td>
<td>(1, 18)</td>
<td>&gt;.001*</td>
</tr>
<tr>
<td><strong>BDI-II</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>8.3 (6.3)</td>
<td>2.5 (3.2)</td>
<td>5.56</td>
<td>(1, 16)</td>
<td>&lt;.05*</td>
</tr>
<tr>
<td><strong>HLVT-R</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trial One Recall</td>
<td>5.0 (1.5)</td>
<td>8.3 (1.7)</td>
<td>21.26</td>
<td>(1, 18)</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>Trial Two Recall</td>
<td>5.7 (1.3)</td>
<td>10.5 (8.5)</td>
<td>100.66</td>
<td>(1, 18)</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>Trial Three Recall</td>
<td>6.8 (1.8)</td>
<td>11.1 (1.1)</td>
<td>43.22</td>
<td>(1, 18)</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>Total Immediate</td>
<td>17.5 (4.0)</td>
<td>29.9 (2.8)</td>
<td>63.65</td>
<td>(1, 18)</td>
<td>&gt;.001*</td>
</tr>
<tr>
<td>Delayed Recall</td>
<td>5.0 (1.9)</td>
<td>10.5 (1.6)</td>
<td>49.95</td>
<td>(1, 18)</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>Retention Percentage</td>
<td>73.7 (22.7)</td>
<td>93.4 (8.2)</td>
<td>6.67</td>
<td>(1, 18)</td>
<td>&lt;.05*</td>
</tr>
<tr>
<td>Recognition</td>
<td>8.9 (2.1)</td>
<td>11.6 (.52)</td>
<td>15.15</td>
<td>(1, 18)</td>
<td>≤.001*</td>
</tr>
<tr>
<td><strong>VSLT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Designs Recognized</td>
<td>23.8 (4.0)</td>
<td>30.4 (4.2)</td>
<td>11.41</td>
<td>(1, 16)</td>
<td>&gt;.01*</td>
</tr>
<tr>
<td>Correct Positions</td>
<td>13.2 (10.8)</td>
<td>26.6 (4.7)</td>
<td>10.61</td>
<td>(1, 16)</td>
<td>&lt;.01*</td>
</tr>
<tr>
<td>Correct Position and Design</td>
<td>9.6 (8.9)</td>
<td>24.1 (6.0)</td>
<td>15.71</td>
<td>(1, 16)</td>
<td>≤.001*</td>
</tr>
<tr>
<td>Recall Designs Recognized</td>
<td>5.5 (1.4)</td>
<td>6.6 (1.1)</td>
<td>3.7</td>
<td>(1, 16)</td>
<td>.073</td>
</tr>
<tr>
<td>Recall Correct Positions</td>
<td>3.2 (2.4)</td>
<td>6.1 (1.8)</td>
<td>7.96</td>
<td>(1, 16)</td>
<td>&lt;.05*</td>
</tr>
<tr>
<td>Recall Correct Position and Design</td>
<td>2.3 (2.6)</td>
<td>6.1 (1.8)</td>
<td>12.54</td>
<td>(1, 16)</td>
<td>&lt;.05*</td>
</tr>
<tr>
<td><strong>D-KEFS Color Word Interference</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Color Naming</td>
<td>53.4 (14.4)</td>
<td>27.7 (6.0)</td>
<td>27.24</td>
<td>(1, 18)</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>Word Reading</td>
<td>42.3 (11.3)</td>
<td>22.8 (6.1)</td>
<td>23.00</td>
<td>(1, 18)</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>Inhibition</td>
<td>88.1 (25.5)</td>
<td>51.6 (10.8)</td>
<td>17.36</td>
<td>(1, 18)</td>
<td>≤.001*</td>
</tr>
<tr>
<td>Inhibition/ Switching</td>
<td>113.2 (49.3)</td>
<td>54.6 (12.2)</td>
<td>13.31</td>
<td>(1, 18)</td>
<td>&lt;.01*</td>
</tr>
<tr>
<td><strong>D-KEFS Verbal Fluency</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Letter Fluency</td>
<td>29.2 (8.4)</td>
<td>40.6 (10.4)</td>
<td>7.25</td>
<td>(1, 18)</td>
<td>&lt;.05*</td>
</tr>
<tr>
<td>Category Fluency</td>
<td>24.7 (7.5)</td>
<td>42.1 (6.4)</td>
<td>31.28</td>
<td>(1, 18)</td>
<td>&gt;.001*</td>
</tr>
<tr>
<td>Category Switching</td>
<td>10.0 (2.7)</td>
<td>15.2 (2.3)</td>
<td>21.43</td>
<td>(1, 18)</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td><strong>WMS-III Verbal Paired Associates</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate Recall</td>
<td>5.8 (3.1)</td>
<td>20.9 (10.9)</td>
<td>17.8</td>
<td>(1, 18)</td>
<td>&lt;.01*</td>
</tr>
<tr>
<td>Slope</td>
<td>2.5 (1.7)</td>
<td>3.6 (2.221)</td>
<td>1.58</td>
<td>(1, 18)</td>
<td>.225</td>
</tr>
<tr>
<td>Delayed Recall</td>
<td>3.0 (1.6)</td>
<td>.73 (1.5)</td>
<td>39.53</td>
<td>(1, 18)</td>
<td>.001*</td>
</tr>
<tr>
<td>Percent Retention</td>
<td>85.0 (33.7)</td>
<td>90.0 (31.6)</td>
<td>0.117</td>
<td>(1, 18)</td>
<td>.736</td>
</tr>
<tr>
<td><strong>Benton Judgment of Line Orientation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>22.1 (4.7)</td>
<td>25.1 (3.3)</td>
<td>2.39</td>
<td>(1, 16)</td>
<td>.14</td>
</tr>
</tbody>
</table>

*Represents significance.
revealed that there were no significant differences between the HD patients and the normal controls on the judgment of line orientation task, $F(1, 16) = 2.39, p = .14$.

**PEARSON r CORRELATIONS**

Pearson $r$ correlations were computed to evaluate relationships between performance on the temporal order memory task and performance on the standardized neuropsychological measures with significant between group differences (HD patients, normal controls). All correlations are displayed in Table 4.
Table 4. Pearson $r$ Correlations Between Performance on the Temporal Order Memory Task and Performance on the Standardized Neuropsychological Measures With Significant Differences Between Groups (HD Patients, Normal Controls)

<table>
<thead>
<tr>
<th></th>
<th>Temporal Separation Lag</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0 Lag</td>
<td>2 Lag</td>
<td>4 Lag</td>
</tr>
<tr>
<td>DRS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>$r = .66$ $p &lt; .01^*$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BDI-II</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>$r = .11$ $p = .66$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HLVT-R</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trial One Recall</td>
<td>$r = .55$ $p &lt; .05^*$</td>
<td>$r = .19$ $p = .43$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trial Two Recall</td>
<td>$r = .54$ $p &lt; .05^*$</td>
<td>$r = .24$ $p = .32$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trial Three Recall</td>
<td>$r = .59$ $p &lt; .01^*$</td>
<td>$r = .29$ $p = .22$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Immediate</td>
<td>$r = .59$ $p &lt; .01^*$</td>
<td>$r = .25$ $p = .29$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delayed Recall</td>
<td>$r = .57$ $p &lt; .01^*$</td>
<td>$r = .37$ $p = .11$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retention Percentage</td>
<td>$r = .35$ $p = .13$</td>
<td>$r = .45$ $p &lt; .05^*$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recognition</td>
<td>$r = .40$ $p = .09$</td>
<td>$r = .26$ $p = .27$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VSLT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Designs Recognized</td>
<td>$r = .78$ $p &lt; .01^*$</td>
<td>$r = .57$ $p &lt; .05^*$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Correct Positions</td>
<td>$r = .70$ $p &lt; .01^*$</td>
<td>$r = .37$ $p = .13$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Correct Position and Design</td>
<td>$r = .73$ $p &lt; .01^*$</td>
<td>$r = .41$ $p = .09$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recall Correct Positions</td>
<td>$r = .72$ $p &lt; .01^*$</td>
<td>$r = .43$ $p = .07$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recall Correct Position and Design</td>
<td>$r = .73$ $p &lt; .01^*$</td>
<td>$r = .39$ $p = .11$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D-KEFS Color Word Interference</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Color Naming</td>
<td>$r = -.62$ $p &lt; .01^*$</td>
<td>$r = -.48$ $p &lt; .05^*$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Word Reading</td>
<td>$r = -.33$ $p = .15$</td>
<td>$r = -.42$ $p = .07$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inhibition</td>
<td>$r = -.63$ $p &lt; .01^*$</td>
<td>$r = -.48$ $p &lt; .05^*$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inhibition/Switching</td>
<td>$r = -.33$ $p = .16$</td>
<td>$r = -.37$ $p = .11$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D-KEFS Verbal Fluency</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Letter Fluency</td>
<td>$r = .52$ $p &lt; .05^*$</td>
<td>$r = .44$ $p = .05$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Category Fluency</td>
<td>$r = .61$ $p &lt; .01^*$</td>
<td>$r = .42$ $p = .07$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Category Switching</td>
<td>$r = .68$ $p &lt; .01^*$</td>
<td>$r = .50$ $p &lt; .05^*$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WMS-III Verbal Paired Associates</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate Recall</td>
<td>$r = .72$ $p &lt; .01^*$</td>
<td>$r = .40$ $p = .08$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delayed Recall</td>
<td>$r = .76$ $p &lt; .01^*$</td>
<td>$r = .40$ $p = .08$</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Represents significance.
CHAPTER 4

DISCUSSION

The purpose of the present study was to evaluate temporal interference and its effects on temporal order memory in HD patients. It was hypothesized that normal controls would outperform HD patients. Also, it was predicted that as the temporal separation lag increased, performance on the temporal order memory task would improve due to a decrease in temporal interference. HD patients were predicted to be more impaired on performance on proximal separation lags (0, 2, 4 lags) than controls, but were expected to match controls on the most distal temporal separation lag (6 lag). In accordance with the hypothesis, analyses revealed that HD patients were more impaired overall on the temporal order memory task compared to the normal controls, as evidenced by a significant main effect of group. Additionally, a significant main effect of temporal lag demonstrated that performance increased as temporal separation lag increased. However, contrary to predictions, there were no significant differences between groups for performance on the 2 temporal separation lag, and there were significant differences between groups on the most distal temporal separation lag (6 lag). This suggests that HD patients’ performance was impaired even with minimal temporal interference.

As mentioned previously, a study by Pirogovsky et al. (2009) provided evidence that premanifest HD gene carriers close to estimated disease onset were significantly impaired on the temporal order memory task relative to premanifest HD gene carriers further from
estimated disease onset and normal controls. Participants closer to disease onset performed significantly worse on the proximal lags (0, 2, 4 lags) compared to participants further from disease onset and normal controls, but showed no significant difference in performance on the most distal lag (6 lag). In the present study, findings revealed that the HD patients performed similarly to normal controls for the 2 temporal separation lag, and were significantly more impaired on the 0, 4, and 6 temporal separation lags. The lack of a difference on the 2 temporal separation lag is likely due to low sample. Normal controls’ performance decreased on the 2 temporal separation lags compared to the 0 temporal separation lags, indicating that performance may increase with more participants. Pirogovsky et al. (2009) included 18 normal control participants in their study and demonstrated that performance increased as temporal separation lag increased. Therefore, evidence from the present study shows that the performance on the temporal order memory task worsens as the disease progresses.

Temporal order memory dysfunction in HD may be a result of neuropathological alterations in the striatum, and the consequent disturbance in frontostriatal circuitry. Studies using neuroimaging techniques (e.g., structural, functional, and diffusion tensor imaging studies) have shown that premanifest HD gene carriers evidence dysfunction in the frontal cortex, striatum, and other areas of frontostriatal circuitry prior to clinical diagnosis (Aylward et al., 1994; Ciarmiello et al., 2006; Gomez-Anson et al., 2007; Paulsen et al., 2004; Paulsen et al., 2006, Reading et al., 2004; Reading et al., 2005; Rosas et al., 2006; Thieben et al., 2002; Wolf, Vasic, Schonfeldt-Lecuona, Landwehrmeyer, & Ecker, 2007; Zimbelman et al., 2007). This finding suggests that the dysfunction of the frontostriatal circuitry may occur before disease onset, thus, dysfunction is likely to increase with disease progression.
Neuroimaging studies in HD patients (Aylward et al., 1997; Bäckman, Robins-Wahlin, Lundin, Ginovart, & Ferde, 1997; Bamford, Caine, Kido, Cox, & Shoulson, 1995; Bamford, Caine, Kido, Plassche, & Shoulson, 1989; Harris et al., 1996; Starkstein et al., 1992) have shown evidence of damage to areas of frontostriatal circuitry after disease onset, demonstrating that the deterioration of the frontal cortex, striatum, and areas of frontostriatal circuitry continues to worsen throughout the disease process. As mentioned earlier, there is mounting evidence from both human and animal studies supporting the frontal cortex as an integral component in temporal order memory (Chiba et al., 1997; Kesner et al., 1994; McAndrews & Milner, 1991; Milner et al., 1991). Therefore, temporal order memory may be related to frontostriatal neuropathology in HD.

Although a difference between the HD patients and the normal controls on the most distal temporal separation lag (6 lag) was not expected, there are several possible explanations for the findings. First, inefficient pattern separation may have led to the deficits observed in the current study. It may be possible that the HD patients’ temporal order memory was so impaired that they were unable to resolve interference even at the 6 temporal separation lag. If the task had been manipulated so that the number of locations increased to more distal lags (8, 10 lags), interference may have been low enough to detect an improvement in the HD patients’ performance. However, prior to conducting their study, Pirogovsky et al. (2009) attempted to increase the number of locations on the temporal order task, but findings showed that including the 8 and 10 temporal separation lags resulted in a poor performance for normal controls on the 2 and 4 temporal separation lags. Thus, increasing the number of locations alters task performance in normal controls and prohibits comparisons with previous studies using this task (e.g., Pirogovsky et al., 2009).
A second explanation for differences on the 6 temporal separation lag trials might be that HD patients may have difficulty learning a temporal sequence, or even possess an inability to do so. To date, there are no standardized tests to measure temporal sequence memory. A test was recently developed in Dr. Paul Gilbert’s lab at San Diego State University, which may provide insight as to whether or not HD patients are capable of learning a temporal sequence. However, there are no published studies at the present time investigating sequence learning in HD. Working memory also may be a potential explanation for the present findings. A neuroimaging study by Wolf, Vasic, Schonfeldt-Lecuona, Ecker, and Landwehrmeyer (2009) used functional magnetic resonance imaging coupled with a parametric verbal working memory task to examine working memory performance in HD patients. It was observed that HD patients performed significantly worse on the verbal working memory task compared to the normal controls. These results suggest that working memory may be impaired in HD patients, which could have a significant negative impact on performance for tasks of temporal order memory that involve a working memory component.

Finally, deficiencies in visuospatial memory may be contributing to the impairment of the present task. Analysis of performance on the VSLT showed that normal controls outperformed HD patients on all but one subscale, “recall designs recognized,” of this task. The HD patients were impaired relative to normal controls on designs recognized, correct positions, correct position and design, recall correct positions, and recall correct position and design, and performance on these subscales was highly positively correlated with performance on the 0, 4, and 6 temporal separation lag of the temporal order memory task, but were not correlated with the 2 temporal separation lag, with the exception of the designs recognized scale. These results suggest a relationship between performance on the VSLT and
the present temporal order memory task, especially for the temporal separation lags that presented a challenge for HD patients (0, 4, 6 lags).

In contrast to performance on the VSLT, there were no differences between groups on the Benton Judgment of Line Orientation task. These findings indicate that perceptual memory was not impaired in HD patients compared to controls. A study by Maki, Bylsma, and Brandt (2000) supports this conclusion by demonstrating that HD patients were not impaired on a task of perceptual implicit memory relative to normal controls. Therefore, although HD patients’ difficulty with visuospatial memory may have accounted for the poor performance on the temporal order memory task, the deficits were not due solely to impaired visuospatial perceptual processing.

Along with the temporal order memory task, participants were administered a battery of standardized neuropsychological tests. According to results of the current study, HD patients were impaired relative to the normal controls on all subscales of the HVLT-R (recall, delayed recall, retention, and recognition). These results conflict with studies that demonstrated recognition memory to remain intact in HD (Butters et al., 1985; Moss et al., 1986), but are consistent with several previous studies that have shown both recall and recognition to be deficient in HD (Brandt & Munro, 2002; Brandt, Shpritz, Munro, Marsh, & Rosenblatt, 2005; Montoya, Pelletier, et al., 2006; Solomon et al., 2007; Zizak et al., 2005). Pirogovsky et al. (2009) found that premanifest HD participants closer to disease onset were impaired on the total immediate recall and the recognition portions of the HVLT-R relative to the premanifest HD participants further from disease onset and normal controls. No differences were observed between the three groups on delayed recall or retention. This suggests that delayed recall and retention diminish after disease onset. Furthermore, all
subscales of the HVLT-R were highly positively correlated with the 6 temporal separation lag, and subscales of recall and delayed recall were shown to be positively correlated to the 0 and 4 temporal separation lag. Also, retention was significantly positively correlated with the 2, 4, and 6 temporal separation lags. These results suggest a relationship between performance on the current temporal order task and performance on tasks that measure recall, delayed recall, retention, and recognition memory, especially for the most distal temporal separation lag (6 lag).

In the present study, HD patients were significantly impaired on performance for the D-KEFS Color-Word Interference Test and the Verbal Fluency Test relative to normal controls. Both of these measures were chosen to assess executive function. These findings add to the body of literature that supports executive dysfunction as a prominent feature of HD. It is important to note that significant negative correlations were observed between all temporal separation lags (0, 2, 4, 6 lags) and the inhibition subscale, and the 6 temporal separation lag and the inhibition/switching subscale of the D-KEFS Color-Word Interference Test, which are both sensitive to frontal lobe function. Scoring for this measure was recorded as the amount of time needed to complete the task; consequently, a negative correlation translates to a comparable level of performance with the scores measured in the current temporal order memory task.

Impairments in phonemic and semantic fluency have previously been found to be an identifiable cognitive deficit in individuals diagnosed with HD (Henry et al., 2005). In the present study the phonemic (letter fluency), semantic (category fluency), and switching subscales of the D-KEFS Verbal Fluency Test all were positively correlated with the 0 and 6 temporal separation lags. The semantic subscale also was positively correlated with the 4
temporal separation lags and the switching subscale positively correlated with the 2 temporal separation lag. These results support deficits in phonemic and semantic fluency in HD patients and show that the deficits may be related to the present temporal order memory task. Furthermore, no differences on the D-KEFS Verbal Fluency Test were found between premanifest HD gene carriers close to disease onset, those further from disease onset, and normal controls in the study by Pirogovsky et al. (2009), which suggests that these deficits manifest during disease progression. Thus, there may be an association between the temporal order task and standardized measures of executive function, which supports the theory that damage to the frontal cortex negatively impacts the ability to organize events as they occur in time.

Evaluation of the current analyses also revealed differences between groups for performance on the immediate and delayed recall subscales of the WMS-III Verbal Paired Associates measure. This significant difference indicates that verbal memory may be impaired in HD patients compared to normal controls. Significant positive correlations between these subscales and the 0, 4, and 6 temporal separation lags were observed. HD patients displayed a weak performance on these same temporal separation lags, which suggests that deficiencies in verbal memory may be correlated with poor performance on the temporal order memory task.

As predicted, HD patients were impaired relative to normal controls on the DRS. Further analysis revealed a significant positive correlation between the DRS scores and all four temporal separation lags (0, 2, 4, 6 lags). HD patients’ deficient performance on this measure of global cognitive function and the temporal order memory task may be related.
Finally, as mentioned previously, depression is commonly experienced among HD patients (Paulsen et al., 2005). Results of the present study showed that HD patients endorsed significantly more depressive symptoms as measured by the BDI-II compared to normal controls. These findings are consistent with the nature of the disorder, and the extensive literature that documents depression as a symptom of HD (Crawford & Snowdon, 2002; Paulsen et al., 2005; Rosenblatt et al., 1999; Slaughter, Martens, & Slaughter, 2001). No significant correlations were found between performance on the temporal separation lags and the BDI-II.

LIMITATIONS

Sample size was a limitation in the current study, due to the limited number of accessible HD patients that were rated in the early stages of disease progression and still able to perform the task. Given the difficulties in recruiting these individuals, the present sample was larger than expected over the span of approximately 18 months. Administrative errors also introduced a limitation to the current study; thus, two normal control subjects from the study by Pirogovsky et al. (2009) were used as replacement normal control participants. The necessary replacement of two normal controls due to administrative error may have affected interpretation of the performance on the VSLT and the BDI-II in the control group because these tasks were not administered. Therefore, two new controls will be tested for future publication of this study.

Another limitation of the study was the level of interference presented by using only four temporal separation lags. As noted earlier, it may be advantageous to add more distal temporal separation lags to the task in order to properly evaluate temporal order memory in
HD patients. An attempt was made to increase the memory span and hence, increase the
temporal separation lags; however, normal controls were not able to perform well when the
additional distal lags were included. Future researchers interested in studying temporal order
memory may want to consider the possibility of including more distal temporal separation
lags, and the benefits and drawbacks that may result therein.

**CONCLUSION AND IMPLICATIONS**

In conclusion, the present study found that temporal order memory was significantly
impaired in HD patients compared to normal controls. In addition, overall performance
increased as temporal separation lag increased. Contrary to the a priori hypothesis, the
performance of HD patients on the most distal temporal separation lag (6 lag) significantly
differed from the performance of the normal controls. Therefore, the results demonstrate
deficits in temporal order memory for HD patients at high, moderate, and even minimal
levels of temporal interference. Furthermore, in comparison with the findings of Pirogovsky
et al. (2009) data indicate that temporal order memory deteriorates with disease progression.
Future studies should focus on developing and refining new tasks to assess temporal order
memory to further understand the effects of HD on this cognitive function that is critical to
execution of many daily living tasks. New discoveries in this area of research may lead to the
identification of specific cognitive deficits associated with HD. The identification of a key-
processing deficit in temporal order memory may result in behavioral interventions to
structure daily living tasks, minimize temporal interference, and improve function.
REFERENCES


